ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2020 October 24; 11(10): 761-853

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Monthly Volume 11 Number 10 October 24, 2020

REVIEW

761 Colorectal liver metastases: Current management and future perspectives

Martin J, Petrillo A, Smyth EC, Shaida N, Khwaja S, Cheow H, Duckworth A, Heister P, Praseedom R, Jah A, Balakrishnan A, Harper S, Liau S, Kosmoliaptsis V, Huguet E

809 Critically ill patients with cancer: A clinical perspective

Martos-Benítez FD, Soler-Morejón CDD, Lara-Ponce KX, Orama-Requejo V, Burgos-Aragüez D, Larrondo-Muguercia H, Lespoir RW

ORIGINAL ARTICLE

Retrospective Cohort Study

836 Primary small cell oesophageal carcinoma: A retrospective study of different treatment modalities

Alfayez M

CASE REPORT

844 Albumin-bound paclitaxel as new treatment for metastatic cholangiocarcinoma: A case report

Martin Huertas R, Fuentes-Mateos R, Serrano Domingo JJ, Corral de la Fuente E, Rodríguez-Garrote M

World Journal of Clinical Oncology

Monthly Volume 11 Number 10 October 24, 2020

Contents

ABOUT COVER

Associate editor of *World Journal of Clinical Oncology*, Dr. Felipe Couñago studied medicine at the University of Santiago de Compostela (Galicia, Spain) and completed his residency in radiation oncology at the La Princesa University Hospital (Madrid, Spain) in 2009. He received his PhD from the European University of Madrid in 2017. Currently, he is Attending Physician at the Hospital La Luz (Madrid) and Associate Director of the Department of Radiation Oncology at Quirónsalud University Hospital (Madrid). He is an Adjunct Professor at the European University of Madrid. He continues to be an active researcher, having served as primary investigator in 14 clinical studies and published more than 30 scientific articles, mostly on prostate and lung cancers. He currently serves as the coordinator of the Spanish Oncology Group for the Study of Lung Cancer. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
October 24, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 October 24; 11(10): 761-808

DOI: 10.5306/wjco.v11.i10.761

ISSN 2218-4333 (online)

REVIEW

Colorectal liver metastases: Current management and future perspectives

Jack Martin, Angelica Petrillo, Elizabeth C Smyth, Nadeem Shaida, Samir Khwaja, HK Cheow, Adam Duckworth, Paula Heister, Raaj Praseedom, Asif Jah, Anita Balakrishnan, Simon Harper, Siong Liau, Vasilis Kosmoliaptsis, Emmanuel Huguet

ORCID number: Jack Martin 0000-0001-9545-0298; Angelica Petrillo 0000-0001-5489-5733; Elizabeth C Smyth 0000-0002-4667-1817; Nadeem Shaida 0000-0002-6843-7458; Samir Khwaja 0000-0002-2481-6800; HK Cheow 0000-0002-2334-3597; Adam Duckworth 0000-00028664-4987; Paula Heister 0000-0001-7207-869X; Raaj Praseedom 0000-0001-9541-6356; Asif Jah 0000-0001-5541-1550; Anita Balakrishnan 0000-0001-6406-6066; Simon Harper 0000-0001-6016-8049; Siong Liau 0000-0001-5155-4300; Vasilis Kosmoliaptsis 0000-0001-7298-1387; Emmanuel Huguet 0000-0001-5816-5308.

Author contributions: Martin J designed the structure of the overall manuscript and authored text in all sections; Petrillo A and Smyth EC authored text in the chemotherapy sections; Shaida N authored text in the interventional radiology sections; Khwaja S authored text in imaging sections; Cheow H authored text in the nuclear medicine section; Duckworth A and Heister P authored text in the pathology section; Praseedom R, Jah A, Balakrishnan A, Harper S, Liau S and Kosmoliaptsis V authored text in the surgery sections; Huguet E designed the structure of the overall manuscript and authored text in all sections. All authors

Jack Martin, Raaj Praseedom, Asif Jah, Anita Balakrishnan, Simon Harper, Siong Liau, Vasilis Kosmoliaptsis, Emmanuel Huguet, Department of Surgery, Addenbrookes Hospital, NIHR Comprehensive Biomedical Research and Academic Health Sciences Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, United Kingdom

Angelica Petrillo, Department of Precision Medicine, Division of Medical Oncology, University of Campania "L. Vanvitelli", Napoli 80131, Italy, & Medical Oncology Unit, Ospedale del Mare, 80147 Napoli Italy

Elizabeth C Smyth, Department of Oncology, Addenbrookes Hospital, NIHR Comprehensive Biomedical Research and Academic Health Sciences Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, United Kingdom

Nadeem Shaida, Samir Khwaja, Department of Radiology, Addenbrookes Hospital, NIHR Comprehensive Biomedical Research and Academic Health Sciences Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB22 0QQ, United Kingdom

HK Cheow, Department of Nuclear Medicine, Addenbrookes Hospital, NIHR Comprehensive Biomedical Research and Academic Health Sciences Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, United Kingdom

Adam Duckworth, Paula Heister, Department of Pathology, Addenbrookes Hospital, NIHR Comprehensive Biomedical Research and Academic Health Sciences Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, United Kingdom

Corresponding author: Emmanuel Huguet, BSc, DPhil, FRCS, MBChB, Surgeon, Surgical Oncologist, University Department of Surgery, Addenbrookes Hospital, NIHR Comprehensive Biomedical Research and Academic Health Sciences Center, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, United Kingdom. emmanuel.huguet@addenbrookes.nhs.uk

Abstract

The liver is the commonest site of metastatic disease for patients with colorectal cancer, with at least 25% developing colorectal liver metastases (CRLM) during the course of their illness. The management of CRLM has evolved into a complex field requiring input from experienced members of a multi-disciplinary team

have read and approved the final manuscript.

Conflict-of-interest statement: All other authors have nothing to disclose.

Manuscript source: Invited manuscript

Received: February 27, 2020
Peer-review started: February 27, 2020
First decision: April 7, 2020
Revised: May 14, 2020
Accepted: August 31, 2020
Article in press: August 31, 2020
Published online: October 24, 2020

P-Reviewer: Fan H, Mikulic D, Romani A
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

involving radiology (cross sectional, nuclear medicine and interventional), Oncology, Liver surgery, Colorectal surgery, and Histopathology. Patient management is based on assessment of sophisticated clinical, radiological and biomarker information. Despite incomplete evidence in this very heterogeneous patient group, maximising resection of CRLM using all available techniques remains a key objective and provides the best chance of long-term survival and cure. To this end, liver resection is maximised by the use of downsizing chemotherapy, optimisation of liver remnant by portal vein embolization, associating liver partition and portal vein ligation for staged hepatectomy, and combining resection with ablation, in the context of improvements in the functional assessment of the future remnant liver. Liver resection may safely be carried out laparoscopically or open, and synchronously with, or before, colorectal surgery in selected patients. For unresectable patients, treatment options including systemic chemotherapy, targeted biological agents, intra-arterial infusion or bead delivered chemotherapy, tumour ablation, stereotactic radiotherapy, and selective internal radiotherapy contribute to improve survival and may convert initially unresectable patients to operability. Currently evolving areas include biomarker characterisation of tumours, the development of novel systemic agents targeting specific oncogenic pathways, and the potential re-emergence of radical surgical options such as liver transplantation.

Key Words: Colorectal; Cancer; Liver; Metastases; Management; Review

Core Tip: The management of colorectal liver metastases is a complex evolving field requiring input from an experienced multi-disciplinary team involving radiology (cross sectional, nuclear medicine and interventional), Oncology, Liver surgery, Colorectal surgery, and Histopathology. Patient management is based on clinical, radiological and biomarker information. Despite incomplete evidence in this very heterogeneous patient group, maximising resection of colorectal liver metastases using all available techniques remains a key objective and provides the best chance of long-term survival. For unresectable patients, optimal systemic and locoregional chemotherapeutic, biological and radiotherapeutic treatments improve survival, and may convert initially unresectable patients to operability.

Citation: Martin J, Petrillo A, Smyth EC, Shaida N, Khwaja S, Cheow H, Duckworth A, Heister P, Praseedom R, Jah A, Balakrishnan A, Harper S, Liau S, Kosmoliaptsis V, Huguet E. Colorectal liver metastases: Current management and future perspectives. *World J Clin Oncol* 2020; 11(10): 761-808
URL: https://www.wjgnet.com/2218-4333/full/v11/i10/761.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i10.761

INTRODUCTION

Colorectal cancer (CRC) represents a major worldwide health care burden, as the second most common cancer diagnosed in women and third most common in men, and accounting for 10% of all annually diagnosed cancers and cancer-related deaths worldwide[1].

As result of improvements in detection through screening[2], better referral pathways[3], centralisation of services[4], effective primary surgery[5], development of systemic chemotherapy[6], biological agents[7], and understanding of tumour biology[8], survival rates following diagnosis have improved[9].

Nevertheless, at least 25%-50% of patients with CRC develop colorectal liver metastases (CRLM) during the course of their illness.

From a historical perspective, the surgical management approach to CRLM has undergone a significant evolution. Starting from an era prior to the 1930s during which liver surgery for malignancy presented insurmountable challenges for technical and oncological reasons, tentative attempts at liver resection for malignancy were

made in the subsequent decades resulting in early reports establishing proof of principle that long term survival following resection of CRLM was possible[10,11]. These results were confirmed and emphasised by larger landmark studies firmly establishing liver surgery as a potentially curative treatment for CRLM[12,13].

The era since has been characterised by progress in understanding of tumour biology as well as surgical and oncological developments. These overlapping and interdependent factors have directed the modern management of CRLM to a multidisciplinary approach involving radiology (cross sectional, nuclear medicine and interventional), Oncology, Liver surgery, Colorectal surgery, Histopathology, and Specialist nursing[14]. The paramount importance of the MDT cannot be overemphasised as it represents the forum where key management decisions are made after consideration of information spanning many different disciplines, with demonstrable benefits in terms of significant treatment alterations[15,16], numbers of patient offered resection[17,18], and ultimately translating into improved survival[19,20].

In the following review, we present modern management of CRLM. In order to assist the reader, section contents are provided below: (1) Diagnosis and staging of CRLM post resection of CRC; (2) Tumour characterisation and biomarkers in CRC; (3) Systemic and locoregional chemotherapy and targeted agents in CRLM management; (4) Surgical management of resectable CRLM; and (5) Histopathological assessment of resected CRLM.

SECTION 1: DIAGNOSIS, STAGING, AND SURVEILLANCE OF COLORECTAL LIVER METASTASES POST RESECTION

The detection of CRLM is achieved during staging investigations in the case of synchronous CRLM and by post CRC resection surveillance programmes in the case of metachronous CRLM. The section below discusses the timing and epidemiology of metachronous CRLM, an understanding of which is essential in judging the effectiveness of post CRC resection surveillance practice. The section also describes current optimal staging of CRLM, and finally current practice as it applies to surveillance after resection of CRLM.

CRLM epidemiology

Colorectal cancer is the third most common cancer worldwide and accounts for 10% of all cancers. It is a major cause of morbidity and the second most common cause of cancer related mortality[1].

Although it is regularly reported that approximately 50% of patients with colorectal cancer develop liver metastases, either as synchronous or metachronous disease[21-25], this is likely an exaggeration of true incidence originating from an historic autopsy study of patients who died with colorectal cancer[26]. Large epidemiological studies from multiple European centres demonstrate the incidence of both synchronous and metachronous liver metastases in patients with colorectal cancer to be lower, at approximately 25%[27-31]. The incidence of synchronous liver metastases in epidemiological studies ranges from 13.8%–17.1%[27,29,30] and the rate of metachronous liver metastases in these studies ranges from 7.6%–15.1%[27,29,30,32]. The interval between primary diagnosis and the detection of metastatic disease used in the literature ranges from the time of primary resection[29], to 3 mo[29,33], or 6 mo after diagnosis, and this lack of a consensus regarding the definition of metachronous metastases may partly explain the reported variation[24,32]. Further confounders include evolution in the sensitivity of pre-operative staging, and the reported increase in synchronous disease[28]. CRLM occur more frequently in male patients and in patients with left sided CRC, relating to embryological origin of the primary tumour[27,30].

With regards to metachronous disease, most recurrences occur early in follow up: 76%-85.3% occur within a year and 83%-97.5% within 3 years, with 30%-40% of patients having disease confined to the liver[33,34]. Approximately 2% of patients will develop liver metastases between 5 and 10 years after resection of the primary tumour[27,29,33].

CRC surveillance programmes

Surveillance programmes accompanied the widespread introduction of liver resection for CRLM, to detect recurrent disease early, with a view to improve survival. A meta-analysis of five randomised controlled trials published in 2002 supported this hypothesis by demonstrating a survival benefit associated with more intensive follow

up regimes[35]. This encouraged the introduction of more intensive surveillance programmes, although a subsequent large multicentre randomised control trial performed in the United Kingdom by Primrose *et al*[36] failed to replicate these findings. In this study, intensive surveillance regimes with computed tomography (CT) with or without carcino-embryonic antigen (CEA) resulted in an increased rate of surgical treatment with curative intent, but this failed to translate to improved survival when compared to the minimal surveillance group[36]. Interestingly, the reported incidence of metachronous disease in this study was markedly lower than that reported in the previous meta-analysis (8.4% *vs* 32%). The stage-specific case mix and risk of recurrence within tumour stage across studies remained similar but one explanation for this reported difference was possibly superior pre-operative staging. This would provide an explanation for the previously reported improved benefit of more intensive follow up programmes with early recurrence in these older studies representing undetected residual disease[36]. A further meta-analysis published in 2016 of 15 randomised controlled trials came to a similar conclusion to that of Primrose *et al*[36] and demonstrated no overall survival benefit with more intensive follow up regimes[36,37].

In summary, surveillance programmes with either regular CEA or CT increase the likelihood of detecting recurrent disease and result in an increased proportion of patients undergoing surgical treatment with curative intent. This has not, however, been shown to translate into improved patient survival in trials. This counter-intuitive finding may partially be explained by the failure of randomised trials to detect small differences: If 25% of patients develop CRLM post CRC resection, of which 25% are operable, and of which 25% are 10 year survivors, the difference in overall survival in a surveillance group may prove beyond detection. In practice, the real world observation of lives saved following resection of metachronous CRLM has resulted in the continued adoption of surveillance programmes using CT and serum CEA, although the additional value of the latter has been difficult to demonstrate in trials[36].

CRLM characterisation and staging

Imaging has an important role in defining optimal treatment of CRLM. Knowing the size, location and vascular relationships of CLRM is essential prior to treatment planning and assessment of neoadjuvant response. Imaging techniques include ultrasound, CT, magnetic resonance imaging (MRI) and fluoro-18-deoxyglucose (FDG) positron emission tomography (PET-CT).

Ultrasound: Ultrasound has a limited role in pre-operative evaluation as it has a low sensitivity (64%) for CRLM compared with other imaging modalities[38]. In recent years contrast-enhanced ultrasound (CEUS) has become widely used to characterise liver lesions based on dynamic assessment of tumour vascularity. CEUS has a reported sensitivity of 80%–90%, comparable to CT and is significantly more sensitive than grey-scale ultrasound for detecting small CRLM less than 10 mm[39,40]. Nevertheless, CEUS does not offer comprehensive information needed for surgical planning as compared to CT or MRI. Intra-operative ultrasound (IOUS) has an established role in lesion detection and mapping of major hepatic vessels during surgery. IOUS has been shown to identify new lesions in 16% of patients and alter clinical management in 9%[41]. Contrast enhanced IOUS has higher sensitivity and specificity than traditional IOUS particularly for detection of "disappearing" lesions in the setting of neoadjuvant therapy[42,43].

Computed tomography: CT is the modality of choice for detection of liver and extrahepatic metastases. The high spatial resolution of CT combined with isotropic pixel size enables reformatted images in various planes, which enables better delineation of tumour and adjacent vascular structures for accurate segmental localisation[44]. The portal venous phase (approximately 60-70 s after administration of contrast agent) is the most reliable phase for detection of CRLM with a detection rate of 85% and a positive predictive value of 96%[45]. CRLM are typically hypovascular with variable heterogeneity depending on size and previous treatment. Since CRLM are hypovascular, arterial phase imaging does not improve detection but is helpful for pre-surgical or pre-embolisation planning[46]. The performance of CT is somewhat limited in detecting CRLM < 10 mm which are interpreted as too small to characterise[47]. In addition fatty liver is not uncommon post chemotherapy which can further limit detection of liver metastases.

Magnetic resonance imaging: Compared to CT, MRI has superior soft tissue contrast which makes it an invaluable tool for detection and characterisation of CRLM particularly those below < 10 mm[48]. CRLM are typically T1-hypointense, mildly T2-

hyperintense with heterogeneous but predominantly rim enhancement in the arterial phase and hypo-enhancement in portal venous and delayed phases. Two advances which have revolutionised the role of MRI in the last decade are diffusion weighted imaging (DWI) and the use of hepatocyte-specific contrast agents. DWI measures the mobility of water molecules in tissues. Apparent diffusion coefficient values are quantitative estimates of diffusion restriction. CRLM show restricted diffusion of water molecules due to their hypercellular nature which manifests as high signal intensity lesions with low apparent diffusion coefficient values. Addition of DWI improves sensitivity and specificity for lesion detection and characterisation[49,50]. Hepatocyte-specific contrast agents are highly sensitive for detection of small lesions, which may be virtually occult on other sequences[51]. This also allows for detection of "disappearing" lesions which can mimic complete response to neoadjuvant therapy[52]. Gadobenate dimeglumine (MultiHance, Bracco) and gadoxetate disodium (Eovist, Bayer) are both hepatocyte-specific contrast agents which are preferentially taken up by hepatocytes and excreted into the biliary tree. In the delayed hepatobiliary phase (10–120 min after administration) normal hepatocytes are hyperintense compared to liver metastases, which do not retain the contrast agent. DWI has similar sensitivity and specificity as MRI with extracellular contrast agent but lower sensitivity than MRI with hepatocyte-specific contrast agent[53].

Positron emission tomography/computed tomography: There is lack of clinical evidence to show that Fluorine^{18} labelled Positron Emission Tomography/Computed Tomography (^{18}FDG PET-CT) has significant impact on the clinical management of localised non-metastatic colorectal cancer preoperatively[54]. Its role in the initial assessment colorectal cancer, therefore, is not yet established[55]. Most centres do not carry out a routine ^{18}FDG PET-CT at this stage.

^{18}FDG PET-CT is considered to be very accurate and sensitive in the detection of CRLM, especially those greater than 10 mm[56]. However, small liver metastases (< 10 mm) and liver metastases from some mucinous adenocarcinomas can be missed[57-59].

^{18}FDG PET-CT has been found to be accurate in identifying extrahepatic metastasis. Some studies suggest addition of ^{18}FDG PET-CT can lead to change in management in over one-third of patients avoiding unnecessary metastasectomy[60-62], with a significant impact on survival[63]. However, other studies have disputed this and found only a modest 8% change in surgical management with 6% of false positive findings[64,65]. The role of ^{18}FDG PET-CT in addition to standard imaging of CT chest, abdomen and pelvis, and MR liver in presurgical patients remains uncertain. Some authors have proposed it could be used as problem solving modality[66] to identify extrahepatic metastases in high risk patients[48]. Despite its shortcomings, ^{18}FDG PET-CT remains part of our imaging algorithm prior to hepatic metastasectomy.

There is insufficient evidence for the use ^{18}FDG PET-CT on routine surveillance, however, it does have a supplementary role in the context of rising CEA if CT fails to identify the site of disease[67].

Surveillance after resection of CRLM

Given that over half of patients undergoing liver resection for CRLM develop recurrence[68], that approximately half of these are hepatic only[69], and in the light of favourable outcomes after re-hepatectomy (see section 4) for intra hepatic recurrence, there is an intuitive and logical justification for surveillance following resection of CRLM. However, there is considerable heterogeneity in surveillance practice[70], and concerns have been raised regarding the implications of irradiation[71] and health care costs[72].

Defining optimal surveillance requires a knowledge of when recurrence occurs, and how best to detect it. In a retrospective multi-institution cohort study of 2320 patients undergoing initial hepatectomy for CRLMs, Hallet *et al*[73] reported that 89.1% of recurrences developed within 3 years. Recurrence was intrahepatic in 46.2%, extrahepatic in 31.8% and combined intra/extrahepatic in 22%.

Despite this concentration of recurrence in the early years, and many surveillance protocols suggesting follow up for 5 years[69,74], there is consistent evidence of recurrence occurring beyond 5 years in a significant minority of patients. Pulitanò *et al*[75] reported that whilst 93% of recurrences occurred within the first 5 years of follow-up, 11% of patients who were disease-free at 5 years developed later recurrence. Similarly, Tomlinson *et al*[76] found that of patients who were found to be disease free at 5 years, 23% had a documented first recurrence after 5 years, and Viganò *et al*[77] reported that 15% of the patients disease-free at 5 years developed later recurrence.

Heterogeneity applies not only to length of surveillance but also to surveillance type, reflecting the lack of evidence in this area.

However, in a prospective study of 76 patients, Bhattacharjya *et al*[78] reported that the use of CT or tumour markers CEA alone failed to demonstrate early recurrence in 12 and 18 patients respectively, and that the combination of tumour markers and CT detected significantly more recurrence than either modality alone, thus supporting the combination of CT and CEA in the follow-up of patients with resected colorectal liver metastases.

In an attempt to rationalise surveillance in long term survivors, Galjart *et al*[74] produced a stratification risk score based on primary nodal status and disease free interval between primary and CRLM resection to determine surveillance intensity. The authors found that in patients who were disease free after 5 years, recurrence rate beyond 5 years was 3% in the low risk group, but 12% in the high-risk group.

The role of other modalities such as MRI or PET-CT in post-operative surveillance is not defined but is predominantly used to investigate, confirm and characterise recurrence where it is suspected from CT and CEA results.

In conclusion recurrence after resection of CRLM is frequent and occurs mostly in the first 3 years post resection. Nevertheless, up to 23% of patients who are diseased free at 5 years may develop recurrence thereafter, such that protocols ending surveillance at 5 years would miss those patients. Generating good evidence for optimal length, frequency, and type of surveillance is likely to be challenging, and surveillance protocols are likely to be determined by clinician/patient preference as well as health care system resource issues.

SECTION 2: TUMOUR CHARACTERISATION AND BIOMARKERS IN COLORECTAL CANCER

The development of liver resection for CRLM has stimulated attempts to identify prognostic factors to aid in patient selection. Such factors have included primary CRC characteristics (tumour site, TNM stage), CRLM characteristics (size of largest liver metastasis, number of lesions, grade of differentiation, margin status), and other factors such as CEA, presence of additional extra-hepatic disease, and time interval between the emergence of CRC and CRLMs[79-82]. The limitations of individual factors in prognostication prompted their combination to produce risk scores such as the Fong score[83], however even this was found wanting in terms of prognostication[84-86]. It seems likely that the prognostic shortcomings of clinical criteria reflect the fact that they are merely surrogate markers for the underlying molecular biological markers that truly determine tumour biology.

Although a detailed account of current CRC biomarkers is beyond the scope of this review, the following summaries and Figure 1 give an impression of some of the key CRC oncogenic pathways (Figure 1A) and the biomarkers KRAS, NRAS, BRAF, TP53, PIK3CA, APC, and Mismatch Repair Deficiency (MMRD), chosen for their prominence, and also because they inform the rationale for current chemotherapy and biological targeting treatments (Figure 1B).

KRAS

KRAS is a GTP-binding protein and the first member of the KRAS-BRAF-MEK-MAPK pathway which is activated following binding of ligand to Epidermal Growth Factor Receptor (EGFR).

KRAS mutation leads to constitutive activation of the pathway and is one mechanism in EGFR blockade resistance. Once acquired, *KRAS* mutation persists with 96% concordance between primary tumours and metastases[87].

KRAS mutation (predominantly at codon 12[88] and 13[89]) is present in approximately 30% of colorectal cancers, and associated with more aggressive disease and more frequent recurrence after resection of colorectal liver metastases[90], although the poor prognostic effect of mutant *KRAS* may be limited to left sided primary tumours[81].

In terms of its implications for treatment of colorectal liver metastases, it has been reported that mutant *KRAS* is associated with a higher incidence of positive margins[91], with some authors reporting better outcomes in mutant *KRAS* patients whose metastases were resected with wider margins in anatomical (rather than non-anatomical) resections[92]. However, these results have been challenged with the alternative interpretation that the increased recurrence rate in the non-anatomical group may have been related to a higher proportion of radiofrequency ablation (RFA) treated tumours[91]. Thus it may be that the higher recurrence rate seen in mutant *KRAS*

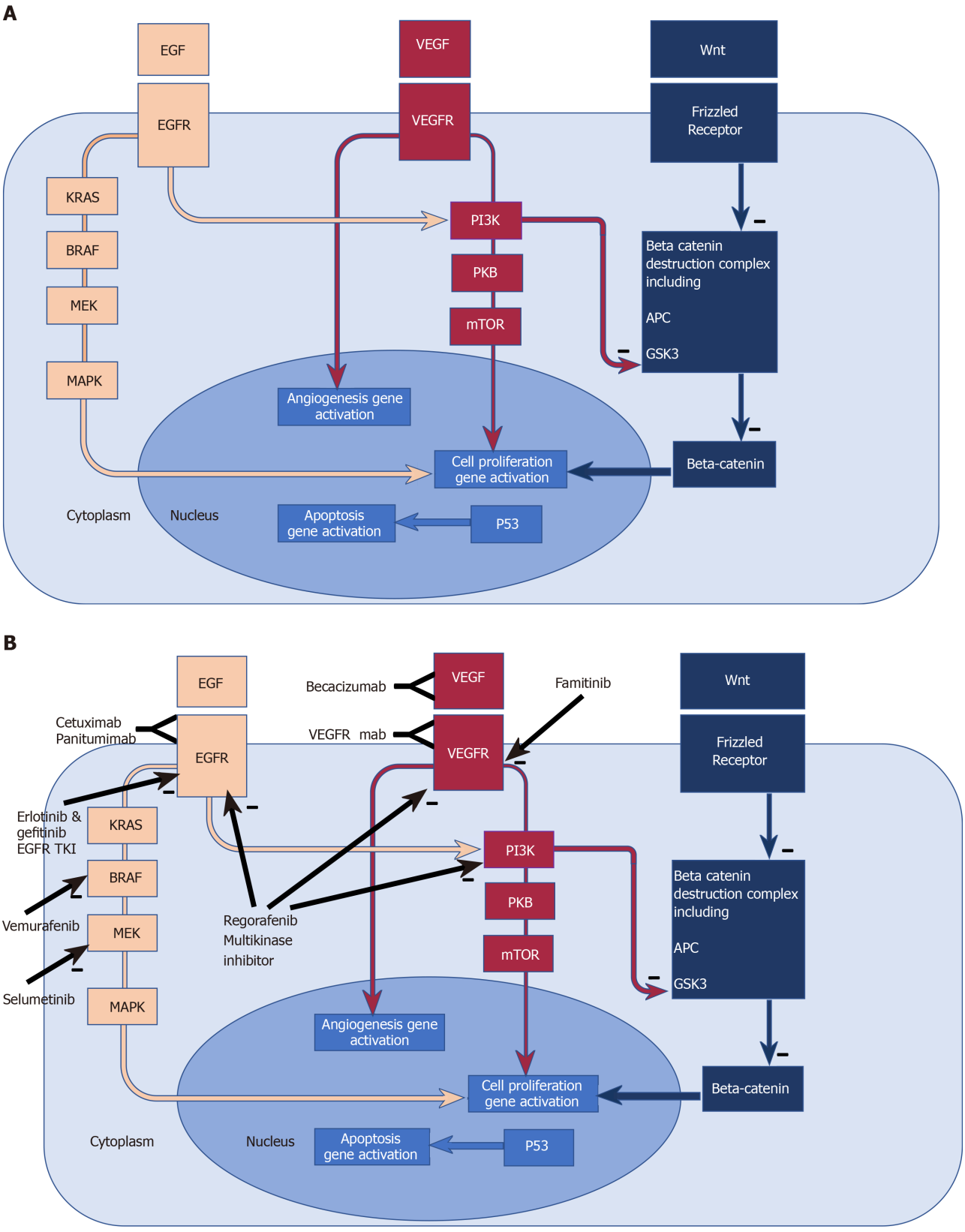

Figure 1 Biomarkers, molecular pathways, existing and emerging therapeutic targets in colorectal cancer. A: Biomarkers and molecular pathways in colorectal cancer. Epidermal Growth Factor Receptor (EGFR) pathway: EGFR is a transmembrane receptor tyrosine kinase[340]. EGF binding to the extracellular domain results in activation of down- stream intracellular signalling pathways such as RAS-RAF-MEK-MAPK, and the PI3K PKB mTOR pathway, amongst others, which favour cell proliferation and survival[341-344]; Angiogenesis pathway: Vascular endothelial growth factors influence angiogenesis in health and disease *via* binding to the vascular endothelial growth factor receptor. Deregulated angiogenesis impacts on progression in solid tumours, thus providing potential anti-angiogenic therapies[345]; Wnt pathway: The *Wnt* genes are vast family of highly conserved genes with wide ranging roles in development, cell proliferation and migration and tumorigenesis[346]. Beta catenin accumulation in the cytoplasm and nucleus leads to cell proliferation. Excess beta catenin accumulation is prevented by

its destruction by the "beta catenin destruction complex" (a multiprotein assembly containing adenomatous polyposis coli and GSK3). Wnt binding to its receptor frizzled leads to impaired function of the Beta catenin destruction complex and hence beta catenin accumulation and cell proliferation[347]. Mutations in adenomatous polyposis coli prevent the formation of the beta catenin complex, and therefore allow beta catenin accumulation and cell proliferation. PI3K inhibits the function of GSK3[112], thereby impairing the beta catenin destruction complex, hence contributing to the tumorigenic accumulation of beta catenin. B: Existing and emerging therapeutic targets in colorectal cancer pathways. B: Cetuximab and Panitumumab are monoclonal antibodies targeting the EGFR, thus blocking activation of downstream signalling pathways. Mutated and constitutively active downstream effectors (such as RAS and RAF) confer resistance to EGFR blockade. Erlotinib and gefitinib are EGFR Tyrosine kinase inhibitors and are associated with improved PFS when combined to Bevacizumab in the DREAM trial[156]. Vemurafenib is a RAF inhibitor which in combination with EGFR blockade[157] has shown marked responses in some case reports[158]. Selumetinib is a MEK kinase inhibitor showing tumour response in some patients with *KRAS* mutant colorectal cancers progressing on Oxaliplatin[159]. Regorafenib inhibits is a multi-kinase inhibitor[153], with OS benefit in randomised double blind control trials[154,155]. Bevacizumab is a Monoclonal antibody against VEGFA with the most prominently established role in the treatment of metastatic colorectal cancer. Famitinib is a multiple tyrosine kinase inhibitor and targets the vascular endothelial growth factor receptor tyrosine kinase. Monoclonal antibodies targeting the VEGF receptors are also under investigation[160]. EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; EGFR TKI: Epidermal Growth Factor Receptor tyrosine kinase inhibitor; K-ras: K-Ras protein (product of the proto-oncogene KRAS); BRAF: BRAF protein (product of the proto-oncogene BRAF; MEK: Mitogen activated protein kinase which activates MAPK (mitogen-activated protein kinase); VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PI3K: phosphoinositide 3-kinase; PKB: Protein kinase B; mTOR: Mammalian target of Rapamycin; Wnt: Wnt protein product of proto-oncogne Wnt; Frizzled Receptor: Receptor for Wnt; APC: Protein product of the tumour suppressor gene APC (Adenomatous polyposis coli); GSK3: Glycogen synthase kinase 3.

patients after resection of colorectal liver metastases is not directly caused by the higher positive margin rate, but that the two are manifestations of underlying aggressive biology[93].

BRAF

BRAF is part of the mitogen-activated protein kinase cascade (MAPK), downstream from KRAS.

BRAF mutation, most commonly at the V600E codon[94], is found in 5%-15% of colorectal cancer patients[94] and is associated with aggressive disease, resistance to EGFR blockade[95], worse overall survival (OS) in patients with non-metastatic primary colorectal cancer[96], and patients with metastatic colorectal cancer treated with palliative chemotherapy[97].

As a result of aggressive and often multisite disease associated with *BRAF* mutation, the incidence of *BRAF* mutation in patients undergoing resection of CRLM is low (2%-4%). Those patients with *BRAF* mutation who do undergo liver resection have a worse overall survival in comparison to patients with wild type BRAF[98]. The most recent and largest case control study[99] suggests this effect is not due to more frequent recurrence, but to the lethal multisite recurrence pattern in those patients in whom disease recurs.

In spite of these findings, in those patients with *BRAF* mutation who do undergo liver resection, long term survival (37% 5 years, and median survival 40 mo) is reported, and compares favourably with systemic chemotherapy[98,99], such that liver resection in these highly selected patients is still deemed indicated, though with appropriate counselling regarding outcome.

TP53 and combination mutations

TP53 is a tumour suppressor gene, the product of which (P53) plays crucial roles in the regulation of the cell cycle, induction of apoptosis, and Deoxyribonucleic acid (DNA) repair[100].

The incidence of *TP53* mutation in patients with CRLM ranges between 40%-60%[101].

Although many studies have associated altered P53 activity with advanced stage[102] and poor survival in primary CRC[103], reports are conflicting in relation to the prognostic significance of mutant in patients undergoing resection of CRLM with Tanaka *et al*[104] identifying it as a predictor of poor survival, in contradiction of other studies[105]. Thus, although mutation undoubtedly has a key role in the early stages of CRC oncogenesis, its part in CRLM specifically is less clear.

The discrepancy in reported studies may also be in part explained by interactions between *P53* and other mutations, as suggested by the poor prognosis associated with the combination of P53 and KRAS[106] in patients undergoing liver resection for CRLM.

Phospoinositide3-kinase catalytic subunit alpha

Phospoinositide3-kinase catalytic subunit alpha (*PIK3CA*) encodes the subunit of phosphoinositide-3 kinase, which controls downstream genes involved in cell proliferation and survival[107]. *PIK3CA* mutations result in loss of apoptosis, increased tumour invasiveness[108], and resistance to EGFR blockade[109].

Mutant *PIK3CA* is reported in 20% of patients with CRLM and associated with

shorter time to relapse following resection[110], and significantly worse OS in patients harbouring the combination of mutation in *PIK3CA* and the Adenomatous Polyposis Coli gene (*APC*)[111]. As further discussed in Figure 1 and in the APC section below, mutant *phosphoinositide-3 kinase* inhibits the function of *glycogen synthase kinase 3*[112], thereby impairing the beta catenin destruction complex, hence contributing to the tumorigenic accumulation of beta catenin.

APC

APC is one component of a protein complex (the beta catenin destruction complex) which degrades beta catenin. Thus *APC* mutations allow the accumulation beta catenin in the cytoplasm and nucleus, resulting in activation of genes promoting cell proliferation and tumorigenesis[113].

APC mutation is reported in 50% of patients with CRLM, and, whilst not prognostic on its own, is associated with significantly worse OS in patients harbouring the combination of mutation in *PIK3CA* and *APC*[111].

This effect may be mediated by the fact that mutant *PIK3CA* inhibits the function of Glycogen synthase kinase 3[112], another component of the beta catenin destruction complex, thereby contributing to the tumorigenic accumulation of beta catenin.

MMRD

The mismatch repair system is a group of enzymes which repair errors which accumulate during DNA replication. When the proteins of the mismatch repair system do not function correctly, errors or mutations occur in the DNA. As a result, tumours which are mismatch repair deficient have high levels of mutation or are "hypermutated". The most common mismatch repair protein which is altered in colorectal cancer is *MLH1* which may be mutated in the germline (approximately 15% of cases), or absent due to promoter hypermethylation (sporadic, 85% of cases). Other proteins which are frequently affected include MSH2, MSH6 and PSM2. Mismatch repair deficiency in tumours can be assessed using protein immunohistochemistry or by examining microsatellites on DNA using Polymerase chain reaction (microsatellite instability)–these tests are highly concordant[114].

Sporadic mismatch repair deficient tumours are more common in older patients and in the right colon, and in early stage cancers. Hypermutation leads to production of high levels of immune stimulating neoantigens and increased immune infiltrates, which in early stage cancers confers a good prognosis. However, in later stages the positive prognostic effect of mismatch repair deficiency becomes lost by a process of immune editing. Mismatch repair deficient tumours are considered chemo refractory and sporadic mismatch repair deficient cancers are often associated with *BRAF* mutations which confer a further negative prognosis. However, the advent of immune checkpoint blockade with anti-PD-1 and anti-CTLA4 inhibitory antibodies has heralded a new era for the small number of patients with advanced MMRD colon cancers[115,116]. Treatment with novel immunotherapy drugs may lead to long term remission for these patients.

Interestingly, MMRD colon cancer may less commonly metastasise to the liver than non MMRD colon cancer. Many MMR tumours downregulated HLA expression as a mechanism of immune evasion, and HLA negative tumours are less common in liver metastases. This is believed to be due to the presence of natural killer cells in the liver which eliminate cells with an absent "self" phenotype[117].

SECTION 3: SYSTEMIC AND LOCOREGIONAL CHEMOTHERAPY AND TARGETED AGENTS IN COLORECTAL LIVER METASTASES MANAGEMENT

Introduction

The role of chemotherapy in the overall management of colorectal liver metastases is evolving and complex, consistent with the multitude of different but sometimes overlapping contexts in which chemotherapy may be considered.

Although evidence exists to guide management in some scenarios, even then decision making remains nuanced in the face of heterogeneity within randomised trial groups, as well as patient specific factors such as individual chemotherapy tolerance, and risks associated with comorbidities.

Seen from the perspective of maximising the chance of liver resection, as the treatment which offers the best chance of long-term survival, these different contexts

may be classified into three broad categories, although it is acknowledged that these may overlap: (1) Patients with unequivocally unresectable disease; (2) Those with up-front resectable disease; and (3) Those patients between these 2 ends of the spectrum, whose disease is deemed initially unresectable, but with the potential of conversion to resectability by downsizing chemotherapy.

The section below discusses chemotherapeutic options for the three categories above in the scenario of metachronous colorectal liver metastases, with synchronous metastases discussed in a later separate section (see section 4).

Prior to describing options for these broad patient groups, we discuss chemotherapy related hepato-toxicity, as this has a significant influence on decision making.

Chemotherapy related toxicity

Chemotherapy associated hepato-toxicity presents in three main entities: Steatosis, steato-hepatitis, and sinusoidal obstruction syndrome.

Steatosis: Liver changes associated with fat accumulation in hepatocytes are termed "non-alcoholic fatty liver disease". Whilst indolent in most patients, a progressive form of "non-alcoholic fatty liver disease" can lead to steato-hepatitis, and thereafter progress to fibrosis and ultimately cirrhosis[118]. 30%-40% of patients treated with 5-Fluorouracil develop reversible steatosis demonstrated radiologically and histologically[119-121]. Steatosis is associated with increased complications post liver resection, though not increased mortality[122].

Steato-hepatitis: Steato-hepatitis is hypothesised to be the end result of the "two hit theory" where the first insult (steatosis) is compounded a second insult in the form of reactive oxygen species. Irinotecan is the drug predominantly associated with steatohepatitis, with high BMI patients particularly at risk, presumably as result of pre-existing steatosis[122]. In terms of its impact on liver surgery, patients with steatohepatitis have been shown to have not only more frequent post-operative complications, but also significantly increased 90d mortality rate (15% *vs* 2%for patients without steatohepatitis[122].

Chemotherapy-associated hepatic sinusoidal obstruction syndrome: Sinusoidal obstruction syndrome (SOS) was first recognised in the context of bone marrow transplantation and treatments involving combinations of several cytotoxic drugs[123]. In the context of chemotherapy for colorectal liver metastases oxaliplatin is the predominant drug associated with SOS, with 78% of patients receiving oxaliplatin having evidence of sinusoidal injury[124]. SOS is associated with Increased morbidity post liver resection, though not mortality[125].

Chemotherapy duration: As well as the type of agent, there is some evidence that the length of chemotherapy course may impact on perioperative complications. In terms of minimising chemotherapy associated hepato-toxicity, Karoui *et al*[125] found that patient receiving fewer than 6 chemotherapy cycles experienced significantly fewer post liver resection complications than those who had received more than 6 cycles (19% *vs* 54% complication rate) although there was no impact on mortality rates.

In the context of other evidence discussed below, hepatoxicity may influence choice of chemotherapeutic agent, for example with a caution in relation to the reported increased mortality associated with irinotecan in patients with pre-existing steatosis who are potential surgical candidates.

Chemotherapy for patients with unequivocally unresectable disease

The subgroup of patients with liver unresectable metastasis represents a very heterogeneous group, and therefore a careful multidisciplinary evaluation of patient and tumour's characteristics as well as treatment toxicities is crucial in the decision-making process. In this setting, patients may be distinguished into three different subgroups: (1) Patients with good performance status but with tumour burden related symptomatic disease; (2) Patients with good performance status but without symptoms related to tumour burden; and (3) Patients with poor performance status. In the first case, the objective of treatment is the tumour shrinkage with the aim of symptom control, whereas in the second subgroup the objective is disease control with improvement of OS and preservation of quality of life. In the third group, best supportive care represents the most appropriate option because active treatment will not be tolerated.

Although a comprehensive description of systemic treatment options for metastatic disease is beyond the scope of this review, this section provides a summary of the current indications for first-line medical treatment in metastatic CRC.

According to international guidelines[126] chemotherapy plus target agents (anti-*EGFR* or anti-vascular endothelial growth factor) provide the best first line treatment for patients with appropriate performance status. In particular, doublet therapy based on fluoropyrimidines (5-FU/capecitabine) and oxaliplatin or irinotecan (FOLFOX/XELOX/FOLFIRI) represents the standard of care in order to improve survival[127-129] More recently, triplet chemotherapy with FOLFOXIRI has been associated with a further 25% increase in median OS, although at the expense of greater toxicity[130,131]. As trials show no difference in the outcomes when using oxaliplatin or irinotecan-based doublets, the choice is mainly related to the different safety profile[132]. In addition, biological agents could be added to chemotherapy according to tumour (*RAS* mutational status, sidedness) and patient characteristics.

EGFR blockade: The key evidence in favour of EGFR blockade in the context of colorectal liver metastases comes from randomised trials demonstrating improved OS and progression free survival (PFS) in patients treated with EGFR blockade added to conventional chemotherapy compared with chemotherapy alone. Summarising this evidence, a meta-analysis of randomised trials showed that combining cetuximab or panitumumab to oxaliplatin or irinotecan regimens increased response rates in patients with initially inoperable CLM[133]. In terms of the relative efficacy of oxaliplatin *vs* irinotecan based regimens in combination with EGFR blockade, the CELIM study comparing the efficacy of FOLFOX + cetuximab to FOLFIRI + cetuximab, showed no significant difference in efficacy between the 2 regimens[134]. In a trial comparing triplet chemotherapy (FOLFOXIRI) + panitumumab to FOLFOXIRI alone, EGFR blockade was associated with improved response rates though no difference in PFS or OS[135].

In terms of the efficacy of EGFR blockade alone, Cetuximab alone was found to be less effective alone than in combination with Irinotecan in the BOND study[136].

In terms of patient selection for EGFR based therapy, CRC harbouring mutations in *KRAS*[137] and *NRAS*[138] genes which result in constitutive activation of the downstream signalling cascade have been demonstrated to be insensitive to treatment with anti-EGFR blockade. Furthermore, some RAS wild type CRC may also prove insensitive to EGFR blockade, possibly due to the presence of other mutations in downstream genes, including that of *BRAF*, present in 9% of CRC, and associated with poor prognosis[139], or amplification of receptor tyrosine kinase genes[140] or mutations in the EGF receptor itself[141]. In addition, there is growing evidence that primary tumour sidedness may also affect response to EGFR blockade, with right sided tumours failing to benefit, even when RAS wild type, as discussed further below[142].

Anti-angiogenic agents: Bevacizumab is the only anti- vascular endothelial cell growth factor agent approved in first line setting for metastatic CRC. Several trials have demonstrated that bevacizumab improves overall response rate, PFS and OS when added to irinotecan based regimens and PFS when added to oxaliplatin based regimens[143,144] regardless of RAS status. Furthermore, a meta-analysis of 6 randomized clinical trials assessing bevacizumab in patients with metastatic CRC reported improved PFS and OS[145]. In terms of combining bevacizumab with triplet chemotherapy, the phase II OLIVIA trial studied the addition of bevacizumab to FOLFOX or FOLFOXIRI in patients with initially unresectable liver and demonstrated improved PFS, overall response rate and R0 rates in the FOLFOXIRI + bevacizumab group[146], with confirmation of these results in the phase III TRIBE trial[147].

Factors influencing choice of targeted therapy: In considering the choice between EGFR blockade and antiangiogenic agents in combination with chemotherapy in RAS WT patients, evidence is somewhat conflicting.

Whilst the FIRE 3 trial[148] (comparing FOLFIRI plus cetuximab *vs* FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer), and the PEAK trial[149] (comparing FOLFOX plus panitumumab *vs* FOLFOX plus bevacizumab) both reported improved OS in the EGFR blockade group, the CALGB 80405 trial showed no difference in OS between EGFR blockade and anti-angiogenic agents[150].

Combination of EGFR blockade with anti- angiogenic agents was examined in the PACCE trial which suggested prohibitive increased toxicity[151], and although this was not confirmed in the combination CAIRO 2 study[152], concerns regarding toxicity have led to an avoidance of the combination of EGFR blockade with anti-angiogenics.

The choice of which targeted therapy is best added to conventional chemotherapy may also be influenced by the sidedness of the primary tumour. It is increasingly recognised that right and left sided colon cancers have different biological and clinical behaviours which impact on their response to systemic treatment. In a systematic review of 6 randomised trials examining treatment regimens for RAS wild type colon

cancer, Arnold *et al*[142] found that right sided tumours had worse prognosis, that EGFR blockade benefit was restricted to left sided tumours, that there may be possible adverse effect of EGFR blockade to right sided tumours, and that right sided tumours may benefit more from anti-angiogenic therapies, thus giving rise to the consideration of triplet therapy combined with *bevacizumab* for right sided tumours.

Novel agents: Novel agents targeting other aspects of known oncogenic pathways (Figure 1B) are also in varying stages of assessment. These include multi-kinase inhibitors, agents targeting other steps in the EGF receptor signalling pathway, antiangiogenic agents, and immune checkpoint inhibitors.

Multi-kinase inhibitors such as regorafenib inhibits a wide range kinases impacting on several oncogenic pathways[153], and has shown OS benefit in randomised double blind control trials[154,155].

EGFR pathway blockade using EGFR tyrosine kinase inhibition by agents such as erlotinib or gefitinib has been associated improved PFS when combined to bevacizumab in the DREAM trial[156].

The *BRAF* mutation, present in 10% of colorectal cancers, and associated with aggressive disease and poor prognosis has been targeted by the agent *vemurafenib* in combination with EGFR blockade[157] with marked responses in some case reports[158].

MEK kinase has been targeted by the inhibitor selumetinib with tumour response shown in some patients with *KRAS* mutant colorectal cancers progressing on oxaliplatin[159].

The potential for exploiting anti-angiogenic pathway is also under investigation with other agents such as famitinib which inhibits multiple receptor tyrosine kinases, and monoclonal antibodies targeting the VEGF receptors[160].

Pembrolizumab is an immune checkpoint inhibitor which impacts on cytotoxic immune responses. In a phase 2 study mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab[115].

Chemotherapy for patients with up-front resectable disease

In patients with up-front resectable colorectal liver metastases, the role of chemotherapy has been investigated in both neoadjuvant and adjuvant roles.

Neoadjuvant chemotherapy: In the context of initially resectable liver metastases, neoadjuvant chemotherapy may have theoretical advantages or objectives such as assessing chemo-responsiveness to inform future treatment strategy, provide tumour shrinkage to increase chance of R0 resection, and to eliminate undetectable micro-metastases. Weighed against these potential advantages are the disadvantages of chemotoxicity, and hepatoxicity in particular. In the midst of these conflicting principles, 2 randomised trials provide evidence.

The first, the EORTC 40983 trial[161], which compared liver resection alone to FOLFOX (6 cycles preop) - liver resection - FOLFOX (6 cycles post op). At 3 years the study showed a significantly better 8% higher PFS in the peri-operative chemo group, but no difference in OS, and significantly more complications in the chemotherapy group (25% *vs* 16%). Moreover, the long term outcome[162] showed no OS benefit in the chemotherapy group. The absence of OS benefit has been attributed to the fact that with a sample size of 364, the trial was powered to detect a PFS, but insufficiently powered for OS. In comparison, trials such as the MOSAIC trial[163] included a relatively large sample size of 2246, and was able to detect a 4.2% OS benefit at 6 years of follow-up for patients treated with FOLFOX over those treated with Leucovorin 5-FU after resected stage III colon cancer.

Thus, despite improved PFS in the peri-operative chemo group, the absence of OS survival and the increased complication rate has not led to peri-operative chemotherapy being used routinely in patients with initially resectable liver metastases. Moreover, in a meta-analysis of 18 studies, neo-adjuvant chemotherapy in resectable colorectal liver metastases was not associated with a survival benefit[164].

The evidence for targeted therapies in the perioperative context is, if anything, weaker. Primrose *et al*[165] compared 2 perioperative systemic regimens (FOLFOX – surgery - FOLFOX *vs* cetuximab + FOLFOX – surgery – cetuximab + FOLFOX) in patients with initially resectable colorectal liver metastases, and found a significantly inferior disease free survival (DFS) in the cetuximab group (20.1 *vs* 14.5 mo). Although some confounding factors have been suggested (possible different baseline characteristics between groups, 11% missing outcome data, and more ablations and more positive margins in cetuximab group), these findings argue against EGFR blockade in patients with upfront resectable liver metastases.

Peri-operative or neoadjuvant bevacizumab in upfront resectable disease has not

been investigated.

In practice the use of neoadjuvant chemotherapy in the context of upfront resectable CRLM is influenced not only by the evidence above, but also by nuances in individual case presentations which blur the boundaries of what is meant by "upfront resectable". Adam *et al*[166] allude to the concept of patients who may be "technically "resectable, but in whom a poor oncological outcome is suspected. A hypothetical example is shown in Figure 2. Both patient A (with a single superficial CRLM) and patient B (with 10 superficial CRLM) are "technically" resectable, but there would likely be consensus amongst MDTs that whilst patient A would best be recommended for upfront liver resection, patient B would best be served by neoadjuvant chemotherapy in the first instance.

In the context of better defining patients who are technically resectable but may have a poor oncological outcome, Fong *et al*[83] developed a preoperative oncological score including five factors: Node-positive disease, disease-free interval from primary to metastases < 12 mo, > 1 hepatic lesion, > 5 cm in the highest hepatic lesion diameter and carcinoembryonic antigen level > 200 ng/mL. Patients with ≤ 2 criteria showed a better outcome, while chemotherapy might be considered in case of patients with ≥ 3 criteria.

This highlights the heterogeneity of "upfront resectable" patients, and MDTs may take additional factors than those included in the Fong score into account in decision making, resulting in a "case by case" approach.

Adjuvant chemotherapy: There is no level I evidence for the use of adjuvant therapy in patients with resected colorectal liver metastases, However, meta-analysis of available trials suggests that there may be a benefit to this approach[167]. Included in this meta-analysis are the report from Portier *et al*[168] who compared Surgery alone *vs* surgery with followed by 6 mo of systemic adjuvant fluorouracil and folinic acid, and demonstrated an improved DFS at 5 years of 33.5% for patients in the chemotherapy group *vs* 26.7% for patients in the control group, though no OS survival benefit.

Kim *et al*[169] compared the outcome of 3 different adjuvant chemotherapy regimens (oxaliplatin/ fluoropyrimidine (group I), irinotecan/fluoropyrimidine (group II) and fluoropyrimidine alone (group III). Median DFS was 23.4 mo in group I and significantly better than the combined other groups, 14.1 mo in group II and 16.3 mo in group III (P = 0.03).

The EORTC 40983 trial[161] also provides some evidence of chemotherapy benefit in PFS, although it is difficult to establish whether this was attributable to adjuvant chemotherapy, as the trial group also received neo-adjuvant treatment.

Thus, in the context of adjuvant chemotherapy for resected colorectal liver metastases there is some, though limited, evidence for improved DFS with certain agents. As a theoretical consideration, adjuvant treatment allows chemotherapy delivery and avoids the increased liver surgery complications associated with neo-adjuvant chemotherapy.

Conversion and down-sizing chemotherapy for patients with initially unresectable disease

The results of downsizing chemotherapy for initially unresectable colorectal liver metastases are well established. In a systematic review including 10 studies of downsizing systemic chemotherapy and rescue liver surgery for initially unresectable CLM, Lam *et al*[170] reported objective response rate of 64% (range, 43%–79%) of patients after systemic chemo-therapy, with 22.5% of patients converted to a resectable status and macroscopically curative liver resection overall. For those resected patients, median overall survival was 45 (range, 36–60 mo) mo with 19% of patients alive and recurrence-free, thus comparing favourably to chemo alone, and to outcomes for patients undergoing up-front resectable liver metastases.

Downsizing regimens based on oxaliplatin[171] and irinotecan[172] have achieve similar response rates in the range of 50% and rates of liver metastases resection of 33%-40%. Moreover, in a randomised controlled trial comparing FOLFIRI and FOLFOX, the two regimens had identical response rates (55%) and similar levels of clear margin (R0) resections[173]. The triplet combination of folinic acid 5FU, oxaliplatin and irinotecan has also been studied, and in randomised trials comparing FOLFOXIRI to FOLIFIRI[130] and FOLFIRINOX to FOLFOX or FOLFIRI[174], the triplet combination was associated with improved response rates, progression free survival, overall survival, and increased resection rates, but at the expense of greater toxicity.

EGFR blockade in downsizing setting: Given the evidence demonstrating the benefit of adding EGFR blockade to conventional chemotherapy in the setting of

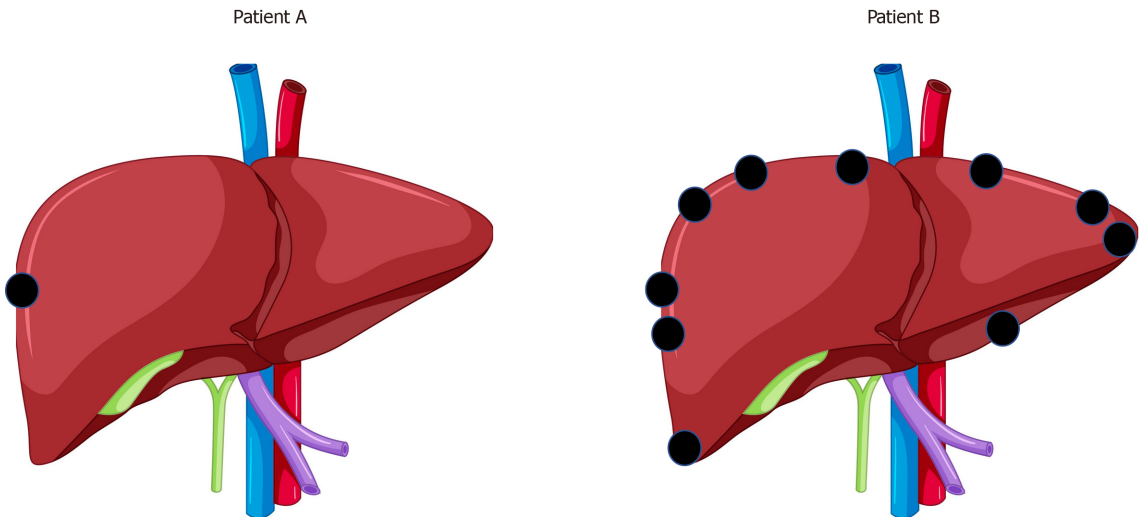

Figure 2 A hypothetical example is shown. A: Patient A (with a single superficial colorectal liver metastases); B: Patient B (with 10 superficial colorectal liver metastases).

unequivocally unresectable colorectal liver metastases[133], the potential for such combination to maximise conversion of initially unresectable liver metastases has also been explored. Thus addition of EGFR blockade to systemic chemotherapy in RAS wild type patients was associated with improved conversion to resectability and R0 rates[175], in comparison to systemic chemotherapy alone. Furthermore, in the CELIM trial comparing cetuximab with either FOLFOX or FOLFIRI, both regimens demonstrated similar high response rates and increased resectability rates[134].

The impact of adding EGFR blockade to triplet chemotherapy has also been studied in The VOLFI trial comparing FOLFOXIRI with panitumumab *vs* FOLFOXFIRI alone, showing improved response rates and resection rates in the panitumumab group[135].

Antiangiogenic therapy in downsizing: Anti-angiogenic therapies have also been studied in the downsizing context. Wong *et al*[176] reported a 40% conversion to operability with XELOX and bevacizumab. Similarly, increased resection rates, R0 rates and PFS were associated with addition of Bevacizumab to triplet chemotherapy in the OLIVIA trial[146].

As discussed in the section relating to inoperable colorectal live metastases, the choice of addition of EGFR blockade or antiangiogenic therapy is a complex one, and is influenced not only by RAS status, but also by primary tumour sidedness[142].

In conclusion, an improvement in OS is clearly demonstrated for patients converted to R0 surgery by use of conversion chemotherapy. Radiological response should be evaluated 2-3 moly by RECIST criteria, taking into account the radiological pattern of response to antiangiogenic agents. Timing of surgery is critical in order to avoid overtreatment of lesions which may disappear and to avoid liver toxicity. The benefit derived from adjuvant treatment (chemotherapy alone or in association with target agents) in patients that received complete resection of liver metastasis after conversion therapy is still unclear.

Locoregional intra-arterial therapies

In addition to the systemic agents described above, the option of locoregional chemotherapy, delivered intra-arterially by a variety of means also exists. The following section describes current knowledge of hepatic arterial infusion (HAI) chemotherapy, and trans arterial delivery of irinotecan coated beads (DEBIRI).

Hepatic arterial infusion chemotherapy: The underlying biological rationale for considering hepatic arterial infusion chemotherapy is based on the fact that the blood supply to colorectal liver metastases is predominantly arterial, and that such infusion provides favourable pharmacodynamics allowing high intrahepatic and low systemic concentrations of drugs[177]. The potential role of hepatic arterial chemotherapy, *via* surgically or percutaneously placed catheters[178], has been studied in varying contexts, including patients with unresectable colorectal liver metastases, but also in downsizing and adjuvant scenarios.

In the unresectable CRLM context, although initial reports from randomised trials of

HAI[179] suggested survival benefit , the modest increase in survival was not widely been felt to justify the quality of life cost brought about by the considerable toxicity associated with Floxouridine. However, further studies with newer agents including Oxaliplatin HAI, 5FU/leucovorin intravenously (IV)[180], Oxaliplatin + Irinotecan + 5FU HAI + cetuximab IV[181] in first or second line settings reported median overall survival of 25 to 27 mo, with conversion to operability in 29% and 37% survival at 4 years for those who underwent resection. Thus, although the place of HAI remains uncertain in the first line setting, these results could form the justification for a randomised trial of HAI *vs* conventional systemic chemotherapy in second line treatment.

In the adjuvant setting one non randomised report[182] studying 2368 consecutive patients after complete resection of CLM suggest a potential significant benefit in OS for patients receiving HAI with significantly improved median OS 67 mo *vs* 47 mo without HAI (P = 0.001) and 10-year survival (38.0% *vs* 23.8% without HAI). In terms of randomised data, although one randomized trial demonstrated increased disease-free survival with systemic chemotherapy (5-FU) plus HAI compared to systemic chemotherapy alone (37.4 *vs* 17.2 mo, $P < 0.01$)[183] , a meta-analysis did not demonstrate an improved OS[184].

In summary, HAI has progressed a great deal since the early reports associated with prohibitive toxicity, and with improvements in catheter placement options. Non-randomised results suggest a potential benefit, although this needs confirmation in carefully designed trials, some of which are in progress[177,185].

DEBIRI: DEBIRI consists of trans arterial delivery of irinotecan coated beads, theoretically allowing slow drug delivery for prolonged antineoplastic effect.

The mechanism of action of DEBIRI[186] presents a paradox in that intra-arterial delivery implies a regional effect of the drug, although irinotecan is a prodrug that requires activation in healthy liver parenchyma to its active Topo-isomerase 1 inhibiting metabolite. Animal models suggest that although much lower overall doses are given in DEBIRI, drug levels at 24 h are higher in tumour and lower in serum than with either intra-arterial or intravenous administration. Further animal model studies suggest that beads cause ischaemic embolization in the predominantly arterial vascularity of tumours. Although beads alone have little tumour burden reducing effect, there is a dose response to DEBIRI beads suggesting that ischaemia and the drug act in concert. This is perhaps as a result of ischaemia induced acid pH, at which the active form of irinotecan is much more effective, and thus perhaps explaining its sparing of neighbouring liver parenchyma where ischaemia is less marked owing to the predominant portal circulation.

The clinical experience of DEBIRI was reviewed by Akinwande *et al*[187] in a systematic review including 11 single arm retrospective and prospective phase studies and two prospective randomized control trials involving 850 patients. Overall toxicity rates were reported at 35% with 10% high grade toxicity, and 2 possible treatment related deaths (0.2%). Overall response rate was 56%, in spite of the fact that patients referred for DEBIRI typically had undergone at least 2 prior lines of chemotherapy. Progression free survival and overall survival was 8.1 mo and 16.8 mo, respectively, comparing favourably with comparable cohorts.

Two randomised trials have examined DEBIRI *vs* conventional chemotherapy. Martin *et al*[188] compared FOLFOX and bevacizumab to FOLFOX, bevacizumab + DEBIRI (FOLFOX - DEBIRI), and found that the DEBIRI patients had significantly better overall response, and improved median progression-free survival (15.3 mo *vs* 7.6 mo). Fiorentini *et al*[189] compared DEBIRI with systemic FOLFIRI, and found that the DEBIRI group had significantly improved OS (OS median 22 and 15 mo respectively, P = 0.031), PFS [median 7 *vs* 4 mo (P = 0.006)], although the study was criticized for the absence of *Cetuximab* in the FOLFIRI arm.

In summary, DEBIRI has been shown to be safe in the treatment of colorectal liver metastases and to have promising response rates in the setting of patients who have been exposed to multiple prior lines of chemotherapy, with some early randomised evidence of favourable results in comparison to systemic chemotherapy. Its ideal role, in terms of patient group and optimal context, remains to be determined by future trials.

Radiation based therapies for unresectable CRLM

In addition to chemotherapy in all its forms, unresectable CRLM may be treated by radiation either by selective internal radiotherapy (SIRT) or stereotactic body radiotherapy (SBRT).

Selective internal radiation therapy: The blood supply of metastatic liver tumours is

predominantly arterial, in contrast to that of hepatocytes which is mostly portal venous[190,191]. This, together with significant arterial neovascularisation in the tumour bed[192], provides the physiological underpinning of SIRT, which achieves tumour destruction by delivery of radioactive microspheres *via* its arterial supply. Ytrium-90, which undergoes beta decay, is the most commonly used radionuclide used to label microspheres, on account of favourable penetration characteristics: Mean and maximal penetration are 2.5 and 10 mm respectively, thus delivering maximal irradiation to the tumour whilst sparing surrounding parenchyma[193]. Currently glass and resin-based versions of the sphere are commercially available. A newer sphere which employs Holmium-166 rather than Ytrium-90 is also available and being evaluated[194].

In the context of colorectal liver metastases, interest in SIRT originated from studies done in patients with unresectable liver or liver dominant metastases who had proved refractory to conventional chemotherapy. These studies suggested response to SIRT in the face of prior chemo refractory status[195,196], and in some reports, significantly improved OS in patients who responded to SIRT[197-199].

On the basis of the above and other studies, 3 randomised prospective trials[200-202] were carried out to investigate the potential role of SIRT by comparing FOLFOX + SIRT *vs* FOLFOX alone as first-line treatment for mCRC with liver-only or liver-predominant metastases. The combined results of the 3 trials were reported by Wasan *et al*[203]. The overall findings were that there was no OS survival benefit to the addition of SIRT to FOLFOX, but that progression within the liver within the first 12 mo of follow-up was significantly lower in the SIRT group.

It was concluded that given the absence of OS survival, SIRT could not be recommended as first line treatment for mCRC with liver-only or liver-predominant metastases, but that its role in other contexts required investigation. In this perspective Gibbs *et al*[204] reviewed the outcomes of the FOXFIRE trials with respect to primary tumour sidedness and found that the median OS for patients with right-sided primaries was significantly higher for patients in the SIRT arm compared to the control group, and that left sided primary tumour patients did not benefit from SIRT.

In summary, the current role of SIRT is evolving and will doubtless be further refined as the results of new trials become available. In the United Kingdom, based on a review of current evidence[205], SIRT is commissioned for use in patients with unresectable or ablatable colorectal liver metastases who have progressed or are refractory to both oxaliplatin-based and irinotecan-based chemotherapy, with five or fewer liver tumours, a percentage tumour to liver volume of ≤ 25%, and World Health Organisation (WHO) performance status 0-1[206].

Stereotactic body radiation therapy for colorectal liver metastases: The results of studies suggesting benefit to local ablative therapies such as RFA[207] in the treatment of colorectal liver metastases has prompted investigation of whether similar benefits could be achieved by radiotherapy. Stereotactic body radiation therapy offers an alternative approach to the treatment of liver metastasis by precise targeted delivery of radiation. The potential benefits would be the use of a non-invasive technique, without need for general anaesthetic, and perhaps an opportunity of overcoming the limitations of ablation such as tumour size restriction, and problems such as heat sink effects in tumours situated near vascular structures.

In a systematic review, Petrelli *et al*[208] analysed the results of a total of 18 studies, encompassing 656 patients, with colorectal liver metastases, numbering 1–2 lesions in most cases, with a size range of 0.7-11.6 cm in size, the majority having received systemic chemotherapy, with a median follow up of two years.

The pooled one and two-year OS were 67.18% and 56.5% respectively, and median PFS and OS were 11.5 and 31.5 mo. The pooled one-year and two-year local control was 67% and 59.3%. In terms of liver related toxicity, pooled grade 1–2 and grade 3–4 liver toxicity[209] were 30.7% and 8.7%, with mild nausea and fatigue reported as other toxicities. There were 4 cases of liver failure (0.6%), and three treatment related deaths (0.004%).

The optimal irradiation dose is likely to be multifactor dependant, but reports suggest improved local control rates after increasing biological equivalent dose, with local control rates of 90% in patients exposed to higher biologically effective dose[210,211], with dose response relation confirmed in a pooled analysis[212]. In terms of lesion size limits, although early reports correlate large tumour size (> 3 cm) with poorer rates of local control[213], more recent studies report local control in tumours 3-6 cm as equivalent to that achieved with tumours less than 3 cm by use of higher irradiation doses[214].

The interpretation of data relating to the effectiveness of SBRT in the treatment of

colorectal liver metastases is difficult for a number of reasons: Firstly the studies are subject to case selection bias, and markedly heterogeneous in terms of population and techniques: The study populations vary in age and performance status, number and size of metastases, median follow-up, subsequent chemotherapy delivery, SBRT techniques, and fractionation. Secondly, the absence of randomised trials makes it difficult to assess the hypothesised additional benefit that SBRT may bring to optimal chemotherapy and existing ablation methods.

In this regard, there is a difficult problem with recruitment to such trials, with 2 examples of such studies (the French OLIVER trial (NCT03296839) investigating chemotherapy +/- SBRT[215], and the Dutch RAS01 trial (NCT01233544)[216] comparing systemic chemo + RFA or SBRT) both closed with insufficient recruitment. Undoubtedly part of the problem with recruitment in such areas is the fact that both patients and clinicians may not perceive equipoise. Furthermore, different techniques are often complementary rather than in competition, such that their indication for use may be subtly but importantly different. For example, a tumour adjacent to a large vein may not be appropriate for ablation because of heat sink effect, but potentially a good indication for SBRT.

In summary, the results of SBRT in terms of local control and overall survival are hard to ignore, especially as they are achieved in the context of patients who have exhausted other treatment options. Although formal comparisons with other treatments will be difficult to carry out, ongoing studies to define SBRT technique such as irradiation dose and fractionation will likely deliver ongoing improvements in outcomes and help to define the niche for SBRT in the armamentarium for treatment of colorectal liver metastases.

SECTION 4: SURGICAL MANAGEMENT OF RESECTABLE COLORECTAL LIVER METASTASES

Introduction

The success of liver resection for CRLM in achieving long term survival has driven the investigation of numerous techniques to increase resection rates. In defining 'resectability', there is distinction to be made between what is technically feasible, and what is oncologically sensible. In this regard, clinical, biochemical and histopathological factors[79-82] and risk scores such as the Fong score[24] (see section 2) have provided some direction in decision making. From the sole perspective of technicality however, CRLM may be thought of as resectable provided that clear margins are achieved, and that the Future Liver Remnant (FLR) is of sufficient size, with adequate arterial supply, portal venous supply, hepatic venous drainage, and biliary outflow. The techniques used to increase resectability include downsizing chemotherapy (discussed in section 3), portal vein embolization (PVE), Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS), and the use of ablation technology. Surgery may be carried out laparoscopically or open, and in selected patients prior to or synchronously with resection of the primary CRC. These considerations are discussed in more detail in this section.

Liver resection for CRLM: General considerations

Biopsy of CRLM: Biopsy of suspected CRLM should be avoided. The problem of needle track seeding with malignant cells following biopsy of malignant liver lesions is well documented in the context of HCC[217]. In terms of this risk in biopsy of CRLM, Rodgers *et al*[218] reported that out of 43 patients who had undergone CRLM biopsy, 7 (16%) developed needle track seeding[218]. In a similar study Ohlson *et al*[219] reported a needle track seeding rate in 5 (10%) of 51 biopsied patients. Jones *et al*[220] reported a 19% rate of needle track seeding and found that following resection of CRLM, biopsied patients had a significantly lower 4 year survival, with biopsy being identified as an independent predictor of poor survival in regression analysis. These findings, taken together with the low percentage (< 2%) of benign lesions resected unnecessarily following incorrect radiological diagnosis of a CRLM argue strongly against pre-operative biopsy of CRLM[221].

Anatomical *vs* non-anatomical resections: In a systematic review of 2505 patients included in 12 studies, Moris *et al*[222] found that there was no difference between anatomical and non-anatomical (parenchymal sparing) hepatectomy in terms of peri-operative and long term oncological criteria, thus arguing in favour of a parenchymal sparing approach whenever appropriate.

Resection margins: There is consensus that positive margins after resection of CRLM remains a negative prognostic factor[223] . Although historical practice suggested a liver resection margin of 1cm in resection of CRLM, a Propensity Score Case-Match study from Hamady *et al*[224] showed that 1 mm cancer-free resection margin achieved 33% 5-year overall disease-free survival, and that additional margin width did not add disease-free survival advantage. Moreover, De Haas *et al*[225] reported that although patients with involved (R1) margins experienced more recurrences, the contraindication of R1 resection should be revisited in the current era of effective chemotherapy because survival was similar, in their study, to that of R0 resection. Thus, although R0 resection is doubtless preferable, the necessity of R1 resection for lesions near structures that cannot be sacrificed, or for preservation of liver parenchyma, may be accepted in selected patients.

Extra-hepatic disease: Whilst a full review of resection of extra-hepatic disease is beyond the scope of this review, there is consensus in favour of proceeding with liver resection of CRLM in particular scenarios[226,227].

Positive retroperitoneal or coeliac lymphadenopathy is still an absolute contraindication to liver resection, but hepatectomy may be carried out in selected patients with hepato-duodenal ligament lymphadenopathy, albeit with less good 5 year survival than for patients without hilar lymphadenopathy[228].

Although studies relating to resection of pulmonary resection should be interpreted with caution, because of significant patient selection bias, a Liver Met Survey registry study reported that selected patients who had resection of liver and lung metastases had similar overall survival to those who had undergone removal of isolated liver metastases[229].

In terms of peritoneal disease, current studies suggest that in selected patients, cytoreductive surgery in combination with chemotherapy is associated with better survival than with chemotherapy alone, but there is controversy regarding the benefit of hyperthermic intraperitoneal chemotherapy over systemic chemotherapy[230].

Laparoscopic and robotic liver resection: Laparoscopic liver surgery has increased rapidly over the last decade with reports of minor and major liver resections[231,232], ALPPS[233] and both paediatric[234] and adult[235] live donor liver donation.

The international consensus conference on laparoscopic liver resection[236] established a range of recommendations and guidelines with an imperative that the innovators in this field deliver high quality evidence to validate its introduction into standard practice, and randomised clinical trials comparing laparoscopic and open liver resection followed as a result[237,238]. The ORANGE II trial[239] closed prematurely after failing to recruit. The OSLO COMET trial[237] compared laparoscopic with open parenchymal sparing liver resection for minor liver resections in 280 patients. The trial demonstrated a significant reduction in 30 d complications with the laparoscopic approach and a shorter hospital stay of 3 compared to 4 d. There was no difference in resection margin status or overall survival between groups. The significantly increased initial operative costs of the laparoscopic approach were offset by the shorter stays in recovery and hospital stay resulting in no overall difference between the two groups.

Thus the evidence from OSLO COMET trial, case series and cohort studies suggest that laparoscopic liver surgery is not inferior to open liver resection in terms of operative mortality, margin negativity and overall survival for both minor and major resections. Furthermore, there may be benefits in terms of reduced length of stay, reduced post-operative pain, and a reduction in the need for blood transfusion. At this time there remains a significant heterogeneity in adoption of not only laparoscopic but also robotic[239] liver surgery and it is appropriate that these evolving techniques should be performed in high volume centres with expertise in advanced minimally invasive procedures[240].

Liver function and volume assessment

Liver failure after resection has mortality of up to 80%[241], and hence there is much interest in the assessment of liver function, in particular the prediction of function in the future remnant liver (FRL), with a view to maximising safety following liver resection.

Although global clinical liver function assessment systems exist, such as the Childs Pugh score for assessment of liver function in the presence of chronic liver disease, and the MELD score for risk stratification of patients with end-stage liver disease awaiting transplantation, neither the Childs Pugh score[242] or MELD score[243] have proved useful in the context of liver resection in patients without underlying liver disease. Moreover, these scoring systems apply to the whole liver and cannot be used to predict function

of a defined part of the liver such as the FRL.

Modern imaging software allows the accurate calculation of volumes of defined parts of the liver, such that the volume of the FRL may be assessed either as an absolute value or as a fraction of the whole liver. Whilst volume alone may be helpful in patients with completely healthy liver, in which case a minimum FRL of 25% has been advocated, in cases where liver parenchyma is suboptimal volume may not correlate with function[244,245], particularly in patients with steatosis, chemotherapy associated liver injury, or after PVE or ALPS. For those on the limit of threshold, decision making is difficult, and thus the shortcoming of purely volumetric assessments has prompted the investigation of dynamic liver function tests, which are discussed below.

Indocyanine Green: Indocyanine Green (ICG) is a tricarbocyanine dye that binds to albumin and is distributed evenly in the blood within minutes of intravenous injection. ICG is taken up by the liver and is excreted in bile without conjugation[246].

Whilst having some value in predicting post op liver failure an death in the context of HCC resection in cirrhotic patients[247], this was not the case in resection of colorectal liver metastases in chemotherapy affected livers[248]. Moreover, ICG clearance provides a global assessment of liver function and does not offer the possibility of assessing parts of the liver, in particular the future remnant liver left in situ after a resection. Although calculating fractional ICG excretion has been reported[249] this assumes homogenous liver function, and in this regard, Hepato-biliary scintigraphy offers potential opportunities.

Hepatobiliary scintigraphy: Hepato-biliary scintigraphy (HBS) uses a gamma camera detection system in combination with cross-sectional imaging to quantitatively assess hepatic processing of a labelled molecule, both globally and/ or regionally in the liver, thus allowing future remnant liver functional assessment. Two main labelled molecules, Galactosyl human Serum Albumin and iminodiacetic acid (IDA) derivatives have been reported on most widely. (1) Technetium-99 m galactosyl human serum albumin scintigraphy: Galactosyl human Serum Albumin is exclusively taken up in the liver by an active transport mechanism on the sinusoidal surface of hepatocytes, and is thereafter degraded in lysosomes without biliary excretion, thus offering the advantage of not being affected by high bilirubin concentrations. Its use has been developed significantly in Japan where it is reported as a useful technique in the prediction of post liver resection liver failure[250], but little used outside Japan owing to availability; (2) Hepatobiliary scintigraphy using IDA derivatives: Technitium labelled IDA derivatives, of which Mebrofenin is the most effective because of its high hepatic specificity and low competitive displacement by bilirubin, are taken up in the liver and then excreted into bile by active transport mechanisms. Protocols reviewed by Rassam *et al*[251] allow the calculation of hepatic extraction of Tc99 Mebrofenin as a percentage of total dose per minute, adjusted for body surface area. Single-photon emission CT-computed tomography (SPECT-CT) is combined with the extraction data to provide values for total liver or future remnant liver. Early studies determined that pre-operative values calculated for future remnant liver function correlated well with actual future remnant function measured post operative[244], thus suggesting the technique as a valuable pre-operative function assessment of the FLR; (3) Use in predicting post hepatectomy liver failure: Dinant *et al*[245] studied 46 patients with mixed tumour histology requiring liver resection, with and without underlying liver parenchymal disease. Patients with uptake above 2.5%/min/m^2 had a 3% chance of liver failure in comparison to those with uptake below 2.5%/min/m^2 who had a 56% chance of liver failure. Moreover, patients with uptake above 2.2%/min/m^2 had a 3% chance of mortality whilst those with uptake below 2.2%/min/m^2 had a 50% chance of liver failure. The volume of the future remnant was not significantly associated with any of the outcome parameters. Similarly, in a review of 55 high-risk patients undergoing major liver resection, de Graaf *et al*[252] identified patients who developed postoperative liver failure. Thus, patients with values above and below 2.69%/min/m^2 had 2.4% and 57% chance of developing liver failure respectively. Likewise, Chapelle *et al*[253] studied 88 patients undergoing liver resection and found that post op liver failure was strongly associated with FRL- F but not future remnant volume, and that no liver failure mortality was observed in patients with FRL-F of above 2.3%/min/m^2; and (4) Tc 99 Mebrofenin use in post PVE situation and ALPPS: Cieslak *et al*[254] studied 163 patients undergoing liver resection whose need for PVE was based on FRL-F by Tc99Mebrofenin extraction, with a cut off value of 2.7%/min/m^2. The authors noted that 8/29 patients required PVE based on low HBS values in spite of satisfactory volume assessments, thus suggesting

that HBS may have prevented post op liver failure in those patients. Similarly, Chapelle *et al*[255] used a cut off value of 2.3%/min/m^2 as cut off for proceeding to PVE and found a lower incidence of post op liver failure than observed in a historical control group. Cieslak *et al*[256] identified Mebrofenin hepato-biliary scintigraphy parameters which identified non response to PVE at an earlier stage than conventional volume assessment 6 weeks post PVE, thus potentially allowing early selection of patients who may require ALPS. A significant concern with ALPS is the incidence of post op liver failure after the second stage, raising the impression that liver volume does not correlate well with function in the post ALPS setting, perhaps due to functional immaturity of rapidly proliferating hepatocytes. Supporting this notion, in the second stage of ALPS, Olthof *et al*[257] found that liver volume growth was out of proportion with the increase in function as assessed by HBS, and suggest the use of HBS FLR assessment in this setting rather than just volume. In conclusion, in the context of liver resection for colorectal liver metastases, assessment of the FLR is crucially important to avoid PHLF. Increasing evidence supports the role of hepato-biliary scintigraphy, as a technique which offer a specific functional assessment applicable to defined regions of the liver. Further confirmation and definition of the potential should be forthcoming with the results of a large multicentre prospective trial[258].

Downsizing chemotherapy for conversion of initially inoperable CRLM

The role of downsizing chemotherapy for initially unresectable colorectal liver metastases (discussed in more detail in section 3) is well established, with a systematic review by Lam *et al*[170] and others[259] reporting a response rate of 64%, with 22.5% of patients converted to curative liver resection overall.

The paradox of this chemotherapeutic success is the phenomenon of the disappearing metastasis, which presents a problem for the surgical team.

Disappearing metastasis: Radiologically disappearing metastasis reported with frequencies ranging from 6%[260], 24%[261], and up to 37%[262], Perhaps reflecting differences in imaging practice between centres and also different chemotherapy regimens. The percentage of patients in whom all CLM disappear radiologically is low (0%-6%).

Metastasis disappearance is usually a radiological phenomenon rather than a biological one: In a systematic review of 11 studies describing disappearing colorectal live metastases, it was found that in 65% of cases of "disappeared metastasis", a lesion was found at laparotomy. Moreover, of the 35% of lesions not found at laparotomy and therefore not resected, 80% regrew, at site of radiologically disappeared metastasis[263]. Furthermore, there is not a good correlation with complete radiological response and complete pathological response: In Adam *et al*[264] study, complete pathological response was seen in 4% of patients undergoing liver resection for CLM, but none of these had complete radiological response.

Thus in terms of management of the disappearing liver metastasis the guiding principle is that viable tumour is present at the lesion site in the vast majority of cases, and therefore resecting the target lesion remains the objective. This may be achieved by resecting remnant lesions found at laparotomy visually, by palpation or intra-operative ultrasound. For lesions which are undetectable at laparotomy, a "territorial" resection, encompassing the lesion by reference to fixed landmarks, is sometimes possible. The use of 3D augmented reality imaging software may help in this regard in the future[265].

Some groups have investigated the pre-operative marking of CRLM with Fiducia labels. In a study from Kepenekian *et al*[266] 76 metastases were marked of which 23 disappeared with preoperative chemotherapy. Four complications were associated with marking: Two intrahepatic haematomas, one fiducial migration and one misplacement. After a median follow-up of 47.7 mo, no needle-track seeding was noted. Four disappearing CRLM were resected, with two local recurrences, and other missing lesions were treated with thermoablation. Thus Fiducia label placement presents an option in the management of disappearing CRLM, although concerns regarding selection of which CRLM to mark, procedural complications, and needle track seeding persist.

In the absence of the above strategies, close surveillance of the target area is the default. In future, such lesions may be targeted by image guided stereo-tactic ablation of the disappeared metastasis site.

Portal vein embolization

Portal vein embolization has been credited to various authors[267-269], but most notably to Makuuchi *et al*[270] and Kinoshita *et al*[271] both of whom reported the use of pre-operative PVE to induce hypertrophy prior to liver resection in the 1980s, on the background of prior reports of portal ligation as part of two-stage extended hepatectomies[268]. PVE embolization causes atrophy of the ipsilateral liver segments and a compensatory hypertrophy of the FRL. Assessment of the adequacy of hypertrophy of the FRL remains challenging. Functional liver assessment is well established within Japanese centres[269] but morphological changes in liver volume using CT volumetry as an assessment of hypertrophy remains the mainstay of assessment in many units. When performed, function assessment has traditionally been assessed using indocyanine green clearance however, more recently ^{99}Tc-labelled Mebofenin Hepatobiliary scintigraphy and ^{99}Tc-galactosyl-human serum albumin scintigraphy have been introduced as discussed above.

A systematic review of PVE reported a major complication rate resulting in non-resectability of 0.4% and a mortality rate of 0.1% however, complications in the published literature are likely under reported. Moreover, detailed descriptions of reasons for failure to progress to curative liver resection are frequently lacking in published literature. A systematic review of published cohort series reports an overall failure to proceed to curative liver resection following PVE of 18.7%. The majority of these failures to proceed were due to progression of liver disease (14.2%) and failure to induce sufficient hypertrophy of the FRL (2.8%). The mean time between PVE and liver resection was 36.9 d[268].

The borderline resectability of tumours that necessitate PVE to enable curative resection, combined with concerns regarding the effect of the changes to the liver parenchymal metabolism, gene expression and the microenvironment on tumour growth post-PVE have led some authors to examine the use of chemotherapy during the interval between PVE and resection in an effort to control tumour growth. Cohort series have suggested that continuation of chemotherapy during the interval between PVE and resection does not change hypertrophy of the FLR[272-274]. Some cohort studies have examined the different responses of metastatic disease to neoadjuvant chemotherapy and used this to stratify patients into "slow" and "fast" responders[273,275]. A cohort series has demonstrated subsequent discordant tumour behaviour following PVE between these groups with "slow" responders more likely to demonstrate progression of tumour growth with an accompanying increased risk of failing to progress to curative liver resection[273].

PVE remains an important tool in the armamentarium for management of patients with otherwise unresectable colorectal liver metastases where the FLR would otherwise be insufficient following resection. Despite promising reports from cohort studies, the published literature remains incomplete and frequently lacks detailed descriptions of complications or technical or clinical failure. Moreover, in the most recent systematic review colorectal metastasis comprised 39.6% of the patients and this heterogeneity limits translation of findings to clinical practice[268].

Two-staged hepatectomy

The concept of the "two-staged hepatectomy" was introduced by Adam *et al*[276], as a technique that could be applied to approximately 4% of patients with conventionally irresectable metastases to make them eligible for liver resection with curative intent. This approach involved a combination of systemic chemotherapy to downstage tumours, with or without PVE, with subsequent planned staged operations that permitted curative resection of large tumour burden that would otherwise have been considered unresectable. The interval between operations enabled hypertrophy of the remnant liver to theoretically reduce the chance of liver insufficiency and patients would receive chemotherapy during the interval between operations in an effort to control tumour growth. The reported results from this small early cohort demonstrated a similar risk of failure to proceed second stage operation when compared to PVE, of 19% (3/16). 54% (7/13) developed recurrent disease after completion of the second stage and the median survival was 31 mo from the second hepatectomy[276]. In current practice, the term, "two-staged hepatectomy" as reported by Adam *et al*[276] is used less and considered as part of the multimodal approach which has become a mainstay of current practice.

Associating liver partition and portal vein ligation for staged hepatectomy

The development of ALPPS was the result of an unplanned intraoperative decision by Dr Schlitt from Regensburg, Germany. Motivated by a concern for inadequate FLR

during a planned extended right hemihepatectomy, a decision was made to perform a hepaticojejunostomy on to the left hepatic duct. In order to do so, liver parenchyma along the falciform ligament was divided, thus devascularising segment IV, and the right portal vein was ligated with the hope of causing hypertrophy of the remnant segments II and III. Post-operatively, rapid hypertrophy was observed within 8 d and resection of the in situ diseased hemiliver was completed[277].

The combination of portal vein ligation, inflammatory injury and the absence of cross portal circulation due to the parenchymal transection has been proposed as the mechanism for the observed more rapid hypertrophy compared to PVE alone.

Despite the enthusiasm for this novel technique, the first case series reported a 12% mortality and significant morbidity[278]. This was in excess of the mortality and morbidity of standard practice with a PVE and two staged approach. The rapid introduction of ALPPS to surgical practice with limited scientific rigor has been heavily criticised[278], leading to attempts to rationalise its use[278,279]. The LIGRO trial was a randomised control trial comparing ALPPS with two staged hepatectomy with PVE[280]. This demonstrated a significant increase in the primary endpoint of resection rates (92% *vs* 57%) with ALPPS without a significant increase in 30 or 90d mortality between groups. The rate of inadequate hypertrophy in the two stage hepatectomy group was higher in the trial than that reported in cohort series and salvage ALPPS was performed in 24%, however, 90d mortality in both groups remained high (TSH 6.1% *vs* ALPPS 8.3%)[280].

Advocates for ALPPS suggest that the rate of completion of the second stage is higher with ALPPS compared to the more established two stage approach with PVE. However, this is likely at the expense of a higher peri-operative mortality[281]. More recent case series have suggested that with modifications to the original technique such as; prolonging the interval between operations, performing a more limited or laparoscopic parenchymal transection[282], and the use of the ALPPS risk score[283] the peri-operative mortality can be substantially reduced[284].

Opponents highlight that this remains an experimental, unproven technique that carries a mortality considerably in excess of the 1%-2% mortality observed in high volume units for liver resections following PVE[278] and therefore it should be reserved for highly selected cases such as those considered to be high risk of tumour escape with PVE or as a salvage technique where PVE has failed to produce sufficient FLR hypertrophy. The exact role of ALPPS in the surgical armamentarium remains a matter of debate[284].

Ablation techniques for CRLM

The observation of long term survival after resection of colorectal liver metastases, and evidence suggesting that locoregional resection is oncologically equivalent to major anatomical resection[222] has prompted interest in minimally invasive ablative techniques which might achieve similar results to non-anatomical resection with less morbidity. Radiofrequency ablation and microwave ablation (MWA) have been investigated in the context of a variety of liver tumours including colorectal liver metastases.

Radiofrequency ablation: RFA delivers alternating electrical current to cause ionic agitation, with the resulting heat generation causing denaturation and coagulation of the targeted tissue[285].

The benefit of radiofrequency ablation over systemic chemotherapy alone was suggested by the European Organisation for Research and Treatment of Cancer 40004 CLOCC trial (ClinicalTrials. gov, No. NCT00043004) comparing systemic chemotherapy alone to chemotherapy combined with RFA +/- resection for patients with inoperable CRLM, which showed a significantly improved progression-free survival for patients treated with RFA in the initial analysis[286] and at 9.7 years of median follow up[207].

Whilst this randomised trial provides grounds for a genuine benefit of RFA over chemotherapy alone, comparing the effectiveness of RFA to that of liver resection is difficult, since RFA for CRLM is currently often used in situations where liver resection is not deemed appropriate as a result of unfavourable disease factors or patient comorbidities. In this context, the absence of randomised data makes comparisons of RFA to liver resection subject to a major confounder with an adverse bias against RFA.

Meta-analyses have nevertheless assessed the efficacy of RFA in comparison to liver resection.

In their 2012 meta-analysis, Weng *et al*[287] acknowledged the confounding factors above, but reported that liver resection was significantly superior to RFA in 3 and 5

year overall and disease free survival. Postoperative morbidity was higher in liver resection, but no significant difference was found in mortality between liver resection and RFA. In a subsequent meta-analysis, Van Amerongen *et al*[288] reported similar findings. In the most recent systematic review of 18 studies and 2667 patients[289]. Kron *et al*[289] reported that in 8/18 studies liver resection patients had significantly higher overall survival and disease-free survival, as well as lower local recurrence (LR) rates than RFA treated patients.

Based on HCC results where outcomes for lesions less than 5 cm were oncologically equivalent to resection, and achieved with less morbidity[290], it was hypothesised that RFA may have a particular role in the treatment of small colorectal liver metastases. Berber *et al*[291] reported that tumor size (> 3 cm), ablation margin, and proximity to hepatic vessels > 4 mm were found to be independent predictors of LR local recurrence after RFA. Hur *et al*[292] and Ko *et al*[293] reported similar findings and suggested that for colorectal liver metastases < 3 cm, resection and RFA had similar oncological and local recurrence outcome, but that RFA was less morbid.

However, in contrast to these studies, subgroup analysis from the systemic reviews above does not support idea that CLRM < 3 cm allows results equivalent to resection: Weng *et al*[287] showed poorer OS for lesions < 3 cm treated with RFA compared to resection. In Van Amerongen's *et al*[288] study, subgroup analysis looking exclusively at solitary lesions and lesions of less than 3 cm found that in both cases, there was a significantly higher rate of local recurrence in the RFA group (solitary lesions OR = 7.68, P = 0.001 , and lesions < 3 cm, OR = 8.75, P = 0.001). In Kron's *et al*[289] systematic review, 4 studies provided evidence comparing RFA to resection for lesions < 3 cm. Two of the four studies reported worse OS and higher local recurrence for RFA than liver resection[294,295], but the other 2 studies[292,293] found no OS or LR difference between RFA and liver resection.

Thus, the literature provides conflicting results, raising the question of whether other factors within the group of patients with solitary lesions < 3 cm may account for these differing conclusions, including technical and operator factors. In addition, historical case series data may not reflect modifications and technical advancements in tumour ablation such as better lesion targeting due to the advent of navigation systems and appreciation of the importance of ablation zone validation. For example, there is evidence that open RFA has lower recurrence rates than percutaneous RFA[296-299]. In addition, operator learning curve is reported to impact on outcome[298]. Also, operator training may be relevant. In their meta-analysis, Kron *et al*[289] point out that the clinician carrying out the RFA are surgeons and radiologists in 11% and 33% of studies respectively, with no specified practitioner in 56% of studies, raising another potential confounding factor.

In conclusion, there is randomised evidence showing a benefit for RFA over chemotherapy alone. On the subject of RFA *vs* liver resection, none of the available evidence is randomised, and significantly confounded by patient selection, with patients undergoing RFA typically having adverse disease characteristics and other additional non cancer related comorbidities. In this light, the finding of worse survival outcomes for RFA patients is not surprising, but difficult to interpret. In terms of local recurrence rates, the role of RFA in colorectal liver metastases < 3 cm remains controversial, with conflicting reports. Whilst such controversy may be settled by randomised trials, in practice this may prove difficult to achieve. The LAVA trial[300] closed due to insufficient recruitment, perhaps due to the perception of non-equipoise on the part of both clinicians and patients. The COLLISION trial[301] and HELARC trial (Trial ID NCT02886104)[302] are currently in progress.

Microwave ablation: MWA produces tissue destruction as a result of heat generated by electromagnetic waves. The theoretical advantages of MWA are faster and greater heat generation than in RFA, penetration through tissues with low conductivity and less heat sink effect[303] in instances of tumours near blood vessels.

In terms of the efficacy of MWA in comparison to chemotherapy alone, no randomised studies have been carried out.

In considering MWA *vs* liver resection, a small RCT including a total of 30 patients with multiple metastatic colorectal liver metastases, Shibata *et al*[304] randomised patients to liver resection or MWA, and found equivalent results in OS or DFS at 3 years for both treatment modalities.

In terms of comparing of RFA *vs* MWA, Although a metanalysis by Huo *et al*[305] found MW ablation and RF ablation had similar 1 and 5-year overall survival, disease-free survival, local recurrence rate, and adverse events overall for a variety of tumour types including mostly HCC, the studies that related specifically to CLRM suggested a lower local recurrence for MWA. Thus Correa *et al*[306], in a matched cohort analysis

showed patients in the MWA group had lower ablation-site recurrence rates (6% *vs* 20%; $P < 0.01$), and similar results were reported by Liu *et al*[307]. However, the evidence is not unanimous, with some studies finding no difference in local recurrence rates between RFA and MWA[307].

Some studies have examined potential differences in tissue effects between MWA and RFA, and have found less heat sink for MWA[307] in treating lesions near blood vessels, though more complications[308] for peribiliary lesions.

In conclusion, the confounding factors relating to patient selection that make the RFA studies difficult to interpret apply equally to MWA, with the additional fact that there is generally less data for MWA than RFA. No randomised studies comparing MWA to RFA exist, and it may be that the two techniques have complementary rather than competing roles given the suggestion of slightly different tissue consequences in relation to tumours near blood vessels and bile ducts

Management of synchronous CRLM

Introduction: The scenario of synchronous operable CRLM presents another dilemma in opening the options of carrying out liver resection prior to, or synchronously with, the primary CRC. The section below discusses the evidence relating to synchronous and liver first surgery and is followed by a section on the various scenarios where these options may be considered.

Simultaneous liver and colon surgery: The reported experience of a number of studies analysing the outcome of simultaneous resection of a primary colorectal tumour and liver metastases has allowed some guidance of when this approach is appropriate. In a retrospective multicentre study, Reddy *et al*[309] analysed the outcomes of 610 patients who underwent simultaneous ($n = 135$) or staged ($n = 475$) resections. Combined hospital stay was lower after simultaneous resections (median 8.5 *vs* 14 d, $P < 0.0001$). Mortality and severe morbidity were similar after simultaneous colorectal resection and minor hepatectomy compared with isolated minor hepatectomy. For major hepatectomy (defined as resection of at least three segments) however, simultaneous colorectal resection increased mortality (8.3% *vs* 1.4%, $P < 0.05$) and severe morbidity (36.1% *vs* 15.1%, $P < 0.05$). Moreover, combined severe morbidity after staged resections was lower compared to simultaneous resections (36.1% *vs* 17.6%, $P = 0.05$). Severe morbidity experienced by patients undergoing combined resection included hepatic failure, intestinal anastomotic leaks, fascial dehiscence, intra-abdominal abscesses, isolated and multiple organ failure, aspiration, and pulmonary embolism. Consistent with these conclusions, Jones *et al*[310] reported that the rate of major complications was higher in patients undergoing simultaneous resection.

In a single centre retrospective study, De Haas *et al*[311] reported significantly worse progression free survival in the simultaneous surgery group, but also noted that the staged surgery group had received significantly more chemotherapy, highlighting the difficulty in comparisons in such studies. Similar interpretation questions were raised in a large population study[312] involving 442 and 776 patients undergoing simultaneous and staged resections respectively. The simultaneous resection group had a worse median overall survival, but also had received significantly less chemotherapy.

In a recent meta-analysis involving 32 studies[313], it appeared that the messages from earlier studies relating to avoiding major hepatectomy in the context of simultaneous resections was heeded. In this analysis, the synchronous resection group were found to have a smaller proportion of bilobar disease and underwent less major resections. Consequently, there was no difference between the synchronous and staged resection groups in terms of major morbidity and overall survival.

In conclusion, although interpretation of outcomes is difficult because of patient group heterogeneity, the consistent message from available studies is that simultaneous colon and liver resection can be performed safely in selected patients. Specifically, this excludes liver resections involving 3 or more segments.

Liver-first surgery: The concept of carrying out liver-first surgery in the context of synchronous colorectal liver metastases was first reported by Mentha *et al*[314]. The scenarios where liver first surgery has been advocated include: (1) Following downsizing of initially unresectable liver metastases with an asymptomatic primary tumour in situ, when it is deemed that there is potentially a limited time window for successful liver resection; (2) In the situation of synchronous operable primary and colorectal liver metastases where the colorectal liver metastases are, by virtue of their size or site, deemed most threatening and may become inoperable during time taken

to complete a primary first treatment plan; and (3) In the specific instance of synchronous rectal cancer and liver metastases, where the significant time interval between irradiation of the primary tumour and its resection (3 mo window after long course irradiation) provides an opportunity for metastases to be resected substantially sooner than would be achieved if waiting till after resection of the primary.

Since Mentha's original report, other studies series have been contributed such as that from Brouquet *et al*[315] reporting 156 consecutive patients with synchronous resectable CLM of which 72 patients underwent primary-first surgery, 43 combined, and 27 liver-first strategies, with no difference in morbidity, mortality of long term outcome between the groups.

These studies exemplify the problems of interpretation in this area: The numbers of patients reported on by individual centres are inevitably limited, and the patients are inevitably selected for their most appropriate treatment strategy, thus introducing a selection bias in any comparisons between groups.

Although a number of systematic reviews and meta-analyses have since been written, and thus allowed a greater numbers of patient cases to be studied, the issue of selection bias remains.

Thus, in a report from the Livermet survey, Andres *et al*[316] reported in a total of 787 patients including 58 who underwent liver first surgery. The liver first group included more rectal cancer, neoadjuvant rectal radiotherapy, and underwent more chemotherapy, but overall survival and disease-free survival were similar in both groups.

In their systematic review, Jegatheeswaran *et al*[317] reported on 4 studies in which patients underwent neoadjuvant chemotherapy first, then liver resection, then resection of the primary tumour. 74% completed the entire treatment protocol. 79% proceeded to liver resection, with disease progression on chemotherapy being the principle reason for not undergoing hepatectomy. In a further systematic review, Lam *et al*[318] reported very similar findings and conclusions.

In Network meta-analysis reviews, Kelly *et al*[319] and Gavriilidis *et al*[313] reviewed 18 studies and 32 studies respectively and found no significant differences in long-term survival and major morbidity were found between the surgical approaches.

In conclusion there are no randomised trials comparing liver-first versus primary-first surgery, and the highly specific nature of individual patient presentation in this context is such that it seems very unlikely that such a trial would be feasible. Nevertheless, in selected patients, the liver first approach results in short- and long-term outcomes that are similar to those achieved when the primary tumour is resected first.

Synchronous liver metastases management scenarios: The definition of synchronous has not been uniform in existing studies, with some authors including only metastases diagnosed at the time of or before diagnosis of the primary tumour, whilst other include metastases diagnosed up to 3 or even 6 mo after diagnosis of the primary. Based on prognostic outcomes, the EGOSLIM consensus group suggested a terminology of synchronous liver metastases (detected at or before diagnosis of the primary tumour), Early metachronous metastases (detected within 12 mo after diagnosis or surgery of the primary) and Late metachronous metastases (detected more than 12 mo after diagnosis or surgery of the primary)[320].

One significant aspect of synchronous presentation of primary tumour and liver metastases is the dilemma of which disease site should be treated first, or whether systemic chemotherapy should be the initial treatment. The conventional order of primary resection followed by liver resection, dictated by chronology in the metachronous situation, may not be the most appropriate in synchronous presentation.

In practice, the order of treatment is partly dictated by the constraints of the clinical presentation which may be summarised in Figure 3 according to primary symptomatology and liver disease resectability. (1) Asymptomatic primary and unequivocally unresectable liver metastases. In this scenario there is consensus to treat with up front chemotherapy, with a range of systemic chemotherapy agents combined with EGFR blockade and anti-angiogenic agents, guided by principles as described in the section on unresectable metachronous liver metastases, with the intention of achieving maximal response, survival, and perhaps in some cases conversion to a resectable scenario for the liver metastases. For those patients who are converted to operability, liver first surgery may be considered over colon first. In the context of downstaged liver metastases, simultaneous liver and colon resection should be perhaps be avoided on the strength of Liver Met Survey data showing 5-year survival

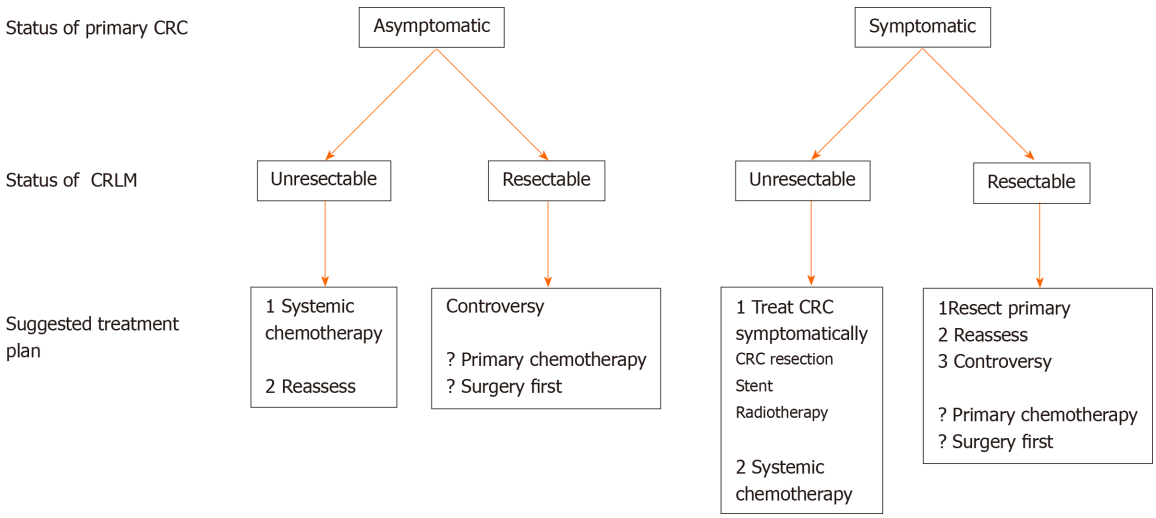

Figure 3 Management options in synchronous colorectal cancer and colorectal liver metastases, according to presentation criteria. CRC: Colorectal cancer; CRLM: Colorectal liver metastases.

rates were 42% for liver first approach compared with 33% for colon first surgery and 28% for one-stage surgery[320]; (2) Symptomatic primary and unequivocally unresectable liver metastases. In this instance, the objective is to deal with symptoms from the primary, and thereafter offer optimal systemic chemotherapy. However, the differing possible scenarios and lack of evidence leaves much freedom for a pragmatic approach based on diverse clinical circumstances with symptomatology in relation to bleeding, obstruction or perforation. Bleeding may respond to systemic chemotherapy and may be managed by blood transfusion, thus avoiding the need for surgery to the primary tumour. Perforation will usually mandate primary resection unless an entirely palliative approach is appropriate. Obstruction may require resection of the primary tumour, though the options of proximal stoma and stenting may also be appropriate, with relative merits of each outside the scope of this review. Once primary symptoms have been addressed, systemic chemotherapy is indicated with the aim of maximising survival and conversion of liver metastases to an operable scenario, once again guided by principles as described in the section on unresectable metachronous liver metastases; (3) Asymptomatic primary and resectable liver metastases. This scenario is perhaps the one that gives rise to most discussion and controversy. Although the EGOSLIM consensus group recommended systemic chemotherapy first for this scenario, there was not unanimity in this recommendation, and it was pointed out that evidence for such a recommendation was lacking[321]. The only randomised evidence in this area comes from the EORTC 40983 trial[161], comparing surgery alone to FOLFOX–surgery-FOLFOX, which showed an improved DFS in the peri-operative chemotherapy group, though no OS advantage in the early or long term[162]. However, the experimental group received both neoadjuvant and adjuvant chemo, such that it is difficult to state whether any survival advantage was associated with neoadjuvant treatment, adjuvant, or both. Arguing against the value of neoadjuvant treatment, Adam *et al*[321] showed no benefit associated with neoadjuvant treatment prior to resection of solitary metachronous liver metastases[321]. Although providing some evidence, both Adam's study and the EORTC trial are nevertheless not directly applicable to the scenario of synchronous liver metastases, as almost 2/3 of the liver metastases in the EORTC trial were metachronous, and Adam's study relates exclusively to metachronous liver metastases. In a retrospective report Bonney *et al*[322] studied 1301 patients with synchronous liver metastases, and compared those who received neoadjuvant chemotherapy prior to liver resection to those who underwent liver surgery without neoadjuvant chemotherapy. Neoadjuvant chemotherapy did not affect outcome and was not associated with any survival advantage. Of note, the surgery up front group had a greater number of solitary metastases, and therefore a separate analysis was undertaken to take this into account. The authors found that for patients with solitary CRLM, neither neoadjuvant nor adjuvant chemotherapy was associated with a survival advantage. In contrast, for patients with multiple liver metastases, although neoadjuvant chemotherapy conferred no benefit, adjuvant chemotherapy was found to be associated with a survival advantage. In summary, the evidence base in this scenario is largely lacking, and to some extent conflicting. It

would appear that the scenario of "synchronous asymptomatic primary and resectable liver metastases" is not a homogeneous scenario to be treated by a "one size fits all" approach, but a very heterogeneous one, requiring approach flexibility by experienced MDT. Current evidence certainly does not justify neoadjuvant chemotherapy in all cases of synchronous resectable liver metastases; and (4) Symptomatic primary and resectable liver metastases. In this scenario, priority is given to dealing with symptoms from the primary as outlined in the section on symptomatic primary and unequivocally unresectable liver metastases. Thereafter however, once recovered from primary surgery, the next most appropriate treatment depends on the results of restaging. If restaging shows progression with now unresectable liver metastases, clearly chemotherapy is indicated. If restaging suggests disease progression in the liver though still resectable, then a period of systemic chemotherapy may be most appropriate to re-establish disease stability prior to reassessing with a view to liver resection. If restaging suggests stable and resectable metastases, then the scenario becomes similar in principle to the situation of "resectable primary and resectable liver metastases", where the evidence for neoadjuvant chemotherapy prior to liver resection is not absolute, and there may be circumstances for proceeding to liver resection, with a view to adjuvant chemotherapy after.

Orthotopic liver transplantation for colorectal liver metastases

Some CRLM remain unresectable on account of proximity to vital structures that cannot be sacrificed, or because of insufficient remnant liver volume. However, the favourable results of liver resection in comparison to chemotherapy alone raises the question of whether total hepatectomy, followed by liver transplantation, might have a place in the management of unresectable liver only metastases.

Studies investigating OLT for unresectable CRLM during the 1990s reported poor outcomes in Europe and the United States with 5 year survival of 12%-21%[323,324], and thus much lower than outcome achieved following transplantation for other indications.

In 2006, on a background of improvements in both liver transplantation and CRLM management, and the favourable organ to recipient ratio in Norway, the Oslo University Hospital group initiated a study to reassess the survival of patients with non resectable CRLM after LT (SECA Trial)[325].

21 patients underwent deceased-donor LT, with 1, 3, and 5-year OS of 95%, 68%, and 60% respectively, thus comparing favourably to 19% OS in a comparative retrospective cohort of patients with unresectable CRLM treated with chemotherapy alone[326]. Median time to recurrence was 6 mo and all patients followed for longer than 11 mo experienced recurrence, most frequently in the lungs[327]. Similarly, Toso *et al*[328] reported the outcomes of 12 patients who underwent OLT for unresectable liver metastases, with a 5 year OS of 50%, and with 4 out of 12 patients showing no sign of recurrence at 48 mo.

The wide inclusion criteria of the SECA 1 study allowed the identification of 4 clinical features associated with a worse survival: Pretransplant tumor diameter > 5.5 cm, a pre-transplant CEA > 80 μg/L, time interval from resection of the primary to transplantation < 2 years, and progression of the metastases under neo-adjuvant chemotherapy. These and other criteria have been used to inform more selective recruitment criteria to the ongoing SECA II trial, with preliminary results showing overall survival at 1, 3, and 5 years of 100%, 83%, and 83%, respectively[329].

Further trial are also in progress, including the TRANSMET (NCT02597348) and SECA III (NCT03494946) trials which compare OLT to optimal systemic chemotherapy in unresectable CRLM.

In conclusion, it appears that in selected patients with unresectable CRLM, OLT is associated with OS Figures which are comparable to those achieved for other OLT indications. The outcome of randomised trials comparing OLT to optimal systemic chemotherapy are eagerly awaited but results favouring OLT would doubtless contribute to the already complex debate regarding organ allocation.

SECTION 5: HISTOPATHOLOGICAL ASSESSMENT OF COLORECTAL LIVER METASTASES

Following resection of CRLM, histopathological assessment is essential, and yields critically important information which directly influences further management. The assessment of margins is an obvious example, affecting decisions regarding re-operation, as well as the timing and intensity of surveillance. Another is the real

response to chemotherapy, which may influence oncological management. The following section describes current practice in CRLM histopathological assessment.

Current best practice

The role of histopathology is predominantly one of post-operative assessment of resected liver specimens, with pre-operative biopsy or intra-operative frozen section being required only rarely (the latter usually in the context of lymph nodes suspicious for metastasis, or unexpected subcapsular lesions not identified on preoperative imaging)[330].

Pre-operative assessment: Preoperative percutaneous needle biopsy is avoided where possible due to the risk of tumour seeding along the biopsy needle tract[330,331]. In rare cases were percutaneous liver biopsy is deemed to be necessary, usually in the context of multiple known primary tumours, the test can be modified to mitigate the risk of tumour seeding. Endoscopic ultrasound fine needle aspiration may be technically feasible in some cases, in particular for intra-abdominal lymph node sampling where reasonable yields can usually be obtained to allow for additional immunohistochemical assessment, if required.

Routine haematoxylin and eosin (H and E) stained slides are examined in the first instance. A limited panel of immunohistochemical stains such as CK20 and CDX-2 can be used to confirm morphological findings suggestive of colorectal origin[332]. An expanded panel to include CK7 and other specific localising antibodies can be undertaken depending on morphological appearance and clinical history[330,332].

The biopsy report should contain a morphological description of the tumour including the degree of differentiation, details of immunohistochemical analysis, and a conclusion indicating the site, or possible sites, of primary origin. A description of the adjacent/background liver tissue should also be included as the presence of chronic liver disease may influence risk assessment for surgery and chemotherapy[333].

Post-operative assessment: The approach to the resected liver specimen involves both macroscopic and microscopic assessment. (1) Macroscopic assessment: The macroscopic assessment should include the size and weight of the resection specimen, along with a description of the capsule, including areas of disruption or adhesions. Surfaces other than the capsule are painted with ink to allow margin identification. Specimens can be sectioned fresh or fixed, with fixed tissues allowing for more accurate slicing[330]. An example of a fixed specimen is shown in Figure 4. Findings should be carefully correlated with the description in the operation note, especially in the case of complex specimens. Tumour deposit number and size should be assessed. It is also important to correlate with imaging data to ensure that all preoperatively and intraoperatively identified lesions are sampled for microscopic assessment. At least one block should be taken of each metastatic deposit, as well as one block of representative background liver[330]; (2) Microscopic assessment: The microscopic assessment should include a morphological description of any lesions present, including degree of differentiation. An example of the histological appearance of a colorectal metastasis is shown in Figure 5. Immunohistochemistry is not routinely carried out, but should be included if the morphological features are unusual or there is diagnostic uncertainty[330]. Other factors that are assessed include evidence of capsular breach by the tumour, distance to the resection margin (a distance of 1 mm or more being considered "not involved"), the presence or absence of lymphovascular invasion, and the number of involved lymph nodes, if present. The presence or absence of background chronic liver disease should be commented upon[330]. Molecular tests (KRAS, BRAF, NRAS, microsatellite instability) should also be conducted if not previously completed on the primary tumour[333]. The results of these molecular tests can be crucial for the selection of the most appropriate chemotherapy agent, to aid with prognostication, and to establish or exclude a diagnosis of a hereditary tumour syndrome[333]. The effect of preoperative neoadjuvant therapy should be evaluated if applicable. This includes an assessment of tumour response and the presence of chemotherapy-induced injury such as sinusoidal obstruction syndrome (more common with oxaliplatin) or steatohepatitis (more common with irinotecan) in the background liver tissue. The former can be assessed using the chemotherapy-induced sinusoidal injury score[333-347]. In cases where selective internal radiotherapy has been administered, therapeutic microspheres may also be present. If preoperative portal vein embolization has been undertaken then embolic material may be present within portal vein branches, along with variable degrees of parenchymal atrophy due to relative ischaemia, shown in Figure 6. Tumour response to chemotherapy involves assessing the percentage area of viable tumour compared to fibrosis and necrosis. The

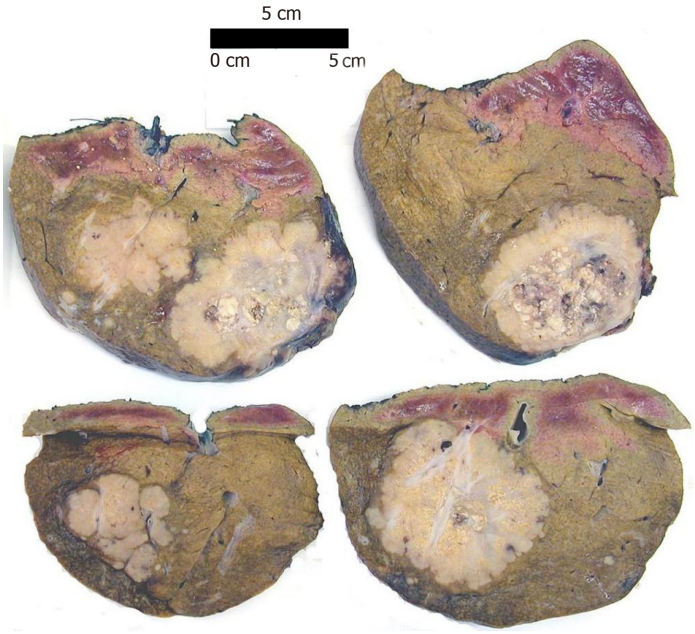

Figure 4 Multiple colorectal metastases in a formalin-fixed liver resection specimen showing a pale cut surface with typical lobulated border. Non-capsular surfaces inked for margin identification (scale bar: 5 cm).

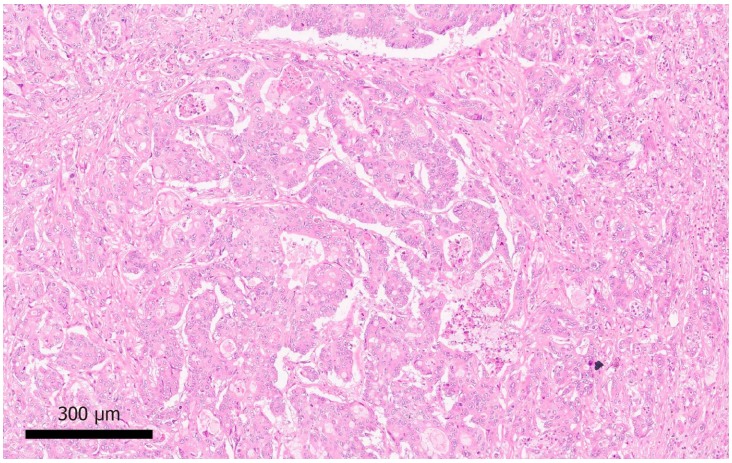

Figure 5 Colorectal metastasis with typical cribriform glandular architecture and central comedonecrosis (Hematoxylin-eosin staining, × 10 magnification).

four tiered system advocated by the American Joint Committee on Cancer based on a modification by Ryan *et al*[335] is currently recommended by the Royal College of Pathologists for assessment of response in primary colorectal carcinoma (Table 1)[336] . While necrosis, as illustrated in Figure 7, is very common, there is evidence to suggest that the most predictive factor for outcome in the assessment of tumour response to chemotherapy is fibrosis (Figure 8)[333,337].

Future perspectives

Several biomarkers are under development which have both prognostic and predictive potential. One such marker is programmed cell death protein (PD-1), whose dominant ligand is PD-L1, expressed on the surface of activated T cells to regulate proliferation and activation. When carcinoma develops tumour cells may express PD-L1 and thus reduce their immunogenicity. Assessment of PD-L1 expression in tumour cells using immunohistochemistry may therefore provide prognostic information and predict response to treatment with PD-1/PD-L1 inhibitors. This has shown encouraging initial results reported in microsatellite instability-high colorectal carcinoma[337,339].

Table 1 Assessment of response to chemotherapy in primary colorectal carcinoma using the Tumour Regression Score (AJCC)

Evaluation	Tumour regression score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near-complete response)	1
Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumour regression (poor or no response)	3

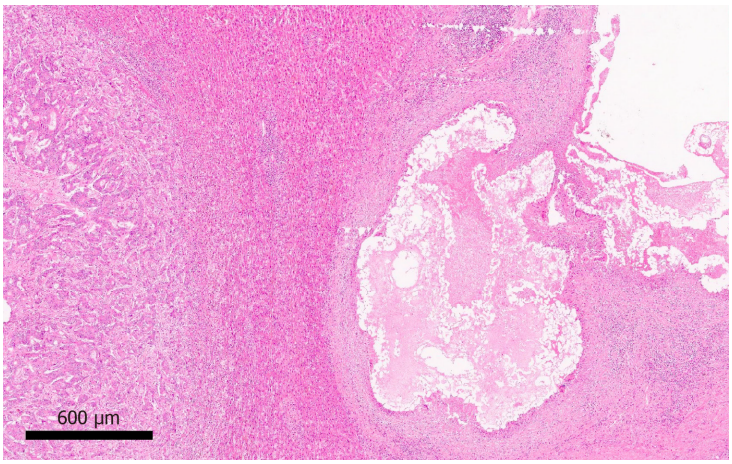

Figure 6 Embolic material within a large portal vein branch, with adjacent adenocarcinoma, in a patient who underwent preoperative portal vein embolization (Hematoxylin-eosin staining, × 4 magnification).

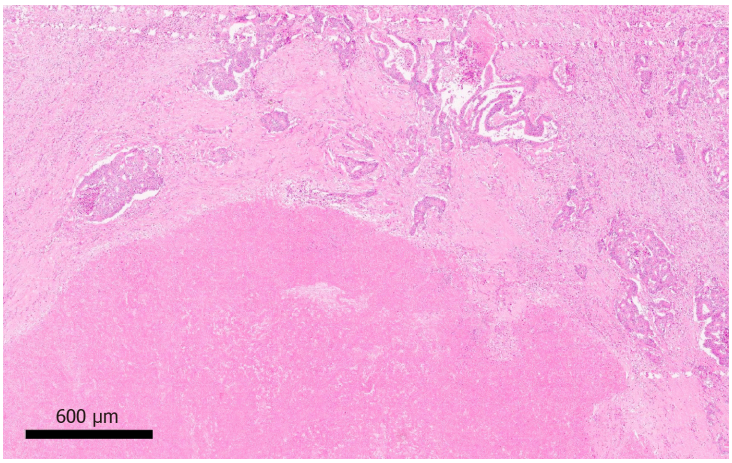

Figure 7 Extensive confluent tumour necrosis with fibrosis in keeping with a partial response to neoadjuvant therapy (Hematoxylin-eosin staining, × 4 magnification).

CONCLUSION

The management of colorectal liver metastases is highly complex owing to multiple treatment modalities. Adding to this complexity is the marked heterogeneity of the patient group, and the nuanced overlap between 'different' scenarios. In this context, no single specialty team, let alone individual clinician, is solely equipped to carry out optimal decision making.

Effective management results from careful and informed discussion from an experienced multi-disciplinary team involving radiology (cross sectional, nuclear medicine and interventional), Oncology, Liver surgery, Colorectal surgery, and Histopathology. Furthermore, it is incumbent on such MDTs to remain up to date in

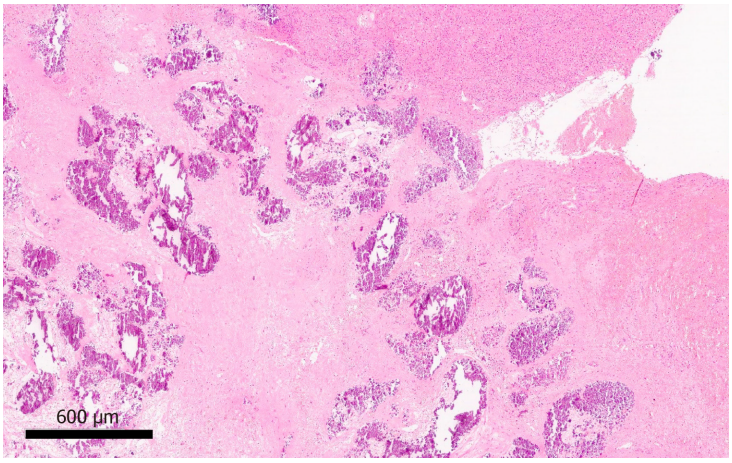

Figure 8 Confluent fibrosis and dystrophic calcification without viable residual tumour cells, consistent with pathological complete response to neoadjuvant therapy (Hematoxylin-eosin staining, × 4 magnification).

what is a fast-evolving field. In the not distant future, geneticists and molecular biologists may be added to the list of specialty representatives required in MDT discussions.

REFERENCES

1 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]

2 **Schreuders EH**, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, Kuipers EJ. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015; **64**: 1637-1649 [PMID: 26041752 DOI: 10.1136/gutjnl-2014-309086]

3 **Neal RD**, Din NU, Hamilton W, Ukoumunne OC, Carter B, Stapley S, Rubin G. Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: analysis of data from the UK General Practice Research Database. *Br J Cancer* 2014; **110**: 584-592 [PMID: 24366304 DOI: 10.1038/bjc.2013.791]

4 **Skipworth RJ**, Parks RW, Stephens NA, Graham C, Brewster DH, Garden OJ, Paterson-Brown S. The relationship between hospital volume and post-operative mortality rates for upper gastrointestinal cancer resections: Scotland 1982-2003. *Eur J Surg Oncol* 2010; **36**: 141-147 [PMID: 19879717 DOI: 10.1016/j.ejso.2009.10.004]

5 **Cecil TD**, Sexton R, Moran BJ, Heald RJ. Total mesorectal excision results in low local recurrence rates in lymph node-positive rectal cancer. *Dis Colon Rectum* 2004; **47**: 1145-9; discussion 1149-50 [PMID: 15164243 DOI: 10.1007/s10350-004-0086-6]

6 **Gustavsson B**, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, Tveit KM, Gibson F. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. *Clin Colorectal Cancer* 2015; **14**: 1-10 [PMID: 25579803 DOI: 10.1016/j.clcc.2014.11.002]

7 **Segelov E**, Chan D, Shapiro J, Price TJ, Karapetis CS, Tebbutt NC, Pavlakis N. The role of biological therapy in metastatic colorectal cancer after first-line treatment: a meta-analysis of randomised trials. *Br J Cancer* 2014; **111**: 1122-1131 [PMID: 25072258 DOI: 10.1038/bjc.2014.404]

8 **Hagland HR**, Berg M, Jolma IW, Carlsen A, Søreide K. Molecular pathways and cellular metabolism in colorectal cancer. *Dig Surg* 2013; **30**: 12-25 [PMID: 23595116 DOI: 10.1159/000347166]

9 **Snaebjornsson P**, Jonasson L, Olafsdottir EJ, van Grieken NCT, Moller PH, Theodors A, Jonsson T, Meijer GA, Jonasson JG. Why is colon cancer survival improving by time? A nationwide survival analysis spanning 35 years. *Int J Cancer* 2017; **141**: 531-539 [PMID: 28477390 DOI: 10.1002/ijc.30766]

10 **Woodington GF**, Waugh JM. Results of resection of metastatic tumors of the liver. *Am J Surg* 1963; **105**: 24-29 [PMID: 14010473 DOI: 10.1016/0002-9610(63)90263-0]

11 **Wilson SM**, Adson MA. Surgical treatment of hepatic metastases from colorectal cancers. *Arch Surg* 1976; **111**: 330-334 [PMID: 1259571 DOI: 10.1001/archsurg.1976.01360220026004]

12 **Scheele J**, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59-71 [PMID: 7740812 DOI: 10.1007/bf00316981]

13 **Fong Y**, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF. Liver resection for colorectal metastases. *J Clin Oncol* 1997; **15**: 938-946 [PMID: 9060531 DOI: 10.1200/JCO.1997.15.3.938]

14 **Weledji EP**. Centralization of Liver Cancer Surgery and Impact on Multidisciplinary Teams Working on Stage IV Colorectal Cancer. *Oncol Rev* 2017; **11**: 331 [PMID: 28814999 DOI: 10.4081/oncol.2017.331]

15 **Oxenberg J**, Papenfuss W, Esemuede I, Attwood K, Simunovic M, Kuvshinoff B, Francescutti V. Multidisciplinary cancer conferences for gastrointestinal malignancies result in measureable treatment changes: a prospective study of 149 consecutive patients. *Ann Surg Oncol* 2015; **22**: 1533-1539 [PMID: 25323473 DOI: 10.1245/s10434-014-4163-y]

16 **Specchia ML**, Frisicale EM, Carini E, Di Pilla A, Cappa D, Barbara A, Ricciardi W, Damiani G. The impact of tumor board on cancer care: evidence from an umbrella review. *BMC Health Serv Res* 2020; **20**: 73 [PMID: 32005232 DOI: 10.1186/s12913-020-4930-3]

17 **Engstrand J**, Kartalis N, Strömberg C, Broberg M, Stillström A, Lekberg T, Jonas E, Freedman J, Nilsson H. The Impact of a Hepatobiliary Multidisciplinary Team Assessment in Patients with Colorectal Cancer Liver Metastases: A Population-Based Study. *Oncologist* 2017; **22**: 1067-1074 [PMID: 28550028 DOI: 10.1634/theoncologist.2017-0028]

18 **Thillai K**, Repana D, Korantzis I, Kane P, Prachalias A, Ross P. Clinical outcomes for patients with liver-limited metastatic colorectal cancer: Arguing the case for specialist hepatobiliary multidisciplinary assessment. *Eur J Surg Oncol* 2016; **42**: 1331-1336 [PMID: 27174600 DOI: 10.1016/j.ejso.2016.03.031]

19 **Lan YT**, Jiang JK, Chang SC, Yang SH, Lin CC, Lin HH, Wang HS, Chen WS, Lin TC, Lin JK. Improved outcomes of colorectal cancer patients with liver metastases in the era of the multidisciplinary teams. *Int J Colorectal Dis* 2016; **31**: 403-411 [PMID: 26662193 DOI: 10.1007/s00384-015-2459-4]

20 **Lordan JT**, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. A 10-year study of outcome following hepatic resection for colorectal liver metastases - The effect of evaluation in a multidisciplinary team setting. *Eur J Surg Oncol* 2009; **35**: 302-306 [PMID: 18328668 DOI: 10.1016/j.ejso.2008.01.028]

21 **Donadon M**, Ribero D, Morris-Stiff G, Abdalla EK, Vauthey JN. New paradigm in the management of liver-only metastases from colorectal cancer. *Gastrointest Cancer Res* 2007; **1**: 20-27 [PMID: 19262699]

22 **Abdalla EK**, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006; **13**: 1271-1280 [PMID: 16955381 DOI: 10.1245/s10434-006-9045-5]

23 **Geoghegan JG**, Scheele J. Treatment of colorectal liver metastases. *Br J Surg* 1999; **86**: 158-169 [PMID: 10100781 DOI: 10.1046/j.1365-2168.1999.01013.x]

24 **Kanas GP**, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, Alexander DD, Choti MA, Poston G. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; **4**: 283-301 [PMID: 23152705 DOI: 10.2147/CLEP.S34285]

25 **Dunne DF**, Jones RP, Malik HZ, Fenwick SW, Poston GJ. Surgical management of colorectal liver metastases: a European perspective. *Hepat Oncol* 2014; **1**: 121-133 [PMID: 30190946 DOI: 10.2217/hep.13.3]

26 **Welch JP**, Donaldson GA. The clinical correlation of an autopsy study of recurrent colorectal cancer. *Ann Surg* 1979; **189**: 496-502 [PMID: 443905 DOI: 10.1097/00000658-197904000-00027]

27 **Engstrand J**, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC Cancer* 2018; **18**: 78 [PMID: 29334918 DOI: 10.1186/s12885-017-3925-x]

28 **van der Geest LG**, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis* 2015; **32**: 457-465 [PMID: 25899064 DOI: 10.1007/s10585-015-9719-0]

29 **Hackl C**, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. *BMC Cancer* 2014; **14**: 810 [PMID: 25369977 DOI: 10.1186/1471-2407-14-810]

30 **Manfredi S**, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; **244**: 254-259 [PMID: 16858188 DOI: 10.1097/01.SLA.0000217629.94941.cf]

31 **Scheele J**, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; **77**: 1241-1246 [PMID: 2253003 DOI: 10.1002/bjs.1800771115]

32 **Landreau P**, Drouillard A, Launoy G, Ortega-Deballon P, Jooste V, Lepage C, Faivre J, Facy O, Bouvier AM. Incidence and survival in late liver metastases of colorectal cancer. *J Gastroenterol Hepatol* 2015; **30**: 82-85 [PMID: 25088563 DOI: 10.1111/jgh.12685]

33 **Elferink MA**, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 2015; **30**: 205-212 [PMID: 25503801 DOI: 10.1007/s00384-014-2085-6]

34 **Chong G**, Cunningham D. Improving long-term outcomes for patients with liver metastases from colorectal cancer. *J Clin Oncol* 2005; **23**: 9063-9066 [PMID: 16301589 DOI: 10.1200/JCO.2005.04.4669]

35 **Renehan AG**, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002; **324**: 813 [PMID: 11934773 DOI: 10.1136/bmj.324.7341.813]

36 **Primrose JN**, Perera R, Gray A, Rose P, Fuller A, Corkhill A, George S, Mant D; FACS Trial Investigators. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014; **311**: 263-270 [PMID: 24430319 DOI: 10.1001/jama.2013.285718]

37 **Jeffery M**, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2016; **11**: CD002200 [PMID: 27884041 DOI: 10.1002/14651858.cd002200.pub3]

38 **Floriani I**, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, Giovagnoni A. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging* 2010; **31**: 19-31 [PMID: 20027569 DOI: 10.1002/jmri.22010]

39 **Cantisani V**, Ricci P, Erturk M, Pagliara E, Drudi F, Calliada F, Mortele K, D'Ambrosio U, Marigliano C, Catalano C, Marin D, Di Seri M, Longo F, Passariello R. Detection of hepatic metastases from colorectal cancer: prospective evaluation of gray scale US versus SonoVue® low mechanical index real time-enhanced US as compared with multidetector-CT or Gd-BOPTA-MRI. *Ultraschall Med* 2010; **31**: 500-505 [PMID: 20408122 DOI: 10.1055/s-0028-1109751]

40 **Rafaelsen SR**, Jakobsen A. Contrast-enhanced ultrasound vs multidetector-computed tomography for

detecting liver metastases in colorectal cancer: a prospective, blinded, patient-by-patient analysis. *Colorectal Dis* 2011; **13**: 420-425 [PMID: 20412096 DOI: 10.1111/j.1463-1318.2010.02288.x]

41 **van Vledder MG**, Pawlik TM, Munireddy S, Hamper U, de Jong MC, Choti MA. Factors determining the sensitivity of intraoperative ultrasonography in detecting colorectal liver metastases in the modern era. *Ann Surg Oncol* 2010; **17**: 2756-2763 [PMID: 20517682 DOI: 10.1245/s10434-010-1108-y]

42 **Takahashi M**, Hasegawa K, Arita J, Hata S, Aoki T, Sakamoto Y, Sugawara Y, Kokudo N. Contrast-enhanced intraoperative ultrasonography using perfluorobutane microbubbles for the enumeration of colorectal liver metastases. *Br J Surg* 2012; **99**: 1271-1277 [PMID: 22829436 DOI: 10.1002/bjs.8844]

43 **Ruzzenente A**, Conci S, Iacono C, Valdegamberi A, Campagnaro T, Bertuzzo F, Bagante F, De Angelis M, Guglielmi A. Usefulness of contrast-enhanced intraoperative ultrasonography (CE-IOUS) in patients with colorectal liver metastases after preoperative chemotherapy. *J Gastrointest Surg* 2013; **17**: 281-287 [PMID: 23065500 DOI: 10.1007/s11605-012-2043-y]

44 **Tirumani SH**, Kim KW, Nishino M, Howard SA, Krajewski KM, Jagannathan JP, Cleary JM, Ramaiya NH, Shinagare AB. Update on the role of imaging in management of metastatic colorectal cancer. *Radiographics* 2014; **34**: 1908-1928 [PMID: 25384292 DOI: 10.1148/rg.347130090]

45 **Soyer P**, Poccard M, Boudiaf M, Abitbol M, Hamzi L, Panis Y, Valleur P, Rymer R. Detection of hypovascular hepatic metastases at triple-phase helical CT: sensitivity of phases and comparison with surgical and histopathologic findings. *Radiology* 2004; **231**: 413-420 [PMID: 15044747 DOI: 10.1148/radiol.2312021639]

46 **Frankel TL**, Gian RK, Jarnagin WR. Preoperative imaging for hepatic resection of colorectal cancer metastasis. *J Gastrointest Oncol* 2012; **3**: 11-18 [PMID: 22811865 DOI: 10.3978/j.issn.2078-6891.2012.002]

47 **Sahani DV**, Bajwa MA, Andrabi Y, Bajpai S, Cusack JC. Current status of imaging and emerging techniques to evaluate liver metastases from colorectal carcinoma. *Ann Surg* 2014; **259**: 861-872 [PMID: 24509207 DOI: 10.1097/SLA.0000000000000525]

48 **Niekel MC**, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010; **257**: 674-684 [PMID: 20829538 DOI: 10.1148/radiol.10100729]

49 **Bruegel M**, Holzapfel K, Gaa J, Woertler K, Waldt S, Kiefer B, Stemmer A, Ganter C, Rummeny EJ. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. *Eur Radiol* 2008; **18**: 477-485 [PMID: 17960390 DOI: 10.1007/s00330-007-0785-9]

50 **Parikh T**, Drew SJ, Lee VS, Wong S, Hecht EM, Babb JS, Taouli B. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. *Radiology* 2008; **246**: 812-822 [PMID: 18223123 DOI: 10.1148/radiol.2463070432]

51 **Owen JW**, Fowler KJ, Doyle MB, Saad NE, Linehan DC, Chapman WC. Colorectal liver metastases: disappearing lesions in the era of Eovist hepatobiliary magnetic resonance imaging. *HPB (Oxford)* 2016; **18**: 296-303 [PMID: 27017170 DOI: 10.1016/j.hpb.2015.10.009]

52 **Charnsangavej C**, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006; **13**: 1261-1268 [PMID: 16947009 DOI: 10.1245/s10434-006-9023-y]

53 **Vilgrain V**, Esvan M, Ronot M, Caumont-Prim A, Aubé C, Chatellier G. A meta-analysis of diffusion-weighted and gadoxetic acid-enhanced MR imaging for the detection of liver metastases. *Eur Radiol* 2016; **26**: 4595-4615 [PMID: 26883327 DOI: 10.1007/s00330-016-4250-5]

54 **Cipe G**, Ergul N, Hasbahceci M, Firat D, Bozkurt S, Memmi N, Karatepe O, Muslumanoglu M. Routine use of positron-emission tomography/computed tomography for staging of primary colorectal cancer: does it affect clinical management? *World J Surg Oncol* 2013; **11**: 49 [PMID: 23445625 DOI: 10.1186/1477-7819-11-49]

55 **Brush J**, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, Glanville J, McIntosh H, Renehan A, Weller D, Dunlop M. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. *Health Technol Assess* 2011; **15**: 1-192, iii-iiv [PMID: 21958472 DOI: 10.3310/hta15350]

56 **Deng J**, Tang J, Shen N. Meta-analysis of diagnosis of liver metastatic cancers: comparison of (18) FDG PET-CT and gadolinium-enhanced MRI. *J Med Imaging Radiat Oncol* 2014; **58**: 532-537 [PMID: 25208683 DOI: 10.1111/1754-9485.12231]

57 **Rohren EM**, Paulson EK, Hagge R, Wong TZ, Killius J, Clavien PA, Nelson RC. The role of F-18 FDG positron emission tomography in preoperative assessment of the liver in patients being considered for curative resection of hepatic metastases from colorectal cancer. *Clin Nucl Med* 2002; **27**: 550-555 [PMID: 12169999 DOI: 10.1097/00003072-200208000-00002]

58 **Ruers TJ**, Langenhoff BS, Neeleman N, Jager GJ, Strijk S, Wobbes T, Corstens FH, Oyen WJ. Value of positron emission tomography with [F-18] fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. *J Clin Oncol* 2002; **20**: 388-395 [PMID: 11786565 DOI: 10.1200/JCO.20.2.388]

59 **Sahani DV**, Kalva SP, Fischman AJ, Kadavigere R, Blake M, Hahn PF, Saini S. Detection of liver metastases from adenocarcinoma of the colon and pancreas: comparison of mangafodipir trisodium-enhanced liver MRI and whole-body FDG PET. *AJR Am J Roentgenol* 2005; **185**: 239-246 [PMID: 15972430 DOI: 10.2214/ajr.185.1.01850239]

60 **Engledow AH**, Skipworth JR, Pakzad F, Imber C, Ell PJ, Groves AM. The role of 18FDG PET/CT in the management of colorectal liver metastases. *HPB (Oxford)* 2012; **14**: 20-25 [PMID: 22151447 DOI: 10.1111/j.1477-2574.2011.00378.x]

61 **Huguet EL**, Old S, Praseedom RK, Balan KK, Gibbs P, Jamieson NV. F18-FDG-PET evaluation of patients for resection of colorectal liver metastases. *Hepatogastroenterology* 2007; **54**: 1667-1671 [PMID: 18019690]

62 **Briggs RH**, Chowdhury FU, Lodge JP, Scarsbrook AF. Clinical impact of FDG PET-CT in patients with potentially operable metastatic colorectal cancer. *Clin Radiol* 2011; **66**: 1167-1174 [PMID: 21867996 DOI: 10.1016/j.crad.2011.07.046]

63 **Abbadi RA**, Sadat U, Jah A, Praseedom RK, Jamieson NV, Cheow HK, Whitley S, Ford HE, Wilson CB, Harper SJ, Huguet EL. Improved long-term survival after resection of colorectal liver metastases following staging with FDG positron emission tomography. *J Surg Oncol* 2014; **110**: 313-319 [PMID: 24737685 DOI: 10.1002/jso.23623]

64 **Truant S**, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. *Br J Surg* 2005; **92**: 362-369 [PMID: 15672427 DOI: 10.1002/bjs.4843]

65 **Moulton CA**, Gu CS, Law CH, Tandan VR, Hart R, Quan D, Fairfull Smith RJ, Jalink DW, Husien M, Serrano PE, Hendler AL, Haider MA, Ruo L, Gulenchyn KY, Finch T, Julian JA, Levine MN, Gallinger S. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. *JAMA* 2014; **311**: 1863-1869 [PMID: 24825641 DOI: 10.1001/jama.2014.3740]

66 **Expert Panel on Gastrointestinal Imaging**, Kaur H, Hindman NM, Al-Refaie WB, Arif-Tiwari H, Cash BD, Chernyak V, Farrell J, Grajo JR, Horowitz JM, McNamara MM, Noto RB, Qayyum A, Lalani T, Kamel IR. ACR Appropriateness Criteria® Suspected Liver Metastases. *J Am Coll Radiol* 2017; **14**: S314-S325 [PMID: 28473088 DOI: 10.1016/j.jacr.2017.01.037]

67 **Mittal BR**, Senthil R, Kashyap R, Bhattacharya A, Singh B, Kapoor R, Gupta R. 18F-FDG PET-CT in evaluation of postoperative colorectal cancer patients with rising CEA level. *Nucl Med Commun* 2011; **32**: 789-793 [PMID: 21760561 DOI: 10.1097/MNM.0b013e3283477dd7]

68 **Angelsen JH**, Viste A, Løes IM, Eide GE, Hoem D, Sorbye H, Horn A. Predictive factors for time to recurrence, treatment and post-recurrence survival in patients with initially resected colorectal liver metastases. *World J Surg Oncol* 2015; **13**: 1–9 [PMID: 26631156 DOI: 10.1186/s12957-015-0738-8]

69 **Metcalfe MS**, Mullin EJ, Maddern GJ. Choice of surveillance after hepatectomy for colorectal metastases. *Arch Surg* 2004; **139**: 749-754 [PMID: 15249408 DOI: 10.1001/archsurg.139.7.749]

70 **Hyder O**, Dodson RM, Mayo SC, Schneider EB, Weiss MJ, Herman JM, Wolfgang CL, Pawlik TM. Post-treatment surveillance of patients with colorectal cancer with surgically treated liver metastases. *Surgery* 2013; **154**: 256-265 [PMID: 23889953 DOI: 10.1016/j.surg.2013.04.021]

71 **Brenner DJ**, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007; **357**: 2277-2284 [PMID: 18046031 DOI: 10.1056/NEJMra072149]

72 **Dinan MA**, Curtis LH, Hammill BG, Patz EF Jr, Abernethy AP, Shea AM, Schulman KA. Changes in the use and costs of diagnostic imaging among Medicare beneficiaries with cancer, 1999-2006. *JAMA* 2010; **303**: 1625-1631 [PMID: 20424253 DOI: 10.1001/jama.2010.460]

73 **Hallet J**, Sa Cunha A, Adam R, Goéré D, Bachellier P, Azoulay D, Ayav A, Grégoire E, Navarro F, Pessaux P; French Colorectal Liver Metastases Working Group, Association Française de Chirurgie (AFC). Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg* 2016; **103**: 1366-1376 [PMID: 27306949 DOI: 10.1002/bjs.10191]

74 **Galjart B**, van der Stok EP, Rothbarth J, Grünhagen DJ, Verhoef C. Posttreatment Surveillance in Patients with Prolonged Disease-Free Survival After Resection of Colorectal Liver Metastasis. *Ann Surg Oncol* 2016; **23**: 3999-4007 [PMID: 27393572 DOI: 10.1245/s10434-016-5388-8]

75 **Pulitanò C**, Castillo F, Aldrighetti L, Bodingbauer M, Parks RW, Ferla G, Wigmore SJ, Garden OJ. What defines 'cure' after liver resection for colorectal metastases? Results after 10 years of follow-up. *HPB (Oxford)* 2010; **12**: 244-249 [PMID: 20590894 DOI: 10.1111/j.1477-2574.2010.00155.x]

76 **Tomlinson JS**, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; **25**: 4575-4580 [PMID: 17925551 DOI: 10.1200/JCO.2007.11.0833]

77 **Viganò L**, Ferrero A, Lo Tesoriere R, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. *Ann Surg Oncol* 2008; **15**: 2458-2464 [PMID: 18463927 DOI: 10.1245/s10434-008-9935-9]

78 **Bhattacharjya S**, Aggarwal R, Davidson BR. Intensive follow-up after liver resection for colorectal liver metastases: results of combined serial tumour marker estimations and computed tomography of the chest and abdomen - a prospective study. *Br J Cancer* 2006; **95**: 21-26 [PMID: 16804525 DOI: 10.1038/sj.bjc.6603219]

79 **Ribero D**, Viganò L, Amisano M, Capussotti L. Prognostic factors after resection of colorectal liver metastases: from morphology to biology. *Future Oncol* 2013; **9**: 45-57 [PMID: 23252563 DOI: 10.2217/fon.12.159]

80 **Jones RP**, Brudvik KW, Franklin JM, Poston GJ. Precision surgery for colorectal liver metastases: Opportunities and challenges of omics-based decision making. *Eur J Surg Oncol* 2017; **43**: 875-883 [PMID: 28302330 DOI: 10.1016/j.ejso.2017.02.014]

81 **Sasaki K**, Margonis GA, Wilson A, Kim Y, Buettner S, Andreatos N, Gani F, Amini N, Spolverato G, Pawlik TM. Prognostic Implication of KRAS Status after Hepatectomy for Colorectal Liver Metastases Varies According to Primary Colorectal Tumor Location. *Ann Surg Oncol* 2016; **23**: 3736-3743 [PMID: 27352204 DOI: 10.1245/s10434-016-5361-6]

82 **Bredt LC**, Rachid AF. Predictors of recurrence after a first hepatectomy for colorectal cancer liver metastases: a retrospective analysis. *World J Surg Oncol* 2014; **12**: 391 [PMID: 25528650 DOI: 10.1186/1477-7819-12-391]

83 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-18; discussion 318-21 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

84 **Roberts KJ**, White A, Cockbain A, Hodson J, Hidalgo E, Toogood GJ, Lodge JP. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. *Br J Surg* 2014; **101**: 856-866 [PMID: 24817653 DOI: 10.1002/bjs.9471]

85 **Kumar R**, Dennison AR, Robertson V, Jones MJ, Neal CP, Garcea G. Clinical risk scores in the current era of neoadjuvant chemotherapy for colorectal liver metastases. *ANZ J Surg* 2018; **88**: E16-E20 [PMID: 27621179 DOI: 10.1111/ans.13688]

86 **Fakih MG**. Metastatic colorectal cancer: current state and future directions. *J Clin Oncol* 2015; **33**: 1809-1824 [PMID: 25918280 DOI: 10.1200/JCO.2014.59.7633]

87 **Knijn N**, Mekenkamp LJ, Klomp M, Vink-Börger ME, Tol J, Teerenstra S, Meijer JW, Tebar M, Riemersma S, van Krieken JH, Punt CJ, Nagtegaal ID. KRAS mutation analysis: a comparison between primary tumours and matched liver metastases in 305 colorectal cancer patients. *Br J Cancer* 2011; **104**: 1020-1026 [PMID: 21364579 DOI: 10.1038/bjc.2011.26]

88 **Margonis GA**, Kim Y, Spolverato G, Ejaz A, Gupta R, Cosgrove D, Anders R, Karagkounis G, Choti MA, Pawlik TM. Association Between Specific Mutations in KRAS Codon 12 and Colorectal Liver Metastasis. *JAMA Surg* 2015; **150**: 722-729 [PMID: 26038887 DOI: 10.1001/jamasurg.2015.0313]

89 **Margonis GA**, Kim Y, Sasaki K, Samaha M, Amini N, Pawlik TM. Codon 13 KRAS mutation predicts patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Cancer* 2016; **122**: 2698-2707 [PMID: 27244540 DOI: 10.1002/cncr.30085]

90 **Brudvik KW**, Kopetz SE, Li L, Conrad C, Aloia TA, Vauthey JN. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. *Br J Surg* 2015; **102**: 1175-1183 [PMID: 26206254 DOI: 10.1002/bjs.9870]

91 **Brudvik KW**, Vauthey JN. Surgery: KRAS mutations and hepatic recurrence after treatment of colorectal liver metastases. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 638-639 [PMID: 28930294 DOI: 10.1038/nrgastro.2017.129]

92 **Margonis GA**, Buettner S, Andreatos N, Sasaki K, Ijzermans JNM, van Vugt JLA, Pawlik TM, Choti MA, Cameron JL, He J, Wolfgang CL, Weiss MJ. Anatomical Resections Improve Disease-free Survival in Patients With KRAS-mutated Colorectal Liver Metastases. *Ann Surg* 2017; **266**: 641-649 [PMID: 28657938 DOI: 10.1097/SLA.0000000000002367]

93 **Margonis GA**, Sasaki K, Kim Y, Samaha M, Buettner S, Amini N, Antoniou E, Pawlik TM. Tumor Biology Rather Than Surgical Technique Dictates Prognosis in Colorectal Cancer Liver Metastases. *J Gastrointest Surg* 2016; **20**: 1821-1829 [PMID: 27384430 DOI: 10.1007/s11605-016-3198-8]

94 **Davies H**, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**: 949-954 [PMID: 12068308 DOI: 10.1038/nature00766]

95 **Tie J**, Desai J. Targeting BRAF mutant metastatic colorectal cancer: clinical implications and emerging therapeutic strategies. *Target Oncol* 2015; **10**: 179-188 [PMID: 25119972 DOI: 10.1007/s11523-014-0330-0]

96 **Taieb J**, Le Malicot K, Shi Q, Penault-Llorca F, Bouché O, Tabernero J, Mini E, Goldberg RM, Folprecht G, Luc Van Laethem J, Sargent DJ, Alberts SR, Emile JF, Laurent Puig P, Sinicrope FA. Prognostic Value of BRAF and KRAS Mutations in MSI and MSS Stage III Colon Cancer. *J Natl Cancer Inst* 2017; **109** [PMID: 28040692 DOI: 10.1093/jnci/djw272]

97 **Siena S**, Rivera F, Taieb J, Peeters M, Prenen H, Koukakis R, Demonty G, Köhne CH. Survival Outcomes in Patients With RAS Wild Type Metastatic Colorectal Cancer Classified According to Köhne Prognostic Category and BRAF Mutation Status. *Clin Colorectal Cancer* 2018; **17**: 50-57.e8 [PMID: 29096990 DOI: 10.1016/j.clcc.2017.09.006]

98 **Gagnière J**, Dupré A, Gholami SS, Pezet D, Boerner T, Gönen M, Kingham TP, Allen PJ, Balachandran VP, De Matteo RP, Drebin JA, Yaeger R, Kemeny NE, Jarnagin WR, D'Angelica MI. Is Hepatectomy Justified for BRAF Mutant Colorectal Liver Metastases?: A Multi-institutional Analysis of 1497 Patients. *Ann Surg* 2020; **271**: 147-154 [PMID: 29995686 DOI: 10.1097/SLA.0000000000002968]

99 **Bachet JB**, Moreno-Lopez N, Vigano L, Marchese U, Gelli M, Raoux L, Truant S, Laurent C, Herrero A, Le Roy B, Deguelte Lardiere S, Passot G, Hautefeuille V, De La Fouchardiere C, Artru P, Ameto T, Mabrut JY, Schwarz L, Rousseau B, Lepère C, Coriat R, Brouquet A, Sa Cunha A, Benoist S. BRAF mutation is not associated with an increased risk of recurrence in patients undergoing resection of colorectal liver metastases. *Br J Surg* 2019; **106**: 1237-1247 [PMID: 31183866 DOI: 10.1002/bjs.11180]

100 **Torén W**, Ansari D, Andersson R. Immunohistochemical investigation of prognostic biomarkers in resected colorectal liver metastases: a systematic review and meta-analysis. *Cancer Cell Int* 2018; **18**: 217 [PMID: 30602942 DOI: 10.1186/s12935-018-0715-8]

101 **Nakayama M**, Oshima M. Mutant p53 in colon cancer. *J Mol Cell Biol* 2019; **11**: 267-276 [PMID: 30496442 DOI: 10.1093/jmcb/mjy075]

102 **Auvinen A**, Isola J, Visakorpi T, Koivula T, Virtanen S, Hakama M. Overexpression of p53 and long-term survival in colon carcinoma. *Br J Cancer* 1994; **70**: 293-296 [PMID: 8054278 DOI: 10.1038/bjc.1994.295]

103 **Remvikos Y**, Tominaga O, Hammel P, Laurent-Puig P, Salmon RJ, Dutrillaux B, Thomas G. Increased p53 protein content of colorectal tumours correlates with poor survival. *Br J Cancer* 1992; **66**: 758-764 [PMID: 1419618 DOI: 10.1038/bjc.1992.352]

104 **Tanaka K**, Shimada H, Miura M, Fujii Y, Yamaguchi S, Endo I, Sekido H, Togo S, Ike H. Metastatic tumor doubling time: most important prehepatectomy predictor of survival and nonrecurrence of hepatic colorectal cancer metastasis. *World J Surg* 2004; **28**: 263-270 [PMID: 14961200 DOI: 10.1007/s00268-003-7088-3]

105 **Yang Y**, Forslund A, Remotti H, Lönnroth C, Andersson M, Brevinge H, Svanberg E, Lindnér P, Hafström L, Naredi P, Lundholm K. P53 mutations in primary tumors and subsequent liver metastases are related to survival in patients with colorectal carcinoma who undergo liver resection. *Cancer* 2001; **91**: 727-736 [PMID: 11241240]

106 **Chun YS**, Passot G, Yamashita S, Nusrat M, Katsonis P, Loree JM, Conrad C, Tzeng CD, Xiao L, Aloia TA, Eng C, Kopetz SE, Lichtarge O, Vauthey JN. Deleterious Effect of RAS and Evolutionary High-risk TP53 Double Mutation in Colorectal Liver Metastases. *Ann Surg* 2019; **269**: 917-923 [PMID: 28767562 DOI: 10.1097/SLA.0000000000002450]

107 **Ogino S**, Lochhead P, Giovannucci E, Meyerhardt JA, Fuchs CS, Chan AT. Discovery of colorectal cancer PIK3CA mutation as potential predictive biomarker: power and promise of molecular pathological epidemiology. *Oncogene* 2014; **33**: 2949-2955 [PMID: 23792451 DOI: 10.1038/onc.2013.244]

108 **Samuels Y**, Diaz LA Jr, Schmidt-Kittler O, Cummins JM, Delong L, Cheong I, Rago C, Huso DL, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE. Mutant PIK3CA promotes cell growth and invasion of human cancer cells. *Cancer Cell* 2005; **7**: 561-573 [PMID: 15950905 DOI: 10.1016/j.ccr.2005.05.014]

109 **Sartore-Bianchi A**, Martini M, Molinari F, Veronese S, Nichelatti M, Artale S, Di Nicolantonio F, Saletti P, De Dosso S, Mazzucchelli L, Frattini M, Siena S, Bardelli A. PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies. *Cancer Res* 2009; **69**: 1851-1857 [PMID: 19223544 DOI: 10.1158/0008-5472.CAN-08-2466]

110 **Løes IM**, Immervoll H, Sorbye H, Angelsen JH, Horn A, Knappskog S, Lønning PE. Impact of KRAS, BRAF, PIK3CA, TP53 status and intraindividual mutation heterogeneity on outcome after liver resection for colorectal cancer metastases. *Int J Cancer* 2016; **139**: 647-656 [PMID: 26991344 DOI: 10.1002/ijc.30089]

111 **Yamashita S**, Chun YS, Kopetz SE, Maru D, Conrad C, Aloia TA, Vauthey JN. APC and PIK3CA Mutational Cooperativity Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colorectal Liver Metastases. *Ann Surg* 2017 [PMID: 28379870 DOI: 10.1097/SLA.0000000000002245]

112 **Hermida MA**, Dinesh Kumar J, Leslie NR. GSK3 and its interactions with the PI3K/AKT/mTOR signalling network. *Adv Biol Regul* 2017; **65**: 5-15 [PMID: 28712664 DOI: 10.1016/j.jbior.2017.06.003]

113 **Ghosh N**, Hossain U, Mandal A, Sil PC. The Wnt signaling pathway: a potential therapeutic target against cancer. *Ann N Y Acad Sci* 2019; **1443**: 54-74 [PMID: 31017675 DOI: 10.1111/nyas.14027]

114 **Sinicrope FA**. DNA mismatch repair and adjuvant chemotherapy in sporadic colon cancer. *Nat Rev Clin Oncol* 2010; **7**: 174-177 [PMID: 20190798 DOI: 10.1038/nrclinonc.2009.235]

115 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]

116 **Overman MJ**, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, Morse MA, Van Cutsem E, McDermott R, Hill A, Sawyer MB, Hendlisz A, Neyns B, Svrcek M, Moss RA, Ledeine JM, Cao ZA, Kamble S, Kopetz S, André T. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol* 2018; **36**: 773-779 [PMID: 29355075 DOI: 10.1200/JCO.2017.76.9901]

117 **Ijsselsteijn ME**, Petitprez F, Lacroix L, Ruano D, van der Breggen R, Julie C, Morreau H, Sautès-Fridman C, Fridman WH, de Miranda NFDCC. Revisiting immune escape in colorectal cancer in the era of immunotherapy. *Br J Cancer* 2019; **120**: 815-818 [PMID: 30862951 DOI: 10.1038/s41416-019-0421-x]

118 **McCullough AJ**. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis* 2004; **8**: 521-533, viii [PMID: 15331061 DOI: 10.1016/j.cld.2004.04.004]

119 **Zeiss J**, Merrick HW, Savolaine ER, Woldenberg LS, Kim K, Schlembach PJ. Fatty liver change as a result of hepatic artery infusion chemotherapy. *Am J Clin Oncol* 1990; **13**: 156-160 [PMID: 2138409 DOI: 10.1097/00000421-199004000-00013]

120 **Peppercorn PD**, Reznek RH, Wilson P, Slevin ML, Gupta RK. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. *Br J Cancer* 1998; **77**: 2008-2011 [PMID: 9667683 DOI: 10.1038/bjc.1998.333]

121 **Moertel CG**, Fleming TR, Macdonald JS, Haller DG, Laurie JA. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. *J Clin Oncol* 1993; **11**: 2386-2390 [PMID: 8246027 DOI: 10.1200/JCO.1993.11.12.2386]

122 **Vauthey JN**, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006; **24**: 2065-2072 [PMID: 16648507 DOI: 10.1200/JCO.2005.05.3074]

123 **Reiss U**, Cowan M, McMillan A, Horn B. Hepatic venoocclusive disease in blood and bone marrow transplantation in children and young adults: incidence, risk factors, and outcome in a cohort of 241 patients. *J Pediatr Hematol Oncol* 2002; **24**: 746-750 [PMID: 12468917 DOI: 10.1097/00043426-200212000-00013]

124 **Rubbia-Brandt L**, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G, Terris B. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004; **15**: 460-466 [PMID: 14998849 DOI: 10.1093/annonc/mdh095]

125 **Karoui M**, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, Nordlinger B. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006; **243**: 1-7 [PMID: 16371728 DOI: 10.1097/01.SLA.0000193603.26265.c3]

126 **Van Cutsem E**, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J,

Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**: 1386-1422 [PMID: 27380959 DOI: 10.1093/annonc/mdw235]

127 **Giacchetti S**, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Lévi F. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; **18**: 136-147 [PMID: 10623704 DOI: 10.1200/JCO.2000.18.1.136]

128 **de Gramont A**, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**: 2938-2947 [PMID: 10944126 DOI: 10.1200/JCO.2000.18.16.2938]

129 **Douillard JY**, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355**: 1041-1047 [PMID: 10744089 DOI: 10.1016/s0140-6736(00)02034-1]

130 **Falcone A**, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G; Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670-1676 [PMID: 17470860 DOI: 10.1200/JCO.2006.09.0928]

131 **Marques RP**, Duarte GS, Sterrantino C, Pais HL, Quintela A, Martins AP, Costa J. Triplet (FOLFOXIRI) versus doublet (FOLFOX or FOLFIRI) backbone chemotherapy as first-line treatment of metastatic colorectal cancer: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2017; **118**: 54-62 [PMID: 28917269 DOI: 10.1016/j.critrevonc.2017.08.006]

132 **Neugut AI**, Lin A, Raab GT, Hillyer GC, Keller D, O'Neil DS, Accordino MK, Kiran RP, Wright J, Hershman DL. FOLFOX and FOLFIRI Use in Stage IV Colon Cancer: Analysis of SEER-Medicare Data. *Clin Colorectal Cancer* 2019; **18**: 133-140 [PMID: 30878317 DOI: 10.1016/j.clcc.2019.01.005]

133 **Petrelli F**, Barni S; Anti-EGFR agents for liver metastases. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. *Int J Colorectal Dis* 2012; **27**: 997-1004 [PMID: 22358385 DOI: 10.1007/s00384-012-1438-2]

134 **Folprecht G**, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, Lang H, Frilling A, Stoehlmacher J, Weitz J, Konopke R, Stroszczynski C, Liersch T, Ockert D, Herrmann T, Goekkurt E, Parisi F, Köhne CH. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010; **11**: 38-47 [PMID: 19942479 DOI: 10.1016/S1470-2045(09)70330-4]

135 **Modest DP**, Martens UM, Riera-Knorrenschild J, Greeve J, Florschütz A, Wessendorf S, Ettrich T, Kanzler S, Nörenberg D, Ricke J, Seidensticker M, Held S, Buechner-Steudel P, Atzpodien J, Heinemann V, Seufferlein T, Tannapfel A, Reinacher-Schick AC, Geissler M. FOLFOXIRI Plus Panitumumab As First-Line Treatment of *RAS* Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109). *J Clin Oncol* 2019; **37**: 3401-3411 [PMID: 31609637 DOI: 10.1200/JCO.19.01340]

136 **Cunningham D**, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337-345 [PMID: 15269313 DOI: 10.1056/NEJMoa033025]

137 **Karapetis CS**, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; **359**: 1757-1765 [PMID: 18946061 DOI: 10.1056/NEJMoa0804385]

138 **Vaughn CP**, Zobell SD, Furtado LV, Baker CL, Samowitz WS. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. *Genes Chromosomes Cancer* 2011; **50**: 307-312 [PMID: 21305640 DOI: 10.1002/gcc.20854]

139 **Clancy C**, Burke JP, Kalady MF, Coffey JC. BRAF mutation is associated with distinct clinicopathological characteristics in colorectal cancer: a systematic review and meta-analysis. *Colorectal Dis* 2013; **15**: e711-e718 [PMID: 24112392 DOI: 10.1111/codi.12427]

140 **Bardelli A**, Corso S, Bertotti A, Hobor S, Valtorta E, Siravegna G, Sartore-Bianchi A, Scala E, Cassingena A, Zecchin D, Apicella M, Migliardi G, Galimi F, Lauricella C, Zanon C, Perera T, Veronese S, Corti G, Amatu A, Gambacorta M, Diaz LA Jr, Sausen M, Velculescu VE, Comoglio P, Trusolino L, Di Nicolantonio F, Giordano S, Siena S. Amplification of the MET receptor drives resistance to anti-EGFR therapies in colorectal cancer. *Cancer Discov* 2013; **3**: 658-673 [PMID: 23729478 DOI: 10.1158/2159-8290.CD-12-0558]

141 **Montagut C**, Dalmases A, Bellosillo B, Crespo M, Pairet S, Iglesias M, Salido M, Gallen M, Marsters S, Tsai SP, Minoche A, Seshagiri S, Serrano S, Himmelbauer H, Bellmunt J, Rovira A, Settleman J, Bosch F, Albanell J. Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer. *Nat Med* 2012; **18**: 221-223 [PMID: 22270724 DOI: 10.1038/nm.2609]

142 **Arnold D**, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, Heinemann V, Van Cutsem E, Pignon JP, Tabernero J, Cervantes A, Ciardiello F. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017; **28**: 1713-1729 [PMID: 28407110 DOI: 10.1093/annonc/mdx175]

143 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342 [PMID: 15175435 DOI: 10.1056/NEJMoa032691]

144 **Saltz LB**, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; **26**: 2013-2019 [PMID: 18421054 DOI: 10.1200/JCO.2007.14.9930]

145 **Macedo LT**, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. *BMC Cancer* 2012; **12**: 89 [PMID: 22414244 DOI: 10.1186/1471-2407-12-89]

146 **Gruenberger T**, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D, Adam R. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2015; **26**: 702-708 [PMID: 25538173 DOI: 10.1093/annonc/mdu580]

147 **Loupakis F**, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014; **371**: 1609-1618 [PMID: 25337750 DOI: 10.1056/NEJMoa1403108]

148 **Heinemann V**, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A, Stintzing S. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15**: 1065-1075 [PMID: 25088940 DOI: 10.1016/S1470-2045(14)70330-4]

149 **Schwartzberg LS**, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS, Go WY. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014; **32**: 2240-2247 [PMID: 24687833 DOI: 10.1200/JCO.2013.53.2473]

150 **Venook AP**, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, Schrag D, Greene C, O'Neil BH, Atkins JN, Berry S, Polite BN, O'Reilly EM, Goldberg RM, Hochster HS, Schilsky RL, Bertagnolli MM, El-Khoueiry AB, Watson P, Benson AB 3rd, Mulkerin DL, Mayer RJ, Blanke C. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. *JAMA* 2017; **317**: 2392-2401 [PMID: 28632865 DOI: 10.1001/jama.2017.7105]

151 **Hecht JR**, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, Deeter R, Shahin S, Amado RG. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 672-680 [PMID: 19114685 DOI: 10.1200/JCO.2008.19.8135]

152 **Tol J**, Koopman M, Rodenburg CJ, Cats A, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, Mol L, Antonini NF, Punt CJ. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Ann Oncol* 2008; **19**: 734-738 [PMID: 18272912 DOI: 10.1093/annonc/mdm607]

153 **Wilhelm SM**, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; **129**: 245-255 [PMID: 21170960 DOI: 10.1002/ijc.25864]

154 **Grothey A**, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 303-312 [PMID: 23177514 DOI: 10.1016/S0140-6736(12)61900-X]

155 **Li J**, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT, Lin JK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015; **16**: 619-629 [PMID: 25981818 DOI: 10.1016/S1470-2045(15)70156-7]

156 **Tournigand C**, Chibaudel B, Samson B, Scheithauer W, Vernerey D, Mésange P, Lledo G, Viret F, Ramée JF, Tubiana-Mathieu N, Dauba J, Dupuis O, Rinaldi Y, Mabro M, Aucoin N, Latreille J, Bonnetain F, Louvet C, Larsen AK, André T, de Gramont A. Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (GERCOR DREAM; OPTIMOX3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2015; **16**: 1493-1505 [PMID: 26474518 DOI: 10.1016/S1470-2045(15)00216-8]

157 **Ducreux M**, Chamseddine A, Laurent-Puig P, Smolenschi C, Hollebecque A, Dartigues P, Samallin E, Boige V, Malka D, Gelli M. Molecular targeted therapy of *BRAF*-mutant colorectal cancer. *Ther Adv Med Oncol* 2019; **11**: 1758835919856494 [PMID: 31244912 DOI: 10.1177/1758835919856494]

158 **Wang Z**, Dai WP, Zang YS. Complete response with fluorouracil and irinotecan with a $BRAF^{V600E}$ and EGFR inhibitor in BRAF-mutated metastatic colorectal cancer: a case report. *Onco Targets Ther* 2019; **12**: 443-447 [PMID: 30662270 DOI: 10.2147/OTT.S180845]

159 **Lee SY**, Oh SC. Advances of Targeted Therapy in Treatment of Unresectable Metastatic Colorectal Cancer. *Biomed Res Int* 2016; **2016**: 7590245 [PMID: 27127793 DOI: 10.1155/2016/7590245]

160 **Tampellini M**, Sonetto C, Scagliotti GV. Novel anti-angiogenic therapeutic strategies in colorectal cancer. *Expert Opin Investig Drugs* 2016; **25**: 507-520 [PMID: 26938715 DOI: 10.1517/13543784.2016.1161754]

161 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016 [PMID: 18358928 DOI: 10.1016/S0140-6736(08)60455-9]

162 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14**: 1208-1215 [PMID: 24120480 DOI: 10.1016/S1470-2045(13)70447-9]

163 **André T**, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; **27**: 3109-3116 [PMID: 19451431 DOI: 10.1200/JCO.2008.20.6771]

164 **Liu W**, Zhou JG, Sun Y, Zhang L, Xing BC. The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: a systematic review and meta-analysis. *Oncotarget* 2016; **7**: 37277-37287 [PMID: 27074564 DOI: 10.18632/oncotarget.8671]

165 **Primrose J**, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, Hornbuckle J, Peterson M, Rees M, Iveson T, Hickish T, Butler R, Stanton L, Dixon E, Little L, Bowers M, Pugh S, Garden OJ, Cunningham D, Maughan T, Bridgewater J. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; **15**: 601-611 [PMID: 24717919 DOI: 10.1016/S1470-2045(14)70105-6]

166 **Adam R**, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Tabernero J, Teh C, Van Cutsem E; Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012; **17**: 1225-1239 [PMID: 22962059 DOI: 10.1634/theoncologist.2012-0121]

167 **Brandi G**, De Lorenzo S, Nannini M, Curti S, Ottone M, Dall'Olio FG, Barbera MA, Pantaleo MA, Biasco G. Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. *World J Gastroenterol* 2016; **22**: 519-533 [PMID: 26811604 DOI: 10.3748/wjg.v22.i2.519]

168 **Portier G**, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, Belghiti J, Piedbois P, Guimbaud R, Nordlinger B, Bugat R, Lazorthes F, Bedenne L. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* 2006; **24**: 4976-4982 [PMID: 17075115 DOI: 10.1200/JCO.2006.06.8353]

169 **Kim SY**, Kim HJ, Hong YS, Jung KH, Park JW, Choi HS, Oh JH, Park SJ, Kim SH, Nam BH, Chang HJ, Kim DY. Resected colorectal liver metastases: does the survival differ according to postoperative chemotherapy regimen? *J Surg Oncol* 2009; **100**: 713-718 [PMID: 19771561 DOI: 10.1002/jso.21403]

170 **Lam VW**, Spiro C, Laurence JM, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. *Ann Surg Oncol* 2012; **19**: 1292-1301 [PMID: 21922338 DOI: 10.1245/s10434-011-2061-0]

171 **Alberts SR**, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, Levitt R, Rowland K, Nair S, Sargent DJ, Donohue JH. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005; **23**: 9243-9249 [PMID: 16230673 DOI: 10.1200/JCO.2005.07.740]

172 **Pozzo C**, Basso M, Cassano A, Quirino M, Schinzari G, Trigila N, Vellone M, Giuliante F, Nuzzo G, Barone C. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004; **15**: 933-939 [PMID: 15151951 DOI: 10.1093/annonc/mdh217]

173 **Tournigand C**, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**: 229-237 [PMID: 14657227 DOI: 10.1200/JCO.2004.05.113]

174 **Ychou M**, Rivoire M, Thezenas S, Quenet F, Delpero JR, Rebischung C, Letoublon C, Guimbaud R, Francois E, Ducreux M, Desseigne F, Fabre JM, Assenat E. A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial. *Ann Surg Oncol* 2013; **20**: 4289-4297 [PMID: 23955585 DOI: 10.1245/s10434-013-3217-x]

175 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]

176 **Wong R**, Cunningham D, Barbachano Y, Saffery C, Valle J, Hickish T, Mudan S, Brown G, Khan A, Wotherspoon A, Strimpakos AS, Thomas J, Compton S, Chua YJ, Chau I. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal

liver-only metastases not selected for upfront resection. *Ann Oncol* 2011; **22**: 2042-2048 [PMID: 21285134 DOI: 10.1093/annonc/mdq714]

177 **Chapelle N**, Matysiak-Budnik T, Douane F, Metairie S, Rougier P, Touchefeu Y. Hepatic arterial infusion in the management of colorectal cancer liver metastasis: Current and future perspectives. *Dig Liver Dis* 2018; **50**: 220-225 [PMID: 29290599 DOI: 10.1016/j.dld.2017.12.004]

178 **Deschamps F**, Elias D, Goere D, Malka D, Ducreux M, Boige V, Auperin A, de Baere T. Intra-arterial hepatic chemotherapy: a comparison of percutaneous versus surgical implantation of port-catheters. *Cardiovasc Intervent Radiol* 2011; **34**: 973-979 [PMID: 20936286 DOI: 10.1007/s00270-010-9996-6]

179 **Rougier P**, Laplanche A, Huguier M, Hay JM, Ollivier JM, Escat J, Salmon R, Julien M, Roullet Audy JC, Gallot D. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol* 1992; **10**: 1112-1118 [PMID: 1296590 DOI: 10.1200/JCO.1992.10.7.1112]

180 **Ducreux M**, Ychou M, Laplanche A, Gamelin E, Lasser P, Husseini F, Quenet F, Viret F, Jacob JH, Boige V, Elias D, Delperro JR, Luboinski M; gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol* 2005; **23**: 4881-4887 [PMID: 16009952 DOI: 10.1200/JCO.2005.05.120]

181 **Lévi FA**, Boige V, Hebbar M, Smith D, Lepère C, Focan C, Karaboué A, Guimbaud R, Carvalho C, Tumolo S, Innominato P, Ajavon Y, Truant S, Castaing D, De Baere T, Kunstlinger F, Bouchahda M, Afshar M, Rougier P, Adam R, Ducreux M; Association Internationale pour Recherche sur Temps Biologique et Chronothérapie (ARTBC International). Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV. *Ann Oncol* 2016; **27**: 267-274 [PMID: 26578731 DOI: 10.1093/annonc/mdv548]

182 **Groot Koerkamp B**, Sadot E, Kemeny NE, Gönen M, Leal JN, Allen PJ, Cercek A, DeMatteo RP, Kingham TP, Jarnagin WR, D'Angelica MI. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017; **35**: 1938-1944 [PMID: 28426374 DOI: 10.1200/JCO.2016.71.8346]

183 **Kemeny N**, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, Bertino JR, Turnbull AD, Sullivan D, Stockman J, Blumgart LH, Fong Y. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341**: 2039-2048 [PMID: 10615075 DOI: 10.1056/NEJM199912303412702]

184 **Mitry E**, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, Nitti D, Torri V, Elias D, O'Callaghan C, Langer B, Martignoni G, Bouché O, Lazorthes F, Van Cutsem E, Bedenne L, Moore MJ, Rougier P. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; **26**: 4906-4911 [PMID: 18794541 DOI: 10.1200/JCO.2008.17.3781]

185 **Buisman FE**, Homs MYV, Grünhagen DJ, Filipe WF, Bennink RJ, Besselink MGH, Borel Rinkes IHM, Bruijnen RCG, Cercek A, D'Angelica MI, van Delden OM, Donswijk ML, van Doorn L, Doornebosch PG, Emmering J, Erdmann JI, IJzerman NS, Grootscholten C, Hagendoorn J, Kemeny NE, Kingham TP, Klompenhouwer EG, Kok NFM, Koolen S, Kuhlmann KFD, Kuiper MC, Lam MGE, Mathijssen RHJ, Moelker A, Oomen-de Hoop E, Punt CJA, Te Riele WW, Roodhart JML, Swijnenburg RJ, Prevoo W, Tanis PJ, Vermaas M, Versleijen MWJ, Veuger FP, Weterman MJ, Verhoef C, Groot Koerkamp B. Adjuvant hepatic arterial infusion pump chemotherapy and resection versus resection alone in patients with low-risk resectable colorectal liver metastases - the multicenter randomized controlled PUMP trial. *BMC Cancer* 2019; **19**: 327 [PMID: 30953467 DOI: 10.1186/s12885-019-5515-6]

186 **Lewis AL**, Hall B. Toward a better understanding of the mechanism of action for intra-arterial delivery of irinotecan from DC Bead$^{(TM)}$ (DEBIRI). *Future Oncol* 2019; **15**: 2053-2068 [PMID: 30942614 DOI: 10.2217/fon-2019-0071]

187 **Akinwande O**, Dendy M, Ludwig JM, Kim HS. Hepatic intra-arterial injection of irinotecan drug eluting beads (DEBIRI) for patients with unresectable colorectal liver metastases: A systematic review. *Surg Oncol* 2017; **26**: 268-275 [PMID: 28807246 DOI: 10.1016/j.suronc.2017.05.003]

188 **Martin RC 2nd**, Scoggins CR, Schreeder M, Rilling WS, Laing CJ, Tatum CM, Kelly LR, Garcia-Monaco RD, Sharma VR, Crocenzi TS, Strasberg SM. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. *Cancer* 2015; **121**: 3649-3658 [PMID: 26149602 DOI: 10.1002/cncr.29534]

189 **Fiorentini G**, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V, Coschiera P. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. *Anticancer Res* 2012; **32**: 1387-1395 [PMID: 22493375]

190 **Breedis C**, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; **30**: 969-977 [PMID: 13197542]

191 **Ackerman NB**. Experimental studies on the circulation dynamics of intrahepatic tumor blood supply. *Cancer* 1972; **29**: 435-439 [PMID: 5013543 DOI: 10.1002/1097-0142(197202)29:2<435::aid-cncr2820290227>3.0.co;2-k]

192 **Bozkurt MF**, Salanci BV, Uğur Ö. Intra-Arterial Radionuclide Therapies for Liver Tumors. *Semin Nucl Med* 2016; **46**: 324-339 [PMID: 27237442 DOI: 10.1053/j.semnuclmed.2016.01.008]

193 **Campbell AM**, Bailey IH, Burton MA. Tumour dosimetry in human liver following hepatic yttrium-90 microsphere therapy. *Phys Med Biol* 2001; **46**: 487-498 [PMID: 11229728 DOI: 10.1088/0031-9155/46/2/315]

194 **Klaassen NJM**, Arntz MJ, Gil Arranja A, Roosen J, Nijsen JFW. The various therapeutic applications of the medical isotope holmium-166: a narrative review. *EJNMMI Radiopharm Chem* 2019; **4**: 19 [PMID: 31659560 DOI: 10.1186/s41181-019-0066-3]

195 **van Hazel GA**, Pavlakis N, Goldstein D, Olver IN, Tapner MJ, Price D, Bower GD, Briggs GM, Rossleigh MA, Taylor DJ, George J. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. *J Clin Oncol* 2009; **27**: 4089-4095 [PMID: 19652069 DOI: 10.1200/JCO.2008.20.8116]

196 **Hendlisz A**, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, De Keukeleire K, Verslype C, Defreyne L, Van Cutsem E, Delatte P, Delaunoit T, Personeni N, Paesmans M, Van Laethem JL, Flamen P. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol* 2010; **28**: 3687-3694 [PMID: 20567019 DOI: 10.1200/JCO.2010.28.5643]

197 **Cosimelli M**, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, Mancini R, Sperduti I, Pizzi G, Diodoro MG, Perrone M, Giampalma E, Angelelli B, Fiore F, Lastoria S, Bacchetti S, Gasperini D, Geatti O, Izzo F; Italian Society of Locoregional Therapies in Oncology (SITILO). Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. *Br J Cancer* 2010; **103**: 324-331 [PMID: 20628388 DOI: 10.1038/sj.bjc.6605770]

198 **Seidensticker R**, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, Kettner E, Hildebrandt B, Dudeck O, Pech M, Amthauer H, Ricke J. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol* 2012; **35**: 1066-1073 [PMID: 21800231 DOI: 10.1007/s00270-011-0234-7]

199 **Kennedy A**, Cohn M, Coldwell DM, Drooz A, Ehrenwald E, Kaiser A, Nutting CW, Rose SC, Wang EA, Savin MA. Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. *J Gastrointest Oncol* 2017; **8**: 614-624 [PMID: 28890810 DOI: 10.21037/jgo.2017.03.10]

200 **van Hazel GA**, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, Perez D, Robinson BA, Strickland AH, Ferguson T, Rodríguez J, Kröning H, Wolf I, Ganju V, Walpole E, Boucher E, Tichler T, Shacham-Shmueli E, Powell A, Eliadis P, Isaacs R, Price D, Moeslein F, Taieb J, Bower G, Gebski V, Van Buskirk M, Cade DN, Thurston K, Gibbs P. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. *J Clin Oncol* 2016; **34**: 1723-1731 [PMID: 26903575 DOI: 10.1200/JCO.2015.66.1181]

201 **Dutton SJ**, Kenealy N, Love SB, Wasan HS, Sharma RA; FOXFIRE Protocol Development Group and the NCRI Colorectal Clinical Study Group. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. *BMC Cancer* 2014; **14**: 497 [PMID: 25011439 DOI: 10.1186/1471-2407-14-497]

202 **Sharma RA**, Wasan HS, Love SB, Dutton S, Stokes JC, Smith JL; FOXFIRE Trial Management Group. FOXFIRE: a phase III clinical trial of chemo-radio-embolisation as first-line treatment of liver metastases in patients with colorectal cancer. *Clin Oncol (R Coll Radiol)* 2008; **20**: 261-263 [PMID: 18222657 DOI: 10.1016/j.clon.2007.12.008]

203 **Wasan HS**, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, Peeters M, Findlay M, Weaver A, Mills J, Wilson C, Adams R, Francis A, Moschandreas J, Virdee PS, Dutton P, Love S, Gebski V, Gray A; FOXFIRE trial investigators; SIRFLOX trial investigators; FOXFIRE-Global trial investigators, van Hazel G, Sharma RA. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 2017; **18**: 1159-1171 [PMID: 28781171 DOI: 10.1016/S1470-2045(17)30457-6]

204 **Gibbs P**, Heinemann V, Sharma NK, Taieb J, Ricke J, Peeters M, Findlay M, Robinson B, Jackson C, Strickland A, Gebski V, Van Buskirk M, Zhao H, van Hazel G; SIRFLOX and FOXFIRE Global Trial Investigators. Effect of Primary Tumor Side on Survival Outcomes in Untreated Patients With Metastatic Colorectal Cancer When Selective Internal Radiation Therapy Is Added to Chemotherapy: Combined Analysis of Two Randomized Controlled Studies. *Clin Colorectal Cancer* 2018; **17**: e617-e629 [PMID: 30033117 DOI: 10.1016/j.clcc.2018.06.001]

205 **White J**, Carolan-Rees G, Dale M, Morgan HE, Patrick HE, See TC, Beeton EL, Swinson DEB, Bell JK, Manas DM, Crellin A, Slevin NJ, Sharma RA. Analysis of a National Programme for Selective Internal Radiation Therapy for Colorectal Cancer Liver Metastases. *Clin Oncol (R Coll Radiol)* 2019; **31**: 58-66 [PMID: 30297164 DOI: 10.1016/j.clon.2018.09.002]

206 **NHS England Specialised Services Clinical Reference Group for Radiotherapy**. Clinical Commissioning Policy: Selective internal radiation therapy (SIRT) for chemotherapy refractory / intolerant metastatic colorectal cancer (adults) [Internet]. [cited 2020 Jan 26]; Available from: https://www.england.nhs.uk/wp-content/uploads/2018/12/Selective-internal-radiation-therapy-for-chemotherapy-refractory-intolerant-metastatic-colorectal-cancer.pdf

207 **Ruers T**, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, Poston G, Bechstein W, Lentz MA, Mauer M, Folprecht G, Van Cutsem E, Ducreux M, Nordlinger B; European Organisation for Research and Treatment of Cancer (EORTC); Gastro-Intestinal Tract Cancer Group; Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *J Natl Cancer Inst* 2017; **109** [PMID: 28376151 DOI: 10.1093/jnci/djx015]

208 **Petrelli F**, Comito T, Barni S, Pancera G, Scorsetti M, Ghidini A; SBRT for CRC liver metastases. Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. *Radiother Oncol* 2018; **129**: 427-434 [PMID: 29997034 DOI: 10.1016/j.radonc.2018.06.035]

209 **Grigorian A**, O'Brien CB. Hepatotoxicity Secondary to Chemotherapy. *J Clin Transl Hepatol* 2014; **2**: 95-102 [PMID: 26357620 DOI: 10.14218/JCTH.2014.00011]

210 **Méndez Romero A**, Keskin-Cambay F, van Os RM, Nuyttens JJ, Heijmen BJM, IJzermans JNM, Verhoef C. Institutional experience in the treatment of colorectal liver metastases with stereotactic body radiation therapy. *Rep Pract Oncol Radiother* 2017; **22**: 126-131 [PMID: 28490983 DOI: 10.1016/j.rpor.2016.10.003]

211 **Joo JH**, Park JH, Kim JC, Yu CS, Lim SB, Park IJ, Kim TW, Hong YS, Kim KP, Yoon SM, Park J, Kim JH. Local Control Outcomes Using Stereotactic Body Radiation Therapy for Liver Metastases from Colorectal Cancer. *Int J Radiat Oncol Biol Phys* 2017; **99**: 876-883 [PMID: 29063852 DOI: 10.1016/j.ijrobp.2017.07.030]

212 **Chang DT**, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, Dinniwell R, Brierley J, Kavanagh BD, Dawson LA, Schefter TE. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer* 2011; **117**: 4060-4069 [PMID: 21432842 DOI: 10.1002/cncr.25997]

213 **McPartlin A**, Swaminath A, Wang R, Pintilie M, Brierley J, Kim J, Ringash J, Wong R, Dinniwell R, Craig T, Dawson LA. Long-Term Outcomes of Phase 1 and 2 Studies of SBRT for Hepatic Colorectal Metastases. *Int J Radiat Oncol Biol Phys* 2017; **99**: 388-395 [PMID: 28871989 DOI: 10.1016/j.ijrobp.2017.04.010]

214 **Scorsetti M**, Comito T, Clerici E, Franzese C, Tozzi A, Iftode C, Di Brina L, Navarria P, Mancosu P, Reggiori G, Fogliata A, Tomatis S, Torzilli G, Cozzi L. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. *Radiat Oncol* 2018; **13**: 234 [PMID: 30477560 DOI: 10.1186/s13014-018-1185-9]

215 **Servagi S**, UNICANCER. Oligometastases of the LIVer Treated With Chemotherapy With ou Without Extracranial Stereotactic Body Radiation Therapy in Patients With Colorectal Cancer - Full Text View - ClinicalTrials.gov [Internet]. [cited 2020 Jan 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT03532204

216 **Hoyer M**, Danish Center for Interventional Research in Radiation Oncology. Radiofrequency Ablation Versus Stereotactic Radiotherapy in Colorectal Liver Metastases - Full Text View - ClinicalTrials.gov [Internet]. [cited 2020 Jan 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT01233544

217 **Robertson EG**, Baxter G. Tumour seeding following percutaneous needle biopsy: the real story! *Clin Radiol* 2011; **66**: 1007-1014 [PMID: 21784421 DOI: 10.1016/j.crad.2011.05.012]

218 **Rodgers MS**, Collinson R, Desai S, Stubbs RS, McCall JL. Risk of dissemination with biopsy of colorectal liver metastases. *Dis Colon Rectum* 2003; **46**: 454-8; discussion 458-9 [PMID: 12682536 DOI: 10.1007/s10350-004-6581-6]

219 **Ohlsson B**, Nilsson J, Stenram U, Akerman M, Tranberg KG. Percutaneous fine-needle aspiration cytology in the diagnosis and management of liver tumours. *Br J Surg* 2002; **89**: 757-762 [PMID: 12027987 DOI: 10.1046/j.1365-2168.2002.02111.x]

220 **Jones OM**, Rees M, John TG, Bygrave S, Plant G. Biopsy of resectable colorectal liver metastases causes tumour dissemination and adversely affects survival after liver resection. *Br J Surg* 2005; **92**: 1165-1168 [PMID: 15997444 DOI: 10.1002/bjs.4888]

221 **Metcalfe MS**, Bridgewater FH, Mullin EJ, Maddern GJ. Useless and dangerous--fine needle aspiration of hepatic colorectal metastases. *BMJ* 2004; **328**: 507-508 [PMID: 14988193 DOI: 10.1136/bmj.328.7438.507]

222 **Moris D**, Ronnekleiv-Kelly S, Rahnemai-Azar AA, Felekouras E, Dillhoff M, Schmidt C, Pawlik TM. Parenchymal-Sparing Versus Anatomic Liver Resection for Colorectal Liver Metastases: a Systematic Review. *J Gastrointest Surg* 2017; **21**: 1076-1085 [PMID: 28364212 DOI: 10.1007/s11605-017-3397-y]

223 **Andreou A**, Aloia TA, Brouquet A, Dickson PV, Zimmitti G, Maru DM, Kopetz S, Loyer EM, Curley SA, Abdalla EK, Vauthey JN. Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. *Ann Surg* 2013; **257**: 1079-1088 [PMID: 23426338 DOI: 10.1097/SLA.0b013e318283a4d1]

224 **Hamady ZZ**, Lodge JP, Welsh FK, Toogood GJ, White A, John T, Rees M. One-millimeter cancer-free margin is curative for colorectal liver metastases: a propensity score case-match approach. *Ann Surg* 2014; **259**: 543-548 [PMID: 23732261 DOI: 10.1097/SLA.0b013e3182902b6e]

225 **de Haas RJ**, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg* 2008; **248**: 626-637 [PMID: 18936576 DOI: 10.1097/SLA.0b013e31818a07f1]

226 **Carpizo DR**, Are C, Jarnagin W, Dematteo R, Fong Y, Gönen M, Blumgart L, D'Angelica M. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. *Ann Surg Oncol* 2009; **16**: 2138-2146 [PMID: 19495884 DOI: 10.1245/s10434-009-0521-6]

227 **Carpizo DR**, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. *Lancet Oncol* 2009; **10**: 801-809 [PMID: 19647200 DOI: 10.1016/S1470-2045(09)70081-6]

228 **Adam R**, de Haas RJ, Wicherts DA, Aloia TA, Delvart V, Azoulay D, Bismuth H, Castaing D. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? *J Clin Oncol* 2008; **26**: 3672-3680 [PMID: 18669451 DOI: 10.1200/JCO.2007.15.7297]

229 **Andres A**, Mentha G, Adam R, Gerstel E, Skipenko OG, Barroso E, Lopez-Ben S, Hubert C, Majno PE, Toso C. Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases. *Br J Surg* 2015; **102**: 691-699 [PMID: 25789941 DOI: 10.1002/bjs.9783]

230 **Sánchez-Hidalgo JM**, Rodríguez-Ortiz L, Arjona-Sánchez Á, Rufián-Peña S, Casado-Adam Á, Cosano-Álvarez A, Briceño-Delgado J. Colorectal peritoneal metastases: Optimal management review. *World J Gastroenterol* 2019; **25**: 3484-3502 [PMID: 31367152 DOI: 10.3748/wjg.v25.i27.3484]

231 **Dagher I**, O'Rourke N, Geller DA, Cherqui D, Belli G, Gamblin TC, Lainas P, Laurent A, Nguyen KT, Marvin MR, Thomas M, Ravindra K, Fielding G, Franco D, Buell JF. Laparoscopic major hepatectomy: an evolution in standard of care. *Ann Surg* 2009; **250**: 856-860 [PMID: 19806057 DOI: 10.1097/SLA.0b013e3181bcaf46]

232 **Bryant R**, Laurent A, Tayar C, Cherqui D. Laparoscopic liver resection-understanding its role in current practice: the Henri Mondor Hospital experience. *Ann Surg* 2009; **250**: 103-111 [PMID: 19561476 DOI: 10.1097/SLA.0b013e3181ad6660]

233 **Melandro F**, Giovanardi F, Hassan R, Larghi Laureiro Z, Ferri F, Rossi M, Mennini G, Pawlik TM, Lai Q. Minimally Invasive Approach in the Setting of ALPPS Procedure: a Systematic Review of the Literature. *J Gastrointest Surg* 2019; **23**: 1917-1924 [PMID: 31197682 DOI: 10.1007/s11605-018-04092-x]

234 **Samstein B**, Cherqui D, Rotellar F, Griesemer A, Halazun KJ, Kato T, Guarrera J, Emond JC. Totally laparoscopic full left hepatectomy for living donor liver transplantation in adolescents and adults. *Am J Transplant* 2013; **13**: 2462-2466 [PMID: 24034709 DOI: 10.1111/ajt.12360]

235 **Soubrane O**, Perdigao Cotta F, Scatton O. Pure laparoscopic right hepatectomy in a living donor. *Am J Transplant* 2013; **13**: 2467-2471 [PMID: 23865716 DOI: 10.1111/ajt.12361]

236 **Wakabayashi G**, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, Asbun H, O'Rourke N, Tanabe M, Koffron AJ, Tsung A, Soubrane O, Machado MA, Gayet B, Troisi RI, Pessaux P, Van Dam RM, Scatton O, Abu Hilal M, Belli G, Kwon CH, Edwin B, Choi GH, Aldrighetti LA, Cai X, Cleary S, Chen KH, Schön MR, Sugioka A, Tang CN, Herman P, Pekolj J, Chen XP, Dagher I, Jarnagin W, Yamamoto M, Strong R, Jagannath P, Lo CM, Clavien PA, Kokudo N, Barkun J, Strasberg SM. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015; **261**: 619-629 [PMID: 25742461 DOI: 10.1097/SLA.0000000000001184]

237 **Fretland ÅA**, Dagenborg VJ, Bjørnelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW, Hausken J, Tønnessen TI, Abildgaard A, Barkhatov L, Yaqub S, Røsok BI, Bjørnbeth BA, Andersen MH, Flatmark K, Aas E, Edwin B. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. *Ann Surg* 2018; **267**: 199-207 [PMID: 28657937 DOI: 10.1097/SLA.0000000000002353]

238 **Wong-Lun-Hing EM**, van Dam RM, van Breukelen GJ, Tanis PJ, Ratti F, van Hillegersberg R, Slooter GD, de Wilt JH, Liem MS, de Boer MT, Klaase JM, Neumann UP, Aldrighetti LA, Dejong CH; ORANGE II Collaborative Group. Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study). *Br J Surg* 2017; **104**: 525-535 [PMID: 28138958 DOI: 10.1002/bjs.10438]

239 **Troisi RI**, Pegoraro F, Giglio MC, Rompianesi G, Berardi G, Tomassini F, De Simone G, Aprea G, Montalti R, De Palma GD. Robotic approach to the liver: Open surgery in a closed abdomen or laparoscopic surgery with technical constraints? *Surg Oncol* 2020; **33**: 239-248 [PMID: 31759794 DOI: 10.1016/j.suronc.2019.10.012]

240 **Sheen AJ**, Jamdar S, Siriwardena AK. Laparoscopic Hepatectomy for Colorectal Liver Metastases: The Current State of the Art. *Front Oncol* 2019; **9**: 442 [PMID: 31214497 DOI: 10.3389/fonc.2019.00442]

241 **van den Broek MA**, Olde Damink SW, Dejong CH, Lang H, Malagó M, Jalan R, Saner FH. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int* 2008; **28**: 767-780 [PMID: 18647141 DOI: 10.1111/j.1478-3231.2008.01777.x]

242 **Nagashima I**, Takada T, Okinaga K, Nagawa H. A scoring system for the assessment of the risk of mortality after partial hepatectomy in patients with chronic liver dysfunction. *J Hepatobiliary Pancreat Surg* 2005; **12**: 44-48 [PMID: 15754099 DOI: 10.1007/s00534-004-0953-0]

243 **Schroeder RA**, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; **243**: 373-379 [PMID: 16495703 DOI: 10.1097/01.SLA.0000201483.95911.08]

244 **Bennink RJ**, Dinant S, Erdogan D, Heijnen BH, Straatsburg IH, van Vliet AK, van Gulik TM. Preoperative assessment of postoperative remnant liver function using hepatobiliary scintigraphy. *J Nucl Med* 2004; **45**: 965-971 [PMID: 15181131]

245 **Dinant S**, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, van Vliet AK, van Gulik TM. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. *J Nucl Med* 2007; **48**: 685-692 [PMID: 17475954 DOI: 10.2967/jnumed.106.038430]

246 **Paumgartner G**. The handling of indocyanine green by the liver. *Schweiz Med Wochenschr* 1975; **105**: 1-30 [PMID: 1135620]

247 **Levesque E**, Martin E, Dudau D, Lim C, Dhonneur G, Azoulay D. Current use and perspective of indocyanine green clearance in liver diseases. *Anaesth Crit Care Pain Med* 2016; **35**: 49-57 [PMID: 26477363 DOI: 10.1016/j.accpm.2015.06.006]

248 **Wakiya T**, Kudo D, Toyoki Y, Ishido K, Kimura N, Narumi S, Kijima H, Hakamada K. Evaluation of the usefulness of the indocyanine green clearance test for chemotherapy-associated liver injury in patients with colorectal cancer liver metastasis. *Ann Surg Oncol* 2014; **21**: 167-172 [PMID: 23959055 DOI: 10.1245/s10434-013-3203-3]

249 **Yokoyama Y**, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg* 2010; **97**: 1260-1268 [PMID: 20602507 DOI: 10.1002/bjs.7084]

250 **Mizutani Y**, Hirai T, Nagamachi S, Nanashima A, Yano K, Kondo K, Hiyoshi M, Imamura N, Terada T. Prediction of Posthepatectomy Liver Failure Proposed by the International Study Group of Liver Surgery: Residual Liver Function Estimation With 99mTc-Galactosyl Human Serum Albumin Scintigraphy. *Clin Nucl Med* 2018; **43**: 77-81 [PMID: 29232242 DOI: 10.1097/RLU.0000000000001913]

251 **Rassam F**, Olthof PB, Bennink RJ, van Gulik TM. Current Modalities for the Assessment of Future Remnant Liver Function. *Visc Med* 2017; **33**: 442-448 [PMID: 29344518 DOI: 10.1159/000480385]

252 **de Graaf W**, van Lienden KP, Dinant S, Roelofs JJ, Busch OR, Gouma DJ, Bennink RJ, van Gulik TM. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg* 2010; **14**: 369-378 [PMID: 19937195 DOI: 10.1007/s11605-009-1085-2]

253 **Chapelle T**, Op De Beeck B, Huyghe I, Francque S, Driessen A, Roeyen G, Ysebaert D, De Greef K. Future remnant liver function estimated by combining liver volumetry on magnetic resonance imaging with total liver function on (99m)Tc-mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure? *HPB (Oxford)* 2016; **18**: 494-503 [PMID: 27317953 DOI: 10.1016/j.hpb.2015.08.002]

254 **Cieslak KP**, Bennink RJ, de Graaf W, van Lienden KP, Besselink MG, Busch OR, Gouma DJ, van Gulik

TM. Measurement of liver function using hepatobiliary scintigraphy improves risk assessment in patients undergoing major liver resection. *HPB (Oxford)* 2016; **18**: 773-780 [PMID: 27593595 DOI: 10.1016/j.hpb.2016.06.006]

255 **Chapelle T**, Op de Beeck B, Roeyen G, Bracke B, Hartman V, De Greef K, Huyghe I, Van der Zijden T, Morrison S, Francque S, Ysebaert D. Measuring future liver remnant function prior to hepatectomy may guide the indication for portal vein occlusion and avoid posthepatectomy liver failure: a prospective interventional study. *HPB (Oxford)* 2017; **19**: 108-117 [PMID: 27956027 DOI: 10.1016/j.hpb.2016.11.005]

256 **Cieslak KP**, Huisman F, Bais T, Bennink RJ, van Lienden KP, Verheij J, Besselink MG, Busch ORC, van Gulik TM. Future remnant liver function as predictive factor for the hypertrophy response after portal vein embolization. *Surgery* 2017; **162**: 37-47 [PMID: 28365007 DOI: 10.1016/j.surg.2016.12.031]

257 **Olthof PB**, Tomassini F, Huespe PE, Truant S, Pruvot FR, Troisi RI, Castro C, Schadde E, Axelsson R, Sparrelid E, Bennink RJ, Adam R, van Gulik TM, de Santibanes E. Hepatobiliary scintigraphy to evaluate liver function in associating liver partition and portal vein ligation for staged hepatectomy: Liver volume overestimates liver function. *Surgery* 2017; **162**: 775-783 [PMID: 28732555 DOI: 10.1016/j.surg.2017.05.022]

258 **Truant S**. Hepato Biliary Scintigraphy to Assess the Risk of Postoperative Liver Failure Hepatectomies - Full Text View - ClinicalTrials.gov [Internet]. [cited 2020 Jan 16]. Available from: https://clinicaltrials.gov/ct2/show/NCT02753517

259 **Chua TC**, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. *Ann Surg Oncol* 2010; **17**: 492-501 [PMID: 19856028 DOI: 10.1245/s10434-009-0781-1]

260 **Benoist S**, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, Mitry E, Rougier P, Nordlinger B. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006; **24**: 3939-3945 [PMID: 16921046 DOI: 10.1200/JCO.2006.05.8727]

261 **van Vledder MG**, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *J Gastrointest Surg* 2010; **14**: 1691-1700 [PMID: 20839072 DOI: 10.1007/s11605-010-1348-y]

262 **Tanaka K**, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. *Ann Surg* 2009; **250**: 935-942 [PMID: 19953712 DOI: 10.1097/SLA.0b013e3181b0c6e4]

263 **Araujo RLC**, Milani JM, Armentano DP, Moreira RB, Pinto GSF, de Castro LA, Lucchesi FR. Disappearing colorectal liver metastases: Strategies for the management of patients achieving a radiographic complete response after systemic chemotherapy. *J Surg Oncol* 2020; **121**: 848-856 [PMID: 31773747 DOI: 10.1002/jso.25784]

264 **Adam R**, Wicherts DA, de Haas RJ, Aloia T, Lévi F, Paule B, Guettier C, Kunstlinger F, Delvart V, Azoulay D, Castaing D. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? *J Clin Oncol* 2008; **26**: 1635-1641 [PMID: 18375892 DOI: 10.1200/JCO.2007.13.7471]

265 **Tsilimigras DI**, Ntanasis-Stathopoulos I, Paredes AZ, Moris D, Gavriatopoulou M, Cloyd JM, Pawlik TM. Disappearing liver metastases: A systematic review of the current evidence. *Surg Oncol* 2019; **29**: 7-13 [PMID: 31196496 DOI: 10.1016/j.suronc.2019.02.005]

266 **Kepenekian V**, Muller A, Valette PJ, Rousset P, Chauvenet M, Phelip G, Walter T, Adham M, Glehen O, Passot G. Evaluation of a strategy using pretherapeutic fiducial marker placement to avoid missing liver metastases. *BJS Open* 2019; **3**: 344-353 [PMID: 31183451 DOI: 10.1002/bjs5.50140]

267 **de Santibañes E**, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. *Ann Surg* 2012; **255**: 415-417 [PMID: 22330039 DOI: 10.1097/SLA.0b013e318248577d]

268 **van Lienden KP**, van den Esschert JW, de Graaf W, Bipat S, Lameris JS, van Gulik TM, van Delden OM. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol* 2013; **36**: 25-34 [PMID: 22806245 DOI: 10.1007/s00270-012-0440-y]

269 **Nagino M**. Fifty-year history of biliary surgery. *Ann Gastroenterol Surg* 2019; **3**: 598-605 [PMID: 31788648 DOI: 10.1002/ags3.12289]

270 **Makuuchi M**, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunvén P, Yamazaki S, Hasegawa H, Ozaki H. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 1990; **107**: 521-527 [PMID: 2333592]

271 **Kinoshita H**, Sakai K, Iwasa R, Hirohashi K, Kubo S, Fujio N, Lee KC. Results of preoperative portal vein embolization for hepatocellular carcinoma. *Osaka City Med J* 1988; **34**: 115-122 [PMID: 2853317]

272 **Goéré D**, Farges O, Leporrier J, Sauvanet A, Vilgrain V, Belghiti J. Chemotherapy does not impair hypertrophy of the left liver after right portal vein obstruction. *J Gastrointest Surg* 2006; **10**: 365-370 [PMID: 16504881 DOI: 10.1016/j.gassur.2005.09.001]

273 **Pommier R**, Ronot M, Cauchy F, Gaujoux S, Fuks D, Faivre S, Belghiti J, Vilgrain V. Colorectal liver metastases growth in the embolized and non-embolized liver after portal vein embolization: influence of initial response to induction chemotherapy. *Ann Surg Oncol* 2014; **21**: 3077-3083 [PMID: 24743912 DOI: 10.1245/s10434-014-3700-z]

274 **van Gulik TM**, van den Esschert JW, de Graaf W, van Lienden KP, Busch OR, Heger M, van Delden OM, Laméris JS, Gouma DJ. Controversies in the use of portal vein embolization. *Dig Surg* 2008; **25**: 436-444 [PMID: 19212116 DOI: 10.1159/000184735]

275 **Cauchy F**, Aussilhou B, Dokmak S, Fuks D, Gaujoux S, Farges O, Faivre S, Lepillé D, Belghiti J. Reappraisal of the risks and benefits of major liver resection in patients with initially unresectable colorectal liver metastases. *Ann Surg* 2012; **256**: 746-52; discussion 752-4 [PMID: 23095618 DOI: 10.1097/SLA.0b013e3182738204]

276 **Adam R**, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000; **232**: 777-785 [PMID: 11088072 DOI: 10.1097/00000658-200012000-00006]

277 **Schnitzbauer AA**, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Hörbelt R, Kroemer A, Loss M, Rümmele P, Scherer MN, Padberg W, Königsrainer A, Lang H, Obed A, Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012; **255**: 405-414 [PMID: 22330038 DOI: 10.1097/SLA.0b013e31824856f5]

278 **Wigmore SJ**. ALPPS: The argument against. *Eur J Surg Oncol* 2017; **43**: 249-251 [PMID: 28007323 DOI: 10.1016/j.ejso.2016.11.009]

279 **Buac S**, Schadde E, Schnitzbauer AA, Vogt K, Hernandez-Alejandro R. The many faces of ALPPS: surgical indications and techniques among surgeons collaborating in the international registry. *HPB (Oxford)* 2016; **18**: 442-448 [PMID: 27154808 DOI: 10.1016/j.hpb.2016.01.547]

280 **Sandström P**, Røsok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G, Schultz NA, Bjørnbeth BA, Isaksson B, Rizell M, Björnsson B. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). *Ann Surg* 2018; **267**: 833-840 [PMID: 28902669 DOI: 10.1097/SLA.0000000000002511]

281 **Eshmuminov D**, Raptis DA, Linecker M, Wirsching A, Lesurtel M, Clavien PA. Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy. *Br J Surg* 2016; **103**: 1768-1782 [PMID: 27633328 DOI: 10.1002/bjs.10290]

282 **Petrowsky H**, Györi G, de Oliveira M, Lesurtel M, Clavien PA. Is partial-ALPPS safer than ALPPS? A single-center experience. *Ann Surg* 2015; **261**: e90-e92 [PMID: 25706390 DOI: 10.1097/SLA.0000000000001087]

283 **Linecker M**, Stavrou GA, Oldhafer KJ, Jenner RM, Seifert B, Lurje G, Bednarsch J, Neumann U, Capobianco I, Nadalin S, Robles-Campos R, de Santibañes E, Malagó M, Lesurtel M, Clavien PA, Petrowsky H. The ALPPS Risk Score: Avoiding Futile Use of ALPPS. *Ann Surg* 2016; **264**: 763-771 [PMID: 27455156 DOI: 10.1097/SLA.0000000000001914]

284 **Chow FC**, Chok KS. Colorectal liver metastases: An update on multidisciplinary approach. *World J Hepatol* 2019; **11**: 150-172 [PMID: 30820266 DOI: 10.4254/wjh.v11.i2.150]

285 **Guenette JP**, Dupuy DE. Radiofrequency ablation of colorectal hepatic metastases. *J Surg Oncol* 2010; **102**: 978-987 [PMID: 21166002 DOI: 10.1002/jso.21658]

286 **Ruers T**, Punt C, Van Coevorden F, Pierie JP, Borel-Rinkes I, Ledermann JA, Poston G, Bechstein W, Lentz MA, Mauer M, Van Cutsem E, Lutz MP, Nordlinger B; EORTC Gastro-Intestinal Tract Cancer Group, Arbeitsgruppe Lebermetastasen und—tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO) and the National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol* 2012; **23**: 2619-2626 [PMID: 22431703 DOI: 10.1093/annonc/mds053]

287 **Weng M**, Zhang Y, Zhou D, Yang Y, Tang Z, Zhao M, Quan Z, Gong W. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. *PLoS One* 2012; **7**: e45493 [PMID: 23029051 DOI: 10.1371/journal.pone.0045493]

288 **van Amerongen MJ**, Jenniskens SFM, van den Boezem PB, Fütterer JJ, de Wilt JHW. Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis. *HPB (Oxford)* 2017; **19**: 749-756 [PMID: 28687147 DOI: 10.1016/j.hpb.2017.05.011]

289 **Kron P**, Linecker M, Jones RP, Toogood GJ, Clavien PA, Lodge JPA. Ablation or Resection for Colorectal Liver Metastases? A Systematic Review of the Literature. *Front Oncol* 2019; **9**: 1052 [PMID: 31750233 DOI: 10.3389/fonc.2019.01052]

290 **Chen MS**, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; **243**: 321-328 [PMID: 16495695 DOI: 10.1097/01.SLA.0000201480.65519.b8]

291 **Berber E**, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Ann Surg Oncol* 2008; **15**: 2757-2764 [PMID: 18618182 DOI: 10.1245/s10434-008-0043-7]

292 **Hur H**, Ko YT, Min BS, Kim KS, Choi JS, Sohn SK, Cho CH, Ko HK, Lee JT, Kim NK. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. *Am J Surg* 2009; **197**: 728-736 [PMID: 18789428 DOI: 10.1016/j.amjsurg.2008.04.013]

293 **Ko S**, Jo H, Yun S, Park E, Kim S, Seo HI. Comparative analysis of radiofrequency ablation and resection for resectable colorectal liver metastases. *World J Gastroenterol* 2014; **20**: 525-531 [PMID: 24574721 DOI: 10.3748/wjg.v20.i2.525]

294 **Aloia TA**, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, Curley SA, Zorzi D, Abdalla EK. Solitary colorectal liver metastasis: resection determines outcome. *Arch Surg* 2006; **141**: 460-6; discussion 466-7 [PMID: 16702517 DOI: 10.1001/archsurg.141.5.460]

295 **Aliyev S**, Agcaoglu O, Aksoy E, Taskin HE, Vogt D, Fung J, Siperstein A, Berber E. Efficacy of laparoscopic radiofrequency ablation for the treatment of patients with small solitary colorectal liver metastasis. *Surgery* 2013; **154**: 556-562 [PMID: 23859307 DOI: 10.1016/j.surg.2013.03.009]

296 **Mulier S**, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg* 2005; **242**: 158-171 [PMID: 16041205 DOI: 10.1097/01.SLA.0000171032.99149.fe]

297 **Hubert C**, Gras J, Goffette P, Grajeda JM, Van Beers BE, Laurence A, Horsmans Y, Sempoux C, Rahier J, Zech F, Gigot JF. Percutaneous and surgical radiofrequency ablation of liver malignancies: a single institutional experience. *Acta Gastroenterol Belg* 2007; **70**: 188-194 [PMID: 17715632]

298 **Hildebrand P**, Leibecke T, Kleemann M, Mirow L, Birth M, Bruch HP, Bürk C. Influence of operator experience in radiofrequency ablation of malignant liver tumours on treatment outcome. *Eur J Surg Oncol* 2006; **32**: 430-434 [PMID: 16520015 DOI: 10.1016/j.ejso.2006.01.006]

299 **Mulier S**, Ruers T, Jamart J, Michel L, Marchal G, Ni Y. Radiofrequency ablation versus resection for

resectable colorectal liver metastases: time for a randomized trial? An update. *Dig Surg* 2008; **25**: 445-460 [PMID: 19212117 DOI: 10.1159/000184736]

300 **Gurusamy K**, Corrigan N, Croft J, Twiddy M, Morris S, Woodward N, Bandula S, Hochhauser D, Napp V, Pullan A, Jakowiw N, Prasad R, Damink SO, van Laarhoven CJHM, de Wilt JHW, Brown J, Davidson BR. Liver resection surgery versus thermal ablation for colorectal LiVer MetAstases (LAVA): study protocol for a randomised controlled trial. *Trials* 2018; **19**: 105 [PMID: 29439711 DOI: 10.1186/s13063-018-2499-5]

301 **Puijk RS**, Ruarus AH, Vroomen LGPH, van Tilborg AAJM, Scheffer HJ, Nielsen K, de Jong MC, de Vries JJJ, Zonderhuis BM, Eker HH, Kazemier G, Verheul H, van der Meijs BB, van Dam L, Sorgedrager N, Coupé VMH, van den Tol PMP, Meijerink MR; COLLISION Trial Group. Colorectal liver metastases: surgery versus thermal ablation (COLLISION) - a phase III single-blind prospective randomized controlled trial. *BMC Cancer* 2018; **18**: 821 [PMID: 30111304 DOI: 10.1186/s12885-018-4716-8]

302 **Huang M**, Sixth Affiliated Hospital SYU. Comparison of Hepatectomy and Local Ablation for Resectable Synchronous and Metachronous Colorectal Liver Metastasis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) [cited 2020 Jan 22]. Available from: https://clinicaltrials.gov/ct2/show/NCT02886104 NLM Identifier: NCT02886104

303 **Lubner MG**, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol* 2010; **21**: S192-S203 [PMID: 20656229 DOI: 10.1016/j.jvir.2010.04.007]

304 **Shibata T**, Niinobu T, Ogata N, Takami M. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. *Cancer* 2000; **89**: 276-284 [PMID: 10918156 DOI: 10.1002/1097-0142(20000715)89:2<276::aid-cncr11>3.0.co;2-0]

305 **Huo YR**, Eslick GD. Microwave Ablation Compared to Radiofrequency Ablation for Hepatic Lesions: A Meta-Analysis. *J Vasc Interv Radiol* 2015; **26**: 1139-1146.e2 [PMID: 26027937 DOI: 10.1016/j.jvir.2015.04.004]

306 **Correa-Gallego C**, Fong Y, Gonen M, D'Angelica MI, Allen PJ, DeMatteo RP, Jarnagin WR, Kingham TP. A retrospective comparison of microwave ablation vs. radiofrequency ablation for colorectal cancer hepatic metastases. *Ann Surg Oncol* 2014; **21**: 4278-4283 [PMID: 24889486 DOI: 10.1245/s10434-014-3817-0]

307 **Liu Y**, Li S, Wan X, Li Y, Li B, Zhang Y, Yuan Y, Zheng Y. Efficacy and safety of thermal ablation in patients with liver metastases. *Eur J Gastroenterol Hepatol* 2013; **25**: 442-446 [PMID: 23470267 DOI: 10.1097/MEG.0b013e32835cb566]

308 **van Tilborg AA**, Scheffer HJ, de Jong MC, Vroomen LG, Nielsen K, van Kuijk C, van den Tol PM, Meijerink MR. MWA Versus RFA for Perivascular and Peribiliary CRLM: A Retrospective Patient- and Lesion-Based Analysis of Two Historical Cohorts. *Cardiovasc Intervent Radiol* 2016; **39**: 1438-1446 [PMID: 27387188 DOI: 10.1007/s00270-016-1413-3]

309 **Reddy SK**, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, Barbas AS, Abdalla EK, Choti MA, Vauthey JN, Ludwig KA, Mantyh CR, Morse MA, Clary BM. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007; **14**: 3481-3491 [PMID: 17805933 DOI: 10.1245/s10434-007-9522-5]

310 **Jones TJ**, Murphy AE, Tameron A, Hussain LR, Grannan K, Guend H, Dunki-Jacobs EM, Lee DY. Trends and Outcomes of Synchronous Resection of Colorectal Metastasis in the Modern Era-Analysis of Targeted Hepatic NSQIP Database. *J Surg Res* 2019; **238**: 35-40 [PMID: 30735964 DOI: 10.1016/j.jss.2019.01.021]

311 **de Haas RJ**, Adam R, Wicherts DA, Azoulay D, Bismuth H, Vibert E, Salloum C, Perdigao F, Benkabbou A, Castaing D. Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases. *Br J Surg* 2010; **97**: 1279-1289 [PMID: 20578183 DOI: 10.1002/bjs.7106]

312 **Bogach J**, Wang J, Griffiths C, Parpia S, Saskin R, Hallet J, Ruo L, Simunovic M, Serrano PE. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cohort study. *Int J Surg* 2020; **74**: 68-75 [PMID: 31843676 DOI: 10.1016/j.ijsu.2019.12.009]

313 **Gavriilidis P**, Katsanos K, Sutcliffe RP, Simopoulos C, Azoulay D, Roberts KJ. Simultaneous, Delayed and Liver-First Hepatic Resections for Synchronous Colorectal Liver Metastases: A Systematic Review and Network Meta-Analysis. *J Clin Med Res* 2019; **11**: 572-582 [PMID: 31413769 DOI: 10.14740/jocmr3887]

314 **Mentha G**, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg* 2006; **93**: 872-878 [PMID: 16671066 DOI: 10.1002/bjs.5346]

315 **Brouquet A**, Mortenson MM, Vauthey JN, Rodriguez-Bigas MA, Overman MJ, Chang GJ, Kopetz S, Garrett C, Curley SA, Abdalla EK. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg* 2010; **210**: 934-941 [PMID: 20510802 DOI: 10.1016/j.jamcollsurg.2010.02.039]

316 **Andres A**, Toso C, Adam R, Barroso E, Hubert C, Capussotti L, Gerstel E, Roth A, Majno PE, Mentha G. A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. *Ann Surg* 2012; **256**: 772-8; discussion 778-9 [PMID: 23095621 DOI: 10.1097/SLA.0b013e3182734423]

317 **Jegatheeswaran S**, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. *JAMA Surg* 2013; **148**: 385-391 [PMID: 23715907 DOI: 10.1001/jamasurg.2013.1216]

318 **Lam VW**, Laurence JM, Pang T, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. *HPB (Oxford)* 2014; **16**: 101-108 [PMID: 23509899 DOI: 10.1111/hpb.12083]

319 **Kelly ME**, Spolverato G, Lê GN, Mavros MN, Doyle F, Pawlik TM, Winter DC. Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. *J Surg Oncol* 2015; **111**: 341-351 [PMID: 25363294 DOI: 10.1002/jso.23819]

320 **Adam R**, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Teh C, Tejpar S, Van Cutsem E, Vauthey JN, Påhlman L; of the EGOSLIM (Expert

Group on OncoSurgery management of LIver Metastases) group. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev* 2015; **41**: 729-741 [PMID: 26417845 DOI: 10.1016/j.ctrv.2015.06.006]

321 **Adam R**, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, Ijzermans J, Hubert C, Ruers T, Capussotti L, Ouellet JF, Laurent C, Cugat E, Colombo PE, Milicevic M. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010; **252**: 774-787 [PMID: 21037433 DOI: 10.1097/SLA.0b013e3181fcf3e3]

322 **Bonney GK**, Coldham C, Adam R, Kaiser G, Barroso E, Capussotti L, Laurent C, Verhoef C, Nuzzo G, Elias D, Lapointe R, Hubert C, Lopez-Ben S, Krawczyk M, Mirza DF; LiverMetSurvey International Registry Working Group. Role of neoadjuvant chemotherapy in resectable synchronous colorectal liver metastasis; An international multi-center data analysis using LiverMetSurvey. *J Surg Oncol* 2015; **111**: 716-724 [PMID: 25864987 DOI: 10.1002/jso.23899]

323 **Mühlbacher F**, Huk I, Steininger R, Gnant M, Götzinger P, Wamser P, Banhegyi C, Piza F. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc* 1991; **23**: 1567-1568 [PMID: 1989293]

324 **Penn I**. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery* 1991; **110**: 726-34; discussion 734-5 [PMID: 1656538]

325 **Hagness M**, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, Boberg KM, Mathisen O, Gladhaug IP, Egge TS, Solberg S, Hausken J, Dueland S. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 2013; **257**: 800-806 [PMID: 23360920 DOI: 10.1097/SLA.0b013e3182823957]

326 **Dueland S**, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, Foss A, Tveit KM. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? *Ann Surg* 2015; **261**: 956-960 [PMID: 24950280 DOI: 10.1097/SLA.0000000000000786]

327 **Hagness M**, Foss A, Egge TS, Dueland S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg Oncol* 2014; **21**: 1323-1329 [PMID: 24370906 DOI: 10.1245/s10434-013-3449-9]

328 **Toso C**, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A, Clavien PA, Furtado E, Barroso E, Bismuth H; Compagnons Hépato-Biliaires Group. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. *Liver Transpl* 2017; **23**: 1073-1076 [PMID: 28544246 DOI: 10.1002/lt.24791]

329 **Dueland S**, Syversveen T, Solheim JM, Solberg S, Grut H, Bjørnbeth BA, Hagness M, Line PD. Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases. *Ann Surg* 2020; **271**: 212-218 [PMID: 31188200 DOI: 10.1097/SLA.0000000000003404]

330 **Wyatt J**, Hubscher S, Goldin R. Standards and datasets for reporting cancers Dataset for histopathology reporting of liver resection specimens (including gall bladder) and liver biopsies for primary and metastatic carcinoma (2nd ed) 2012. Available from: https://www.rcpath.org/uploads/assets/555302b1-8b11-4d8a-a24431d0693d3287/G167-Dataset-for-histopathological-reporting-of-cancer-of-unknown-primary-CUP-and-malignancy-of-unknown-primary-origin-MUO.pdf

331 **Jones OM**, Rees M, John TG, Bygrave S, Plant G. Biopsy of potentially operable hepatic colorectal metastases is not useless but dangerous. *BMJ* 2004; **329**: 1045-1046 [PMID: 15514363 DOI: 10.1136/bmj.329.7473.1045-c]

332 **National Institute for Helath and Care Excellence**. Metastatic Malignant Disease of Unknown Primary Origin in Adults: Diagnosis and Management. 2010. Available from: https://www.nice.org.uk/Guidance/CG104

333 **Moreno Prats M**, Sasatomi E, Stevenson HL. Colorectal Liver Metastases: A Pathologist's Guide to Creating an Informative Report and Improving Patient Care. *Arch Pathol Lab Med* 2019; **143**: 251-257 [PMID: 29790787 DOI: 10.5858/arpa.2017-0505-RA]

334 **Rubbia-Brandt L**, Giostra E, Brezault C, Roth AD, Andres A, Audard V, Sartoretti P, Dousset B, Majno PE, Soubrane O, Chaussade S, Mentha G, Terris B. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. *Ann Oncol* 2007; **18**: 299-304 [PMID: 17060484 DOI: 10.1093/annonc/mdl386]

335 **Ryan R**, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, O'Donoghue DP, Moriarty M, Fennelly D, Sheahan K. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005; **47**: 141-146 [PMID: 16045774 DOI: 10.1111/j.1365-2559.2005.02176.x]

336 **Li-Chang HH**, Driman DK. Comment on: Pathologic Response to Preoperative Chemotherapy in Colorectal Liver Metastases: Fibrosis, Not Necrosis, Predicts Outcome. *Ann Surg Oncol* 2017; **24**: 607 [PMID: 29181678 DOI: 10.1245/s10434-017-6198-3]

337 **Shen Z**, Gu L, Mao D, Chen M, Jin R. Clinicopathological and prognostic significance of PD-L1 expression in colorectal cancer: a systematic review and meta-analysis. *World J Surg Oncol* 2019; **17**: 4 [PMID: 30609938 DOI: 10.1186/s12957-018-1544-x]

338 **Boland PM**, Ma WW. Immunotherapy for Colorectal Cancer. *Cancers (Basel)* 2017; **9** [PMID: 28492495 DOI: 10.3390/cancers9050050]

339 **Stevenson HL**, Prats MM, Sasatomi E. Chemotherapy-induced Sinusoidal Injury (CSI) score: a novel histologic assessment of chemotherapy-related hepatic sinusoidal injury in patients with colorectal liver metastasis. *BMC Cancer* 2017; **17**: 35 [PMID: 28061766 DOI: 10.1186/s12885-016-2998-2]

340 **Prenzel N**, Fischer OM, Streit S, Hart S, Ullrich A. The epidermal growth factor receptor family as a central element for cellular signal transduction and diversification. *Endocr Relat Cancer* 2001; **8**: 11-31 [PMID: 11350724 DOI: 10.1677/erc.0.0080011]

341 **Rodriguez-Viciana P**, Warne PH, Dhand R, Vanhaesebroeck B, Gout I, Fry MJ, Waterfield MD, Downward J. Phosphatidylinositol-3-OH kinase as a direct target of Ras. *Nature* 1994; **370**: 527-532 [PMID: 8052307 DOI: 10.1038/370527a0]

342 **Datta SR**, Brunet A, Greenberg ME. Cellular survival: a play in three Akts. *Genes Dev* 1999; **13**: 2905-2927 [PMID: 10579998 DOI: 10.1101/gad.13.22.2905]

343 **Kelley GG**, Reks SE, Ondrako JM, Smrcka AV. Phospholipase C(epsilon): a novel Ras effector. *EMBO J* 2001; **20**: 743-754 [PMID: 11179219 DOI: 10.1093/emboj/20.4.743]

344 **Downward J**. Targeting RAS signalling pathways in cancer therapy. *Nat Rev Cancer* 2003; **3**: 11-22 [PMID: 12509763 DOI: 10.1038/nrc969]

345 **Jászai J**, Schmidt MHH. Trends and Challenges in Tumor Anti-Angiogenic Therapies. *Cells* 2019; **8** [PMID: 31540455 DOI: 10.3390/cells8091102]

346 **Mohammed MK**, Shao C, Wang J, Wei Q, Wang X, Collier Z, Tang S, Liu H, Zhang F, Huang J, Guo D, Lu M, Liu F, Liu J, Ma C, Shi LL, Athiviraham A, He TC, Lee MJ. Wnt/β-catenin signaling plays an ever-expanding role in stem cell self-renewal, tumorigenesis and cancer chemoresistance. *Genes Dis* 2016; **3**: 11-40 [PMID: 27077077 DOI: 10.1016/j.gendis.2015.12.004]

347 **Grainger S**, Willert K. Mechanisms of Wnt signaling and control. *Wiley Interdiscip Rev Syst Biol Med* 2018; e1422 [PMID: 29600540 DOI: 10.1002/wsbm.1422]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 October 24; 11(10): 809-835

DOI: 10.5306/wjco.v11.i10.809

ISSN 2218-4333 (online)

REVIEW

Critically ill patients with cancer: A clinical perspective

Frank Daniel Martos-Benítez, Caridad de Dios Soler-Morejón, Karla Ximena Lara-Ponce, Versis Orama-Requejo, Dailé Burgos-Aragüez, Hilev Larrondo-Muguercia, Rahim W Lespoir

ORCID number: Frank Daniel Martos-Benítez 0000-0001-7551-5373; Caridad de Dios Soler-Morejón 0000-0003-2695-3291; Karla Ximena Lara-Ponce 0000-0001-4433-7786; Versis Orama-Requejo 0000-0002-0447-8998; Dailé Burgos-Aragüez 0000-0002-2950-5104; Hilev Larrondo-Muguercia 0000-0002-1085-9666; Rahim W Lespoir 0000-0003-0889-1955.

Author contributions: Martos-Benítez FD contributed with conception, literature review, drafting, critical revision and editing, and final approval of the final version; Soler-Morejón CD, Lara-Ponce KX, Orama-Requejo V, Burgos-Aragüez D, Larrondo-Muguercia H, and Lespoir RW equally contributed with literature review, drafting and critical revision, and final approval of the final version.

Conflict-of-interest statement: The authors declare no potential conflict of interest.

Frank Daniel Martos-Benítez, Caridad de Dios Soler-Morejón, Karla Ximena Lara-Ponce, Versis Orama-Requejo, Dailé Burgos-Aragüez, Hilev Larrondo-Muguercia, Rahim W Lespoir, Intensive Care Unit 8B, Hermanos Ameijeiras Hospital, Havana 10300, Cuba

Corresponding author: Frank Daniel Martos-Benítez, MD, PhD, Doctor, Statistician, Teacher, Intensive Care Unit 8B, Hermanos Ameijeiras Hospital, 702 San Lázaro St, Havana 10300, Cuba. fdmartos@infomed.sld.cu

Abstract

Cancer patients account for 15% of all admissions to intensive care unit (ICU) and 5% will experience a critical illness resulting in ICU admission. Mortality rates have decreased during the last decades because of new anticancer therapies and advanced organ support methods. Since early critical care and organ support is associated with improved survival, timely identification of the onset of clinical signs indicating critical illness is crucial to avoid delaying. This article focused on relevant and current information on epidemiology, diagnosis, and treatment of the main clinical disorders experienced by critically ill cancer patients.

Key Words: Acute respiratory failure; Cancer; Cardiotoxicity; Chemotherapy; Critical care; Infection; Mechanical ventilation; Neutropenia; Postoperative; Sepsis

Core Tip: Cancer patients are commonly admitted to intensive care unit because of acute respiratory failure due to pulmonary infiltrates or pneumonia, healthcare associated infection by multidrug-resistant pathogens, postoperative care, cardiovascular complications, and neurological disorders. Early critical care and organ support is associated with improved outcomes. Standardized diagnosis strategy and evidence-based therapy are critical in the management of specific clinical disorders.

Citation: Martos-Benítez FD, Soler-Morejón CD, Lara-Ponce KX, Orama-Requejo V, Burgos-Aragüez D, Larrondo-Muguercia H, Lespoir RW. Critically ill patients with cancer: A clinical perspective. *World J Clin Oncol* 2020; 11(10): 809-835

URL: https://www.wjgnet.com/2218-4333/full/v11/i10/809.htm

DOI: https://dx.doi.org/10.5306/wjco.v11.i10.809

Manuscript source: Invited manuscript

Received: February 22, 2020
Peer-review started: February 24, 2020
First decision: July 25, 2020
Revised: August 9, 2020
Accepted: September 14, 2020
Article in press: September 14, 2020
Published online: October 24, 2020

P-Reviewer: Guo K, Vega MI
S-Editor: Wang JL
L-Editor: A
P-Editor: Wang LL

INTRODUCTION

Cancer is one of the main causes of morbidity and mortality worldwide[1]. Overall cancer-death rates have decreased in both men and women due to reduced tobacco use, improved early detection (*e.g.*, colorectal, breast, and cervix) and enhanced treatment options[2-4]. Currently, critical care medicine contributes as a supportive care for patients with cancer.

In the past decades, patients with advanced hematological or oncological disease were not candidates for entry to intensive care unit (ICU) due to low survival rates; however, expectancy in life-span has changed over the last 25 years because of a breakthrough in terms of new anticancer therapies and organ support methods[5]. Cancer patients account for 15% of all admissions to ICU[6] and 5% will experience a critical illness resulting in ICU admission[7]. These frequencies may grow considering the current global burden of cancer and demographic features. Analysis from large databases suggests that a higher proportion of cancer patients survive at ICU discharge[7,8]. Since the five-year survival rate is 41%[9], reluctance to admit cancer patients to the ICU must be avoided from medical practice. In fact, most recent evidences support an increased ICU admission because of improved ICU and hospital outcomes[8-11].

Patients with hematological malignancy or solid tumor are at higher risk for ICU admission as a consequence of acute respiratory failure due to pulmonary infiltrates or pneumonia, healthcare associated infection by multidrug-resistant pathogens related or not with immunosuppression, postoperative care, cardiovascular complications, and neurological disorders[6,12-14].

The aim of this article was to provide critical care clinicians with an overview on relevant and current information on epidemiology, diagnosis, and treatment of the main clinical disorders experienced by cancer patients with a critical illness.

ADMISSION CRITERIA TO INTENSIVE CARE UNIT

The main reasons for admitting cancer patients to ICU are postoperative care, acute respiratory failure (ARF), and sepsis. Other clinical situations are cardiac complications, neurological disorders, acute kidney injury, bleeding, and oncological emergencies[15]. Mucositis, acute graft-versus-host disease, diffuse alveolar hemorrhage, cardiac dysfunction, hypertension and hepatic venoocclusive disease are other causes in hematological malignancies[16] (Table 1).

Several studies indicate that early ICU admission is associated with higher survival rates[17-21]; thus, timely identification of patients at onset of clinical signs indicating critical deterioration is crucial to avoid delayed organ support[6]. The ability of physician to identify what patient is expected to benefit from ICU management is limited. As proposed by Ñamendys-Silva *et al*[22], the following criteria may help for this purpose: Sequential Organ Failure Assessment (SOFA) score between 7 and 10 or < 3 organ failures, recent diagnosis of oncohematological disease, cancer-related medical emergencies (*e.g.*, tumor lysis syndrome, pulmonary infiltrates in patients with leukemia or leukostasis as the initial manifestation of leukemia), likelihood of cure or disease control, Eastern Cooperative Oncology Group scale between 0 and 2, and postoperative intensive care for patients undergoing complex surgical procedures who require hemodynamic monitoring and/or ventilatory support.

As decision-making for ICU admission and management may be challenging, the following strategy is recommended: (1) Full-code ICU management: Full organ support methods (*e.g.*, invasive mechanical ventilation, vasopressors, renal replacement therapy, nutritional support) without limitations of ICU resources for patients with curative therapeutic options, patients in remission, and those with expected life-span ≥ 1 year[5]; (2) Time-limited ICU trial: ICU management with full-code status for a limited period. Although the time of full-code should be judged in accordance with the patient´s clinical course rather than with a fixed time, a reasonable interval could be 2 wk in hematology patients (1 wk if multiple organ failure) and 1 wk in patients with solid tumors (4-5 d if multiple organ failure)[5,6,23]; (3) Patients with poor performance status not eligible for further anticancer therapy, dying patients, and those rejecting critical care treatment should not be admitted to the ICU in general[5]; and (4) Other indications: Exceptional ICU admission (same as time-limited ICU trial) for patients in whom new drugs (approved or not) are available; prophylactic ICU admission with full-code for high-risk patients (*e.g.*, patients at risk of tumor lysis syndrome or acute respiratory failure after chemotherapy); palliative ICU admission

Table 1 Reasons for intensive care unit admission in patients with cancer[15]

Cause	Comment
Postoperative care	Elective or emergency
Acute respiratory failure	(1) Infectious: Bacterial, viral, fungal; and (2) Noninfectious: Diffuse alveolar hemorrhage, interstitial lung disease, pulmonary drug toxicity, transfusion-related acute lung injury
Cardiovascular disorders	Sepsis and septic shock, pulmonary embolism, drug-induced cardiomyopathy
Bleeding disorders	Tumor erosion, coagulopathy, thrombocytopenia
Alteration of mental status	(1) Metabolic: Sepsis, drugs, multiorgan system failure, seizure, hyponatremia, hypoxia, hipercapnea; (2) Mass effect: Central nervous system bleeding, tumor effects; and (3) Others: Posterior reversible encephalopathy syndrome
Oncologic emergency	Tumor lysis syndrome, leukostasis, superior vena cava syndrome, cardiac tamponade, hipercalcemia
Acute decompensated chronic comorbidity	Chronic obstructive pulmonary disease, cardiac disorders (*e.g.*, cardiomyopathy, coronary artery disease), chronic kidney disease, chronic hepatopathy
Others	Initiation of chemotherapy for surveillance

for optimizing medical care with noninvasive strategies (*e.g.*, noninvasive ventilation, vasopressors without invasive hemodynamic monitoring, electrical cardioversion, pneumothorax decompression, optimizing pain relieve)[6].

ACUTE RESPIRATORY FAILURE

ARF is the leading cause of unplanned ICU admission in cancer patients[24]. The incidence is higher in patients with acute lymphoblastic leukemia, acute myeloid leukemia, hematopoietic stem cell transplant (HSCT), neutropenia, and lung cancer[25-29]. Ventilatory support is used in 35%-50% of critically ill cancer patients[11,30,31]; the associated ICU and hospital mortality rate is as high as 50% and 65%, respectively[31,32] (Table 2). Mortality-related factors in patients with ARF can be grouped into five categories: (1) Respiratory failure associated with organ dysfunction; (2) Factors inherent to delayed ICU admission; (3) Factors associated with chronic underlying comorbidities; (4) Factors involved with the initial treatment of respiratory failure; and (5) Factors related to the etiology of respiratory failure.

Five major pathophysiological mechanisms can explain ARF in cancer patients (Table 3). Ventilation/ perfusion mismatch is the most common mechanism, usually caused by pulmonary infiltrates, pneumonia, atelectasis or pulmonary embolism. Increased intrapulmonary shunt occurs in primary or secondary acute respiratory distress syndrome. Drug-associated interstitial lung disease and high-degree metastasized lungs explain disorders of oxygen diffusion[33].

Primary tumor location, clinical stage, admission from the emergency department, medical admission, malignancy-unrelated ICU admission, sepsis, adverse event to chemotherapy, and Acute Physiology And Chronic Health Evaluation (APACHE) II score have been found as risk factor for severe ARF requiring invasive mechanical ventilation[34]. Causes of ARF in patients with cancer are depicted in Table 4[35].

Direct actions focused on the best therapeutic options are required in cancer patients with ARF. Clinical examination is crucial since pulmonary infiltrates and respiratory symptoms (*e.g.*, increased respiratory rate, cough, sputum, rales, thoracic pain, and hemoptysis) are associated with increased ventilatory support and mortality rates[13]. DIRECT approach may suggest the cause of ARF[36]: Identification of the type and duration (D) of respiratory symptoms, assessment of immunosuppressive (I) therapy, interpretation of X-ray (R) pattern, clinician's experience (E), clinical (C) finding, and high-resolution computed tomography scan (T)[36,37]. Figure 1 depicts a diagnostic algorithm for ARF.

Bacterial infection, usually in immunocompromised patients, is the main cause of ARF[30]. It is common in early stages of lymphoproliferative disorders[38]. Opportunistic infections have been reported prior to initiation of anticancer therapy in patients with T-cell diseases[39]. Noninfectious causes (*e.g.*, lung infiltrates, leukemic infiltrates, diffuse alveolar hemorrhage, drug-related interstitial lung diseases, and noninfectious lung diseases after HSCT) are difficult to identify, therefore more invasive diagnostic studies are needed for reaching diagnosis such as bronchoscopy and bronchoalveolar lavage (BAL)[25,26,40]. Thrombocytopenia, bleeding disorders, and hypoxemia may preclude bronchoscopy and/or lung biopsy. Pattern of computed tomography (CT)

Table 2 Incidence and mortality of acute respiratory failure in cancer patients[25]

	Incidence	Need for ICU admission	Hospital mortality
Hematological malignancy			
Acute myeloid leukemia	22%-84 %	66%	45%
Acute lymphoblastic leukemia	7%-18.5%	12%-15%	38.5%
Lymphoproliferative diseases	8%	8%	40%-50%
Myelodysplastic syndrome	29.4%	20%	17%
Autologous hematopoietic stem cell transplant	3%-28%	42%	3%-55%
Allogeneic hematopoietic stem cell transplant	24%-30%	50%	51%
Prolonged neutropenia	8%-29.5%	11%-16%	5%-12%
Solid tumor			
Lung cancer	26%-50%	100%	11.2%-60%
Other solid tumors	0.7%-10.3%	100%	6.1%-55%
Patients on immunotherapy	1.3%-3.6%	1.3%	-

ICU: Intensive care unit.

Table 3 Mechanisms and features of hypoxemia

Mechanism	PaO_2	$PaCO_2$	$D_{A\text{-}a}O_2$	Comments
Disorders in oxygen diffusion	↓	↓	↑	Decreased surface area or short time for hematosis (*e.g.*, hydrostatic edema, interstitial pneumonia, drug-associated interstitial lung disease, high-degree metastasized lungs)
Ventilation/ perfusion mismatch	↓	↑	↑	(1) Decreased ventilation in normally perfused lung regions (*e.g.*, pulmonary infiltrates, pneumonia, atelectasis); and (2) Declined perfusion in normally ventilated lung areas (*e.g.*, pulmonary embolism)
Increased intrapulmonary shunt	↓	↓	↑↑	Pulmonary venous blood bypasses ventilated alveoli without be oxygenated (*e.g.*, acute respiratory distress syndrome)
Hypoventilation	↓	↑↑	N	Hypoventilation
Decrease in pressure of inspired oxygen	↓	↓	N	Decreased pressure of inspired oxygen

scan may help to identify the cause of ARF[37]. Table 5 summarizes invasive and noninvasive diagnostic procedures in cancer patients with ARF. Infectious and noninfectious causes of pulmonary complications following HSCT are depicted in Figure 2[41].

Etiology of ARF may be identified using the information of clinical, laboratory, imagenological, and invasive investigations as following[25,42-44]: (1) Acute or subacute onset; symptoms of upper respiratory tract with fever plus centrilobular nodules or ground-glass opacities on CT scan: Viral infection or atypical pneumonia. Exclude bacterial co-infection; (2) Acute onset; suspect bacterial infection plus alveolar consolidation on X-ray o CT scan: Bacterial infection. Consider bronchoscopy and BAL if sputum cannot be obtained; (3) Subacute onset; T-cell deficiency without prophylaxis for *Pneumocystis jirovecii* plus diffuse ground-glass opacities on CT scan: Pneumocystis pneumonia; (4) Subacute onset; risk factors for invasive aspergillosis (*e.g.*, prolonged neutropenia, allogeneic HSCT, graft versus host disease, T-cell deficiency) plus consolidation or cavitation on X-ray or CT scan: Invasive pulmonary aspergillosis; and (5) Acute or subacute onset; variable clinical presentation: Disease-related infiltrates, diffuse alveolar hemorrhage, alveolar proteinosis, drug-related pulmonary toxicity.

Hydrostatic pulmonary edema (Biomarkers: Natriuretic peptide or N-terminal pro-B-type natriuretic peptide; echocardiography), pulmonary embolism (Biomarkers: D-dimer, high-sensitive cardiac troponin; echocardiography; CT pulmonary angiogram), pleural effusion/ pneumothorax (X-ray; ultrasound; CT scan), and cardiac tamponade (Echocardiography) should be ruled out.

Table 4 Causes of acute respiratory failure in patients with cancer[35]

CNS and neuromuscular disorders	Chest wall and pleural disorders	Vascular disorders	Airway disorders	Parenchymal disorders
Drug intoxications: Narcotics; Sedatives; Neuroleptics	**Pleural disorder:** Malignant pleural effusion; Pleural tumor (primary or metastatic); Tension pneumothorax	Acute pulmonary embolism; Tumor embolism; Pulmonary venooclusive disease	**Airway obstruction:** Endobronchial metastases; External airway compression; Primary tumor of periglottic area	**Pneumonitis:** Infection; Chemotherapy; Radiotherapy; Aspiration
Encephalopathies: Infection; Metabolic; Seizure	**Chest wall disorders:** Chest wall tumor (primary or metastatic); Rib fracture		**Others:** Tracheoesophageal fistula; Bronchiolitis obliterans	**Acute respiratory distress syndrome:** Infection; Chemotherapy; Radiotherapy; Transfusion
Intracranial tumors: Primary; Metastatic				**Complications of HSCT:** Peri-engraftment respiratory distress syndrome; Diffuse alveolar hemorrhage; Idiopathic pneumonia syndrome
Neuropathies/myopathies: Nerve palsy				**Others:** Lymphangitic carcinomatosis; Pulmonary leukostasis; Bronchiolitis obliterans organizing pneumonia
Paraneoplastic syndromes: Eaton-Lambert syndrome; Myasthenia gravis; Guillain-Barré syndrome				

CNS: Central nervous system; HSCT: Hematopoietic stem cell transplant.

Treatment of cancer patients with ARF is focused to restore oxygenation, relieve dyspnea and respiratory distress, and improve patient comfort[25]. Mortality rates remain high[17,34]; thus, noninvasive devices are preferred. Although early noninvasive ventilation (NIV) was associated with improved survival rates[45], failure of NIV or high-flow nasal oxygen therapy (HFNO) was associated with increased mortality[24,32]. The most challenging issue is choosing those patients in which a specific respiratory strategy is beneficial over others. Physicians need to consider the following risk factors for NIV failure[5]: (1) Prior to NIV: Vasopressor need, multiple organ failure, airway involvement by malignancy, acute respiratory distress syndrome, unknown etiology of ARF, and delayed-onset ARF; and (2) During NIV: Patient not tolerating NIV, not improvement of arterial blood gases within 6 h, respiratory rate > 30 breath per minute, NIV dependency ≥ 3 d, clinical or respiratory deterioration, and unknown etiology of ARF.

A trial of NIV is recommended for most patients with ARF by reversible underlying cause[32,45,46]; however, HFNO is a promising alternative to NIV[47-50]. In a France-Belgium 28-center-randomized controlled trial of 374 immunocompromised patients with ARF, Lemiale *et al*[51] found no difference in primary and secondary outcomes between intermittent NIV and standard oxygen therapy. A recent meta-analysis of immunocompromised patients showed that intubation rate was lower in the HFNO group than those in the conventional oxygen therapy group and NIV group; however, HFNO did not improve survival or length of stay[52]. The ongoing FLORALI-IM randomized controlled trials may contribute to clarify these findings[53].

NEUTROPENIA AND SEPSIS

Chemotherapy in patients with cancer has resulted in improved survival, although increased the number of cases with neutropenia. Hematological malignancies and myelodysplastic syndromes are other causes of neutropenia[54,55]. Neutropenia is related to severe invasive infections, septic shock, multiple organ dysfunction, and increased mortality[56,57]. Mokart *et al*[57] found a hospital mortality rate of 45.3% in patients admitted to ICU. In 7512 critically ill patients with cancer included in a recent systematic review, neutropenia was independently associated with unfavorable outcomes; nevertheless, granulocyte colony-stimulating factor was related to reduced mortality rate[58].

Table 5 Invasive and noninvasive diagnostic procedures in cancer patients with acute respiratory failure[5]

Diagnostic procedure	Comments
Blood cultures	Hospital-acquired bacteria
Multislice or high-resolution CT scan	In most cases without contrast media; MRI if a pulmonary CT scan is not feasible
Echocardiography	Cardiac evaluation
Sputum examination	Bacteria; Fungi; Mycobacteria
Induced sputum	*Pneumocystis jiroveci*
Nasopharyngeal aspirates or nasal swabs	Adenovirus, metapneumovirus, coronavirus, parainfluenza virus types 1, 2, 3 and 4; influenza virus types A and B, respiratory syncytial virus A and B; rhinovirus A, B, and C; bocavirus and enterovirus
Polymerase chain reaction blood test	Herpesviridae; Cytomegalovirus; Epstein-Barr virus
Circulating *Aspergillus* galactomannan	*Aspergillus spp*.
Serologic tests	*Chlamydia pneumoniae; Mycoplasma pneumoniae; Legionella pneumophila*
Urine antigen	*Legionella pneumophila; Streptococcus pneumoniae*
BAL (mandatory)	(1) Cytospin preparation including Giemsa stain for cytological diagnostics and Gram stain; (2) Quantitative or semi-quantitative bacteriological cultures including culture media to detect *Legionella spp*., mycobacteria and fungi; (3) Calcofluor white or equivalent stain (assessment of fungi); (4) Quantitative (if possible) PCR for *Pneumocystis jirovecii*; (5) Direct immunofluorescence test for *Pneumocystis jirovecii*; (6) *Aspergillus* antigen (Galactomannan ELISA); and (7) *Mycobacterium tuberculosis* PCR, atypical mycobacteria
BAL (optional)	(1) PCR for cytomegalovirus, respiratory syncytial virus, influenza A/B virus, parainfluenza virus, human metapneumovirus, adenovirus, varicella zoster virus, and *Pneumocystis jirovecii* (quantitative); and (2) *Aspergillus* antigen (Galactomannan ELISA); Panfungal or *Aspergillus*/ mucormycetes PCR
Transbronchial biopsies	Not recommended in general in febrile neutropenic and/or thrombocytopenic patients as the first line procedure

CT: Computed tomography; BAL: Bronchoalveolar lavage; PCR: Polymerase chain reaction.

According to the absolute neutrophil count, neutropenia is classified as mild (1000-1500 cells/mm^3), moderate (500-999 cells/mm^3), severe (100-499 cells/mm^3), and deep (< 100 cells/mm^3)[54]. Infection usually appear with severe or deep neutropenia[59]. Febrile neutropenia (FN) is defined as a single oral or axillary temperature > 38.3 °C (101 °Fahrenheit) or a temperature > 38.0 °C (100.4 °Fahrenheit) sustained over 60 min in patients with severe neutropenia[56].

Fever may be the earliest and only sign of infection in neutropenic cancer patient. The incidence of FN varies between 10% and 50% in patients with solid tumors receiving antineoplastic therapy and up to 80% in patients with hematological malignancies[54]. The risk of infection is high in severe neutropenia, moderate neutropenia expected to decline to severe within 48 h, and moderate neutropenia lasting more than seven days.

The main independent prognostic factors for mortality in neutropenic patient are age > 60 years, APACHE scores, Simplified Acute Physiology Score scores, SOFA score, need for mechanical ventilation, high serum procalcitonin, need for renal replacement therapy, and allogeneic HSCT[10,55,57].

Risk-stratification scores allow a quick and objective risk assessment. Several risk scores have been validated to evaluate the risk of complications in patients with FN (Table 6[54,60-62]). Because increased complication and mortality rates, high-risk patients are the following: Group 1-3 of the Talcott classification system, < 20 points in the Multinational Association for Supportive Care in Cancer risk index, and ≥ 3 points in the Clinical Index of Stable Febrile Neutropenia score. High-risk patients generally require in-hospital treatment and intravenous administration of broad-spectrum antibiotics[60-62].

Other risk factors in high-risk patients are the following[55,63-65]: (1) Planned deep neutropenia for more than 7 d; (2) Evidence of liver failure: Abnormal aminotransferases > 5-fold upper limit of normal value or hyperbilirubinemia; (3) Renal impairment: Serum creatinine increase > 50% or > 26.5 μmol/L within 48 h,

Table 6 Risk-stratification tools for patients with febrile neutropenia[54,60-62]

Description/Criteria	Group/ Points
Talcott classification system	
Patients hospitalized at onset of fever and neutropenia (inpatient at presentation)	1
Outpatients at presentation but with comorbidities which require hospitalization	2
Outpatients at presentation with uncontrolled cancer but without comorbidities	3
Outpatients at presentation without comorbidities and controlled cancer	4
Multinational association of supportive care of cancer (MASCC) risk-index	
Burden of febrile neutropenia	
No or mild symptoms: No fever, hemodynamic compromise or clinically significant signs and symptoms of particular site of infection	5
Moderate symptoms: Any others not included in mild or severe symptoms	3
Severe symptoms: High grade fever, any hemodynamic compromise or any of the serious complications requiring high dependency unit support	0
No hypotension (systolic blood pressure > 90 mmHg)	5
Solid tumor or hematological malignancy with no previous fungal infection	4
No chronic obstructive pulmonary disease	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 yr	2
Clinical Index of Stable Febrile Neutropenia (CISNE) score	
Eastern Cooperative Oncology Group performance status ≥ 2	2
Stress-induced hyperglycemia	2
Chronic obstructive pulmonary disease (on steroids, supplemental oxygen, or bronchodilators)	1
Chronic cardiovascular disease (excluding single uncomplicated episode of atrial fibrillation)	1
Mucositis (at least the presence of patchy ulcerations or pseudomembranes, or moderate pain with modified diet)	1
Monocytes < 200 cells/mm^3	1

urine output < 0.5 mL/kg/h for 6 h, or increased concentration in newer biomarkers for sepsis associated-acute kidney injury (*e.g.*, insulin like growth factor binding protein-7, kidney injury molecule-1, neutrophil gelatinase associated lipocalin, tissue inhibitor of metalloproteinase-2); and (4) Pathophysiological imbalance and comorbidities such as, but not limited to: (a) Hemodynamic instability: Hypotension, decreased capillary refill or mottling, hyperlactatemia, central venous oxygen saturation < 70%, and central venous-to-arterial carbon dioxide difference > 6.0 mmHg; (b) Oral or gastrointestinal mucositis interfering with swallowing; (c) Gastrointestinal symptoms: Ileus, severe diarrhea, pain, nausea, and vomiting; (d) Neurological disorders or changes in mental status; (e) Intravascular catheter-related infection; (f) New pulmonary infiltrates or hypoxemia, or decompensated chronic lung disease; and (g) Coagulation abnormalities: International normalized ratio > 1.5, activated partial thromboplastin time > 60 s, or platelet count < 100000 cells/mm^3.

Most patients with FN have scarce clinical features. Clinically documented infection is only reported in 20%-35%[54]. Thus, the International Immunocompromised Host Society recommends three categories of patients[66]: (1) Microbiologically documented infection: Clinical site of infection and the associated pathogen is identified; (2) Clinically documented infection: Clinical site of infection is identified, but without isolation of the pathogen; and (3) Unexplained fever: Clinical site of infection and pathogen are not identified. The most patients with FN have unexplained fever.

Since the risk of infection is related to the intensity and duration of neutropenia, the risk for developing FN and its severity must be anticipated for an early diagnosis and treatment of unexplained fever; underlying disease, immune status, co-morbidities, and type of intervention (*e.g.*, chemotherapy scheme, intrinsic hematological toxicity,

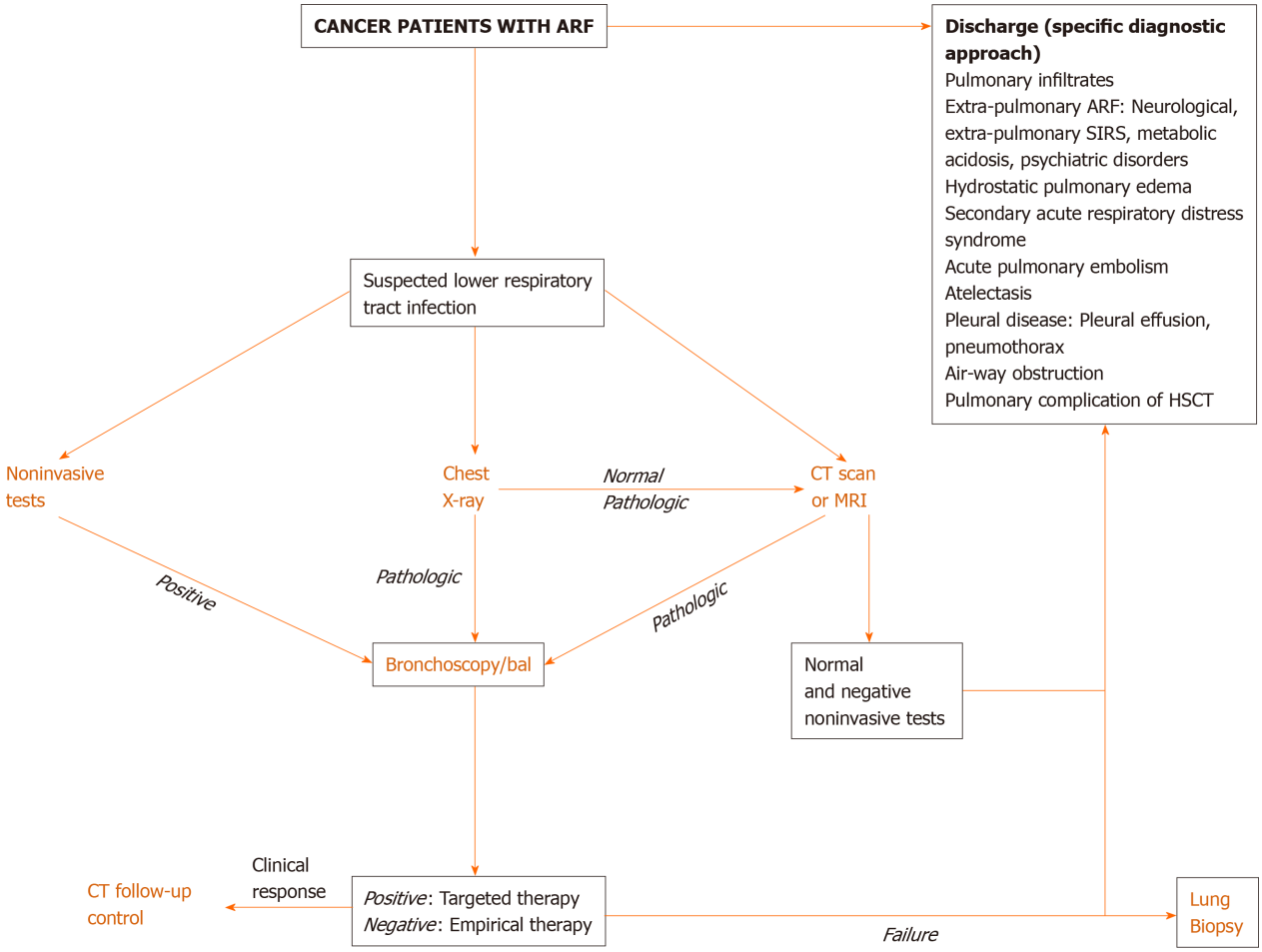

Figure 1 Diagnostic approach for cancer patients with suspected pulmonary infection. ARF: Acute respiratory failure; BAL: Bronchoalveolar lavage; CT: Computed tomography; HSCT: Hematopoietic stem cell transplant; MRI: Magnetic resonance image; SIRS: Systemic inflammatory response syndrome.

dose and duration) need to be evaluated. Qualitative disorders of neutrophil function may also increase the risk of infections even with normal neutrophil count[55].

There has been a change in the epidemiological patterns of infections because of a wide spread multidrug-resistant bacteria amongst humans, animals and environmental reservoirs[67]. Microorganisms causing infection mostly come from the normal flora of the skin, oropharyngeal cavity, and gastrointestinal tract. Infection is localized in approximately 30% of cases, mainly in the upper respiratory tract or skin, but only 20%-40% are microbiologically documented[59]. Among gram-negative bacteria, carbapenem-resistant *Enterobacteriaceae* such as *Escherichia coli*[67-74] and *Klebsiella pneumoniae*[67-69,72-75], *Pseudomonas aeruginosa*[68,69,72-74] and *Acinetobacter baumannii*[67,68,76] prevail. The most common gram-positive pathogens are methicillin-sensible[68] and methicillin-resistant *Staphylococcus aureus*[67,68,77], *Streptococcus viridians*[68,71] and *Streptococcus pneumonia*[68]; vancomycin-resistant *Enteroccocus faecium* may be found[67,69]. The main fungi identified are *Candida* and *Aspergillus* species[55,78]. Approximately 50% of invasive aspergillosis are found in patients with hematological malignancy or imunocompromissed patients with prolonged severe neutropenia[78]. Mortality rates of invasive fungal infection exceeds 30%[79].

The Third International Consensus Definitions for Sepsis and Septic Shock is recommended to use in FN patients (Figure 3)[80]. In a large meta-analysis, neutropenia was independently associated with poor outcomes[81]; therefore FN should be treated as infectious disease until proven otherwise and must be considered as medical emergency. Therapeutic approach is based on the risk of complications and death, presence of life-threatening infection and magnitude and duration of neutropenia. High-risk patients are vulnerable to develop septic shock; early intravenous administration of broad-spectrum antibiotics against gram-negative and gram-positive bacteria is obligatory. Low-risk patients could be treated in-hospital with intravenous antibiotics or as outpatient with oral antibiotics depending on the clinical picture and comorbidities.

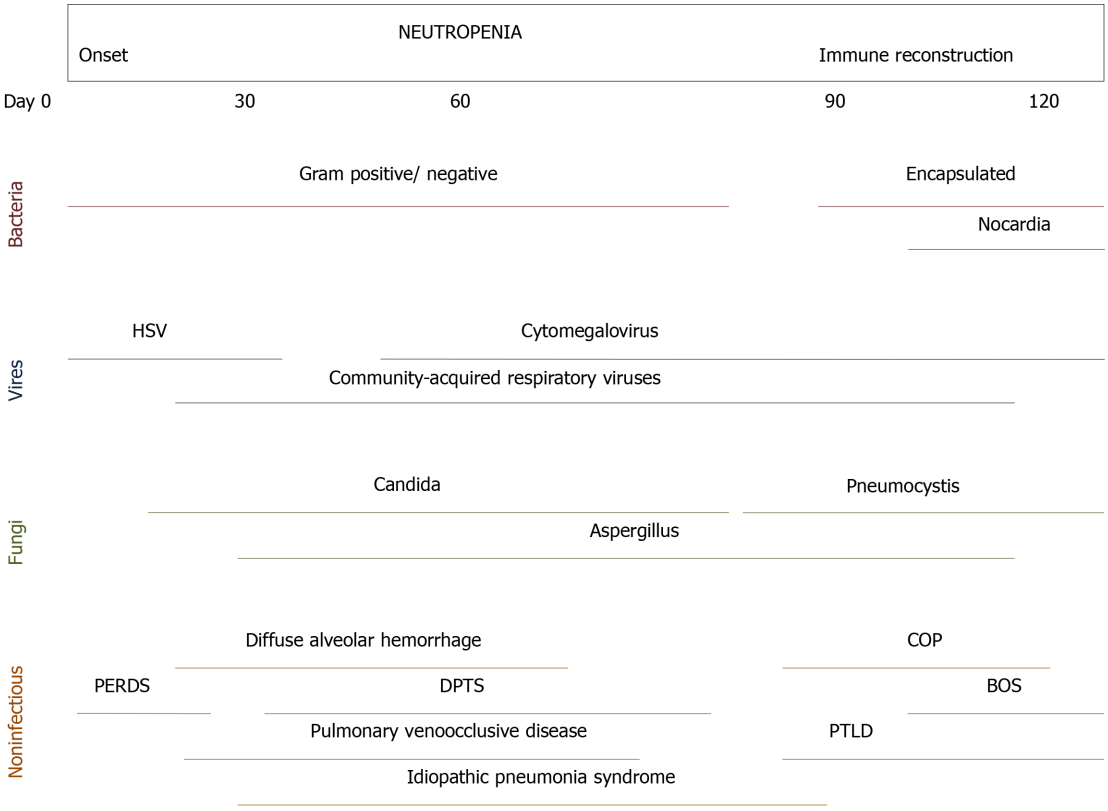

Figure 2 Pulmonary complications in patients with hematopoietic stem cell transplant[41]. BOS: Bronchiolitis obliterans syndrome; COP: Cryptogenic organizing pneumonia; DPTS: Delayed pulmonary toxicity syndrome; HSV: Herpes simplex virus; PERDS: Peri-engraftment respiratory distress syndrome; PTLD: Post-transplant lymphoproliferative disorder.

Culture samples must be taken before the onset of antibacterial agents. Information of the general/local epidemiology and resistance profiles is of paramount importance to guide empirical antibiotic therapy[82]. Broad-spectrum antibiotics covering *Pseudomonas spp*. and methicillin-resistant *Staphylococcus aureus* are used (Table 7 [40,54,55,79,83]). Empirical antimycotic therapy must be promptly started if invasive fungal infection is suspected[79].

Treatment needs to be reassessed within 48-72 h; clinical and microbiological data help to modify therapy. In patients with documented infection, duration of therapy is based on the isolated organism and the site of infection. It is usually continued until recovering severe neutropenia; granulocyte colony-stimulating factors may be used[84]. In patients with FN of unidentified etiology, antibiotic therapy should be discontinued after 72 h of apyrexia and clinical recovery irrespective of absolute neutrophil count[56,85].

CARDIOVASCULAR DISORDERS

Several cardiovascular disorders may be developed in cancer patients such as sepsis/septic shock, chemotherapy-associated cardiotoxic disease (CACD), pulmonary embolism, and cardiac tamponade. In this section we refer to CACD since sepsis/septic shock is treated in other section, and pulmonary embolism and cardiac tamponade are nonspecific complication of cancer patients described in other high-quality articles[86,87].

Cardiovascular diseases and cancer are interwoven because of increased cancer survival and cardiotoxic anticancer therapy[88]. Up to 33% of cancer survivors may die due to heart disease[89]. Mortality rates in patients with CACD are 3.5-fold higher than those in patients with idiopathic cardiomyopathies[90]. Cardiovascular effects of chemotherapy may also affect the quality of life and compromise survival expectation.

Left ventricular dysfunction is the most common and serious consequence of CACD, usually secondary to cardiomyopathy or myocarditis (Table 8)[91,92]. Early

Table 7 Empiric antibiotic therapy in high-risk patients with febrile neutropenia[40,54,55,79,83]

Antibiotherapy	Indication
Antipseudomonal β-lactam agent (cefepime, ceftazidime)	All patients with febrile neutropenia
OR	
Carbapenem (meropenem or mipenem/cilastatin)	Hemodynamic instability
OR	
Piperacillin/tazobactam	
OR	
Novel cephalosporin/β-lactamase inhibitor (Ceftolozane/tazobactam or Ceftazidime/avibactam)	
PLUS	
Aminoglycosides (optional)	
PLUS	
Vancomycin	
Vancomycin, linezolid or daptomycin	Suspected catheter-related infections
	Skin or soft-tissue infection
	Risk of methicillin-resistant *Staphylococcus aureus*
Linezolid or daptomycin	Risk of vancomycin-resistant *Enterococcus spp.*
Carbapenem	Risk of extended-spectrum β-lactamase-producing gram negative bacteria
Polymyxin-colistin or tigecycline	Risk of *Klebsiella pneumonia* carbapenemase
Ciprofloxacin + clindamycin	Penicillin-allergic patients
OR	
Aztreonam + vancomycin	
Trimethoprim/sulfamethoxazole	Suspected *Pneumocystis* pneumonia
Antifungal drugs (echinocandins, amphotericin B lipid-based formulations)	Suspected invasive mycosis

Table 8 Main cardiovascular complications of oncological therapy[91,92]

Cardiovascular complications	Types	Oncological therapies
Left ventricular dysfunction	Cardiomyopathy or myocarditis	Anthracyclines (*e.g.*, doxorubicin, aunorubicin, epirubicin, idarubicin), antiangiogenic agents (*e.g.*, bevacisumab, sunitinib, sorafenib), alkylating agents (*e.g.*, cyclophosphamide, cisplatin), monoclonal antibodies (*e.g.*, trastuzumab, lapatinib), tyrosine kinase inhibitors (*e.g.*, imatinib, dasatinib, nilotinib, sunitinib, sorafenib, lapatinib)
Arrhythmias	QT prolongation, bradycardia, heart block; Atrial arrhythmias; Ventricular arrhythmias or sudden cardiac death	Taxanes, arsenic trioxide, tyrosine kinase inhibitors (*e.g.*, imatinib, dasatinib, nilotinib, sunitinib, sorafenib, lapatinib), anthracyclines(*e.g.*, doxorubicin, aunorubicin, epirubicin, idarubicin)
Coronary artery disease	Acute coronary syndromes (included acute myocardial infarction); Chronic ischemic heart disease	Antimetabolites (*e.g.*, gemcitabine, cytarabine), cisplatin, taxanes, thalidomide, bevacisumab, radiotherapy
Pericardial disease	Pericarditis (effusive or constrictive form)	Radiotherapy
Hypertension	New-onset or worsening	Vascular endothelial growth factor inhibitors, antiangiogenic agents (*e.g.*, bevacisumab, sunitinib, sorafenib), cisplatin, interleukins, interferon

CACD may be detected in up to 48% while late-onset disorders may be seen in up to 30%[93]. The highest incidence of CACD is reached by anthracyclines such as doxorubicin (3%-26%), alkylating agents such as cyclophosphamide (7%-28%), and monoclonal antibody such as trastuzumab (2%-28%)[94].

CACD is classified as type 1 or type 2 depending on the administered therapy[95].

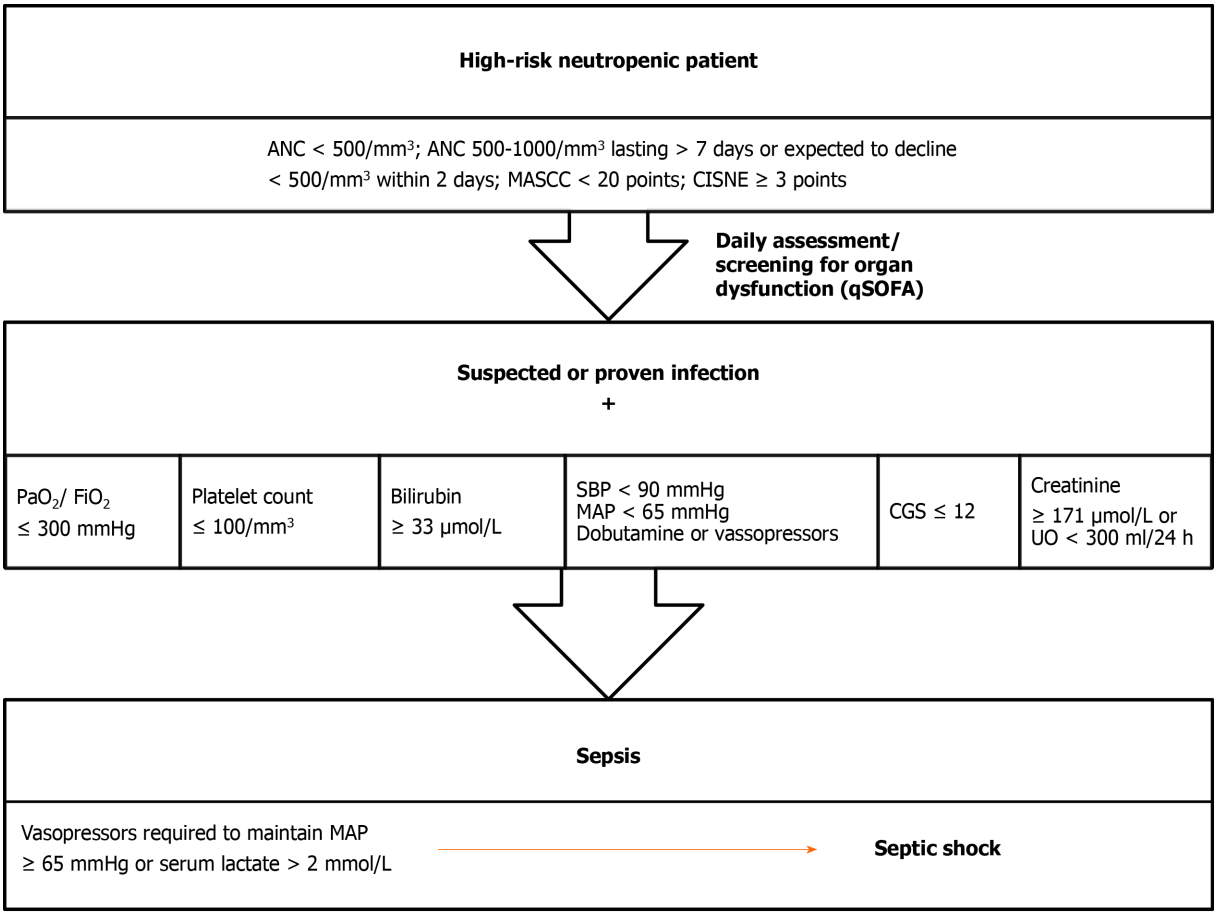

Figure 3 Sepsis diagnosis and treatment in neutropenic patients. ANC: Absolute neutrophil count; CISNE: Clinical Index of Stable Febrile Neutropenia score; CGS: Coma Glasgow Scale; MAP: Mean arterial pressure; MASCC: Multinational association of supportive care of cancer risk-index; SBP: Systolic blood pressure; UO: Urine output.

CACD type 1 is typically related to anthracycline drugs, not reversible with cessation of therapy, and dose-dependent; necrosis, vacuoles and disruption of sarcomeres are seen as histopathological findings. CACD type 2, usually associated with monoclonal antibodies such as trastuzumab, is reversible with cessation of therapy, dose-independent, and no ultrastructural disruption in cardiomyocyte cell is found.

There is no consensus to define CACD, but there is convergence regarding clinical or echocardiographic left ventricular dysfunction as the main condition[95]. Diagnosis of CACD can be made if at least one of the following criteria is reached[95,96]: (1) Cardiomyopathy with compromised left ventricular function; (2) Symptoms or signs of heart failure linked to the presence of third noise, tachycardia, or both; (3) Left ventricular ejection fraction (LVEF) less than 55% with a symptomatic decrease of 5%, or an asymptomatic decrease of 10%; and (4) Reduced LVEF > 10% from baseline or LVEF < 53% (the normal reference value for 2D echocardiography), confirmed in two consecutive echocardiography assessments within 2-3 wk apart.

Echocardiography was widely disseminated due to its easy availability, low cost, free of radiation, and information concerning the hemodynamic status and valvular diseases. There is no agreement regarding the time and frequency to achieve echocardiography in cancer patients on chemotherapy, although it is suitable before starting therapy (especially if there are cardiovascular risk factors or history of cardiac disease), during treatment, and 6 to 12 mo after completion[97].

Measurement of LVEF alone may overlook small changes. A variation in myocardial deformation, assessed by myocardial strain image, may precede significant decline in LVEF[98-100]. Magnetic resonance image (MRI) is very useful to determine the size of heart chambers and their function, but cannot be used at bedside for critically ill patients in the ICU. Thus, it should be used when other tests are inconclusive[91,95].

The high-sensitive cardiac troponins and N-terminal pro-B-type natriuretic peptide are cardiac biomarkers without general recommendation for diagnosis of cardiotoxicity; however, these noninvasive diagnostic methods are cheaper than other imaging studies or myocardial biopsy. Cardiac troponins are associated with

prognosis in patients on anticancer therapy; thus, higher plasma concentration requires closer monitoring and a possible therapy modification[91,101]. Cut-off points have not been established.

The treatment of adverse-side effects of antineoplastic therapy should be individualized depending on the risk factors for cardiotoxicity, severity, and prognosis (Figure 4[92,102,103]). The International Cardio Oncology Society-One trial found beneficial effects of prophylactic enalapril in patients on anthracycline therapy[104]. A recent study conducted in Brazil showed that carvedilol administered during chemotherapy reduced troponin levels and the risk of systolic dysfunction[105]. A recent meta-analysis showed the usefulness of β-blockers to preserve left ventricular function during anthracycline therapy[106]. Consequently, we would expect an increased cardiac tolerability with higher doses of chemotherapy with little or no interruption.

β-blockers may have further positive effects on malignancy. Since β-adrenergic receptors are overexpressed in malignant breast tissue, propranolol was tested on early-stage breast cancer patients[107]. Molecular analysis showed reduced Ki67 protein expression and decreased phosphorylation of mitogenic signaling regulators; additionally, reduced tumor proliferative indices, metastases rate, and mortality rate were also found[107]. Propranolol also modifies mitogenic and apoptotic signaling in late-stage breast cancer[108]. Long-term β-blockers improved survival outcomes in older ovarian cancer patients with cardiovascular disease[109].

Statins are drugs commonly used in patients with cardiovascular diseases and cancer. Statins regulates cell membrane integrity, cell signaling, protein synthesis, and cell cycle progression; they also modify angiogenesis and tumor growth[110]. Several studies demonstrated that statins are associated with reduced mortality rates in patients with breast cancer, renal cell carcinoma, and colorectal cancer[111,112]. A recent meta-analysis showed that statins was associated with improved outcomes in patients with lung cancer[113], but it was not supported by powered randomized controlled trials. Conversely, other meta-analysis of randomized controlled trials evidenced that statins did not improve overall survival rates or progression-free survival rates in patients with active cancer[114].

For patients with severe heart failure or cardiogenic shock, inotropic drugs and left ventricular mechanical support devices must be considered[115,116]. Glucocorticoids are the first-line therapy, and tumor necrosis factor-α inhibitors as second choice, for myocarditis with lymphocyte infiltration in patients treated with immune checkpoint inhibitors[91]. Cardiac transplant may be an option in selected patients. As expected, the criteria for transplanting these patients differ according to institution and country because active malignancy is generally considered as an absolute contraindication; nevertheless, it is interesting that survival rates after cardiac transplant in cancer patients is similar to those in noncancer patients[102,117].

Recently, cardio-oncology has emerged as a clinical (and scientific) area dedicated to diagnose and treat anticancer therapy-related cardiovascular complications to avoid interruption of treatment. This new discipline combine together cardiologists, oncologists, and hematologists in specialized units[118,119]. In institution without cardio-oncology unit, cancer patients with potentially fatal cardiovascular complications must be admitted to the ICU. Thus, it is necessary to adopt clinical guidelines according to the center resources to provide the best care, especially in cases with acute decompensated heart failure, cardiogenic shock, hypertensive emergency, and arrhythmias.

PERIOPERATIVE CARE

ICU is commonly required for cancer patients in the postoperative period because of the complexity of surgical procedure and potential complications. Topics regarding anesthetic management and surgical issues were addressed in this review.

General considerations

Effects of chemotherapy and radiotherapy on respiratory system must be recognized before orotracheal intubation. Severe mucositis lead to pseudomembranous material, edema, and bleeding, which compromises the airway and increases the risk of aspiration during endotracheal intubation. Radiation on the head and neck region may produce permanent tissular fibrosis limiting mouth opening and tongue mobility. Radiotherapy-associated airway fibrosis and tracheal stenosis, usually not recognized on physical examination, may affect intubation and ventilation[120]; thus, monitoring of pulse oximetry and arterial blood gases in perioperative period is mandatory.

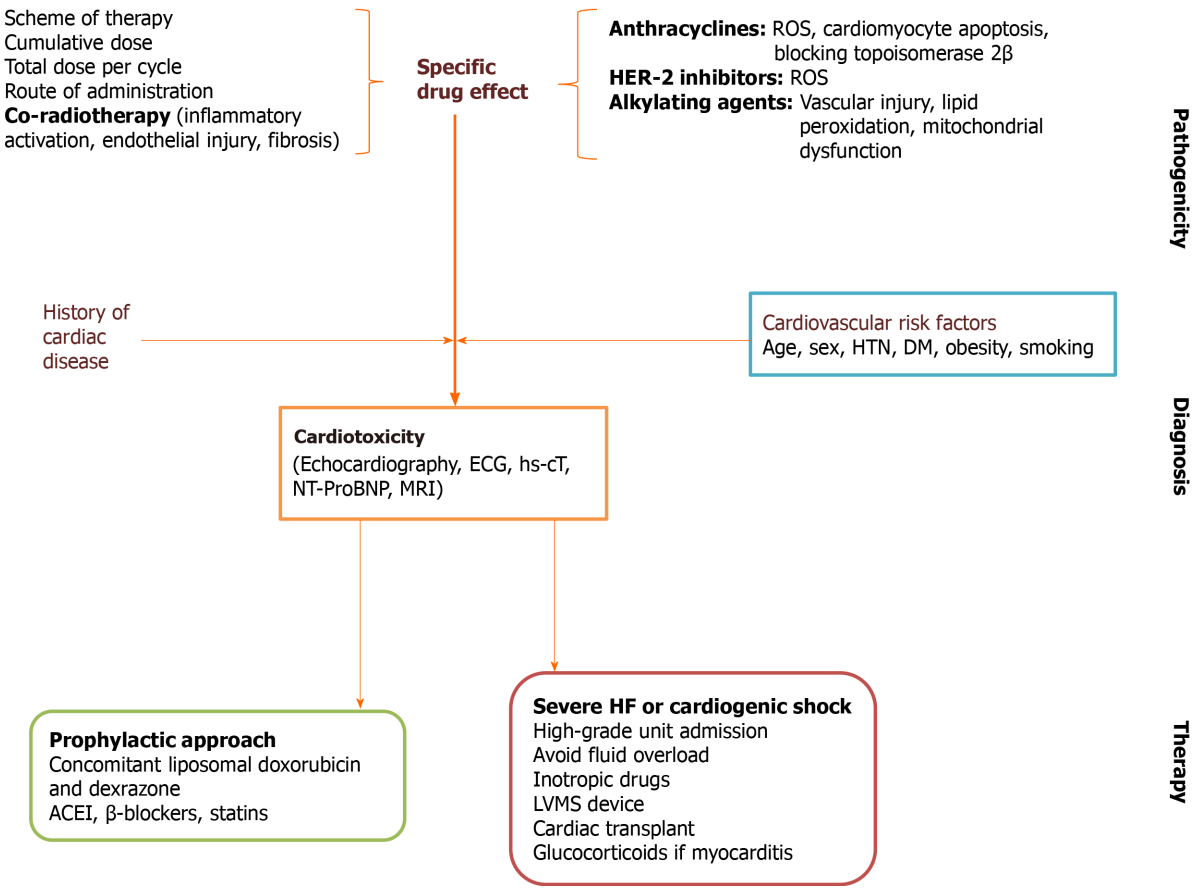

Figure 4 Pathogenic, diagnostic and therapeutic approach of chemotherapy-associated cardiac dysfunction[92,102,103]. ACEI: Angiotensin-converting enzyme inhibitor; ECG: Electrocardiography; DM: Diabetes mellitus; hs-cT: High-sensitive cardiac troponins; HTN: Arterial hypertension; LVMS: Left ventricular mechanical support; MRI: Magnetic resonance image; NT-ProBNP: N-terminal pro-B-type natriuretic peptide; ROS: Reactive oxygen species.

Excessive perioperative fluid administration has been correlated with surgical and pulmonary complications; therefore, fluid administration need to be monitored using dynamic indexes to optimize volume status[121,122]. Chemotherapy drugs such as bleomycin and mitomycin may cause lung toxicity[123]. However, in a large cohort of patients from the cancer registry of the Mayo Clinic, only seven patients receiving systemic bleomycin developed acute respiratory distress syndrome after surgery[124].

Transfusion-related immunomodulation is associated with decreased survival rates in cancer patients. This is a secondary phenomenon produced by multiple immunomodulatory mediators derived from white blood cells, red blood cells, and platelets of the donor[125]. Transfusion of red blood cells in the perioperative period affects the survival of cancer patient; thus, reducing blood transfusions could have a positive impact on outcome[126]. On the other hand, Manning-Geist *et al*[127] observed that perioperative transfusion of red blood cells after debulking surgery in ovarian cancer was not related with wound complication and thrombosis.

Anesthetic topics

Cancer surgery induces neuroendocrine and immune stress response, which may be reduced by regional anesthesia. Surgical manipulation is associated with spreading of tumorigenic cells and releasing cancer-growth factors[128]; thus, immune system modulation may contribute to reduce the incidence of metastases[129].

Changes in immune system has been reported with anesthetic gases[130]. Volatile anesthetics inhibit leukocyte activity and stimulate angiogenesis and metastases[131]; however, evidence is not conclusive because most studies were carried out *in vitro*. In ovarian cancer cells, isoflurane was related to cell cycle progression and cell proliferation, and increased expression of tumorigenic markers such as insulin-like growth factor 1 within the first 24 h[131]. In breast cancer surgery, preserved natural killer (NK) cells activity was found with propofol-paravertebral anesthesia while reduced NK activity was demonstrated using sevoflurane[132].

Hong *et al*[133] found that cancer patients treated with volatile inhaled anesthesia had

a 5-year overall survival rate similar to those on total intravenous anesthesia. The ENIGMA-II trial did not show negative effects of nitrous oxide on cancer recurrence or mortality[134]. Further randomized controlled trials are required.

Recent studies suggest that opioids inhibit the cellular and humoral immunity, promote proliferation and migration of tumor cells, and facilitate angiogenesis[129,135]. Opioid-induced immunomodulation is manifested in two ways: (1) Direct effects on immune cells *via* μ receptor and toll-like receptor 4 expressed in the surface of NK cells, macrophages and T-cells (peripheral effects)[136]; and (2) Indirect effects through the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, which suppress lymphocyte proliferation and NK cell cytotoxicity in lymphoid organs (central effects)[137,138]. Nonetheless, the type of drug and the administration period may modify the immunological effects of opioids[139,140] (Table 9[131,140-142]).

Propofol, a sedative drug commonly used in operating room and ICU, has been associated with tumor growth inhibition and reduced risk of metastasis. In patients undergoing hepatectomy for hepatocellular carcinoma and colon cancer surgery, propofol-based total intravenous anesthesia was associated with improved survival rates and reduced postoperative metastases compared with desflurane anesthesia[143,144]. Instead, Huang *et al*[145] observed no significant difference in locoregional recurrence or overall 5-year survival rates using desflurane or propofol anesthesia in patients undergoing breast cancer surgery.

Surgical topics

High-local chemotherapy concentration is reached using the hyperthermic intraperitoneal chemotherapy method. Systemic toxicity, including hematological toxicity, is less common than those with systemic administration of chemotherapy[146]; nonetheless, hematological and pulmonary toxicity may be occasionally produced with potentially fatal outcomes[147].

The Enhanced Recovery After Surgery (ERAS) program reduces surgical stress and improve recovery for an early hospital discharge. This approach includes three components[148,149]: (1) Preoperative: Preadmission counseling, early discharge planning, reduced fasting duration, carbohydrate loading, no/selective bowel preparation, antibiotic prophylaxis, thromboprophylaxis, pre-warming, and no premedication; (2) Intraoperative: Short-acting anesthetic agents, mid-thoracic epidural anesthesia/ analgesia, surgical techniques, no drains, avoidance of fluid overload, and maintenance of normothermia; and (3) Postoperative: Mid-thoracic epidural analgesia, no nasogastric tube, prevention of nausea and vomiting, avoidance of salt and fluid overload, early removal of catheters, early oral nutrition, nonopioid oral analgesia/nonsteroidal anti-inflammatory drugs, early mobilization, stimulation of gut motility (*e.g.*, chewing gum), defined discharge criteria, and audit of compliance and outcomes.

ERAS program has become a widely accepted surgical practice worldwide. Positive outcomes have been found in several surgical locations including elective and emergency surgery[149-151]. ERAS protocols have led to decreased length of hospitalization by 30% to 50%, as well as reduced complications, readmission rates, and health costs[149,142].

Laparoscopic surgery within ERAS protocols in cancer patients has also shown optimistic outcomes[153,154]. ERAS program resulted in improved outcomes, reduced hospitalization cost, and enhanced quality of life as shown by Wang *et al*[155] in a meta-analysis of elective gastric cancer surgery.

NEUROLOGICAL DISORDERS

Neurological symptoms and signs are commonly seen in cancer patients. Neurological symptoms may be the initial expression of undiagnosed cancer, emerge during the course of disease, or appear linked to treatment[156]. Cancer patient may also develop nonmalignancy-related neurological disorders, which require a rational approach to exclude cancer-related complications.

Neurological disorders require early diagnosis and treatment to reduce functional loss. Surgical treatment is often required, for which the multidisciplinary approach is mandatory[157]. Neurological disorders in cancer patient is produced by[158]: (1) Direct effects of tumor: Brain metastases, cerebral edema, seizures, spinal cord compression, hydrocephalus, leptomeningeal carcinomatosis; (2) Indirect effects of tumor: Paraneoplastic syndromes, stroke, cerebral venous thrombosis, infection, metabolic and electrolytic disorders; and (3) Treatment effects: Convulsions, cerebrovascular

Table 9 Immunological effects of opioids

Opioids	Immunological effects
Morphine	Decreased NK cell cytotoxicity[131]; Impaired intestinal barrier function[140]
Fentanyl and sufentanil	Decreased NK cell cytotoxicity[141]; Inhibition of cellular and humoral immunity[141]
Tramadol	Reverse the immunosuppression after surgery[142]

NK: Natural killer.

accident (*e.g.*, intracranial hemorrhage due to thrombocytopenia, venous sinus thrombosis), leukoencephalopathy, loss of vision or hearing, peripheral neuropathy, aseptic meningitis, opportunistic infections, acute or late post-radiation necrosis.

The most common neurological emergencies are brain metastases, seizures, and obstructive hydrocephalus[156]. Intracranial hypertension related to cerebral edema, hydrocephalus or mass effect is commonly seen.

Brain metastases

Brain metastases complicate up to 20% of cancer patients and are 10-fold more frequent than primary brain tumors[159]. Cancer producing metastases are lung (*e.g.*, nonsmall cells), breast (*e.g.*, HER-2), kidney and melanoma[158,160]. Fifty percent of metastases are solitarylesion. Distribution of brain metastases are cerebral hemispheres (80%), cerebellum (15%) and brainstem (3%). Cerebral edema associated with metastases produces intracranial hypertension. Pathogenesis of edema is complex, including vasogenic edema secondary to capillary leakage, venous stasis, and cerebrospinal fluid obstruction[159,160].

Cerebral metastases may be the initial feature of cancer in 8-10% of cases. It may be characterized by intracranial hypertension with alterations in level of consciousness, headache, and vomiting; focal neurological deficit such as sensory or motor defects, speech disorders, instability, and cognitive impairment; or asymptomatic. Seizures almost always occur when there are multiple metastases, intralesional bleeding, herniation, hydrocephalus, or sudden-onset ischemia of large vessels[158,160]. Diagnosis is made by contrast enhanced MRI. Contrasted CT is useful if MRI is contraindicated or intracranial hemorrhage is suspected, but it is less sensitive for posterior fossa or small tumors[159,160].

Treatment is discouraging. Several factors such as type and location of primary tumor, age, and extracranial disease are involved in prognosis. Therapeutic options include surgical resection, radiotherapy, stereotactic radiosurgery and chemotherapy[159-167]. In patients with good performance status and known primary tumor, surgical resection of unique lesions of noneloquent areas followed by radiation therapy is recommended[159]. In eloquent area lesions, radiation therapy is preferred. Radiation of the entire skull is chosen for multiple and symptomatic metastases, although prognosis is not improved and almost half of patients die due to neurological progression[162,163]. Traditional cytotoxic chemotherapy is not routinely used in the treatment of brain metastases because of low response rates[164]; however, germ-cell tumors and non-Hogdkin lymphoma with nervous system involvement are treated with chemotherapy[166,167]. Metastases secondary to melanoma and renal carcinoma do not respond to chemotherapy[158]. Targeted therapies and immunotherapy are promising oncospecific therapies[168-172].

Despite aggressive treatment, many patients develop malignant cerebral edema and seizures. Cerebral edema occurs through disruption of blood-brain barrier by direct effect of metastases, as well as released several cytokines and growth factors by the tumor cells including the endothelial vascular growth factor with promoting angiogenesis[159]. These factors favor endothelial clefts formation with fragmentation and fenestration of endothelium, and consequently, injury to the basement membrane[159]. Vasogenic edema with fluid leakage and increased interstitial fluid pressure is then developed. Peritumoral edema eventually leads to symptoms and signs of mass effect and increased intracranial pressure.

Glucocorticoids are indicated for all symptomatic patients with metastases-associated cerebral edema. Dexamethasone is the most used due to its long half-life and lower mineralocorticoid activity. Recommended dose is 4-8 mg/d (up to 16 mg/d in very severe symptomatic patients). Higher doses have not additional benefits and side effects may occur. Dexamethasone doses should be progressively decreased in 2

or more weeks to avoid complications of chronic steroid administration (*e.g.*, immunosuppression, hyperglycemia, increased risk of opportunistic infections)[173]. Other therapies include hyperventilation, hypertonic sodium chloride or mannitol 20% in severe intracranial hypertension to prevent herniation in neurocritically ill patients[174].

Seizure

Seizure complicating brain tumor is commonly found as simple, complex-partial or generalized epilepsy[158]. Status epilepticus may also be developed. Seizures depend on the type and location of brain tumor, as well as cancer-related complication. The reasons of cancer-related seizure are listed in Table 10. Diagnosis is made by clinical feature and electroencephalography showing epileptic changes on brain waves. Epileptiform waves could be present even in absence of clinically visible seizures[175]. Hemiplegia and other focal symptoms may appear up 75% of patients depending on tumor location; infratentorial disease is related toataxia, vomiting, dysarthria and nystagmus[158].

Seizure prophylaxis is not recommended for patients with brain tumor; however, this is a controversial recommendation because of improved accurate diagnosis and prognosis using the current continuous electroencephalography, and the introduction of newer and less toxic anticonvulsants (*e.g.*, levetiracetam, lamotrigine, and lacosamide)[176]. Once airway, breathing, circulation, and "dextrose" (the "ABCDs") have been addressed, acute seizure is treated with parenteral benzodiazepines (*e.g.*, IV lorazepam or diazepam; intramuscular midazolam) as first-line agents. Second-line therapy (*e.g.*, phenytoin/fosphenytoin, valproic acid, phenobarbital, or levetiracetam) should be initiated within 30 min if first-line treatment failed. If second-line agents are ineffective, treatment is escalated to anesthetic agents such as continuous infusion of midazolam, propofol, or pentobarbital[177]. When mass effect or worsening edema is present, dexamethasone can be effective in controlling seizures. For metastasis-related seizures, chemotherapy, radiotherapy and surgery are alternative therapies. Surgical resection is recommended for patients with tumor located in the posterior fossa. Early diagnosis and urgent correction are required for metabolic or electrolytic imbalance-induced seizures.

Maintenance anticonvulsant medication requires more careful evaluation since the old anticonvulsants (*e.g.*, phenytoin, carbamazepine, and phenobarbital) simultaneously induce CYP coenzymes. These coenzymes accelerate the metabolism of steroids and chemotherapeutic agents. Newer antiepileptic drugs such as levetiracetam, without CYP metabolism, are recommended in these circumstances. Other options are gabapentin, pregabalin, lamotrigine, and lacosamide[178].

Acute hydrocephalus

Acute hydrocephalus is a medical emergency caused by a stopped cerebrospinal fluid (CSF) flow or an increased CSF content. Table 10 lists the reasons of acute hydrocephalus in cancer patients. Since 80% of maximum ventricular dilation is reached in almost 6 h, acute hydrocephalus may be rapidly developed. Clinical diagnosis is suspected in patients presenting headache, blurred vision, transient loss of visual field, ataxia, vomiting, and impaired consciousness. Headache is present in 50% of cases (on occipital region if increased intracranial pressure), exacerbates with the Valsalva maneuver, and is associated with nausea and vomiting[158,160]. Papilledema and focal neurological signs may be present. Tumor interference the CSF flow with a valve-way mechanism at the level of third or fourth ventricle may result in periodic increased intracranial pressure[160]. Noncontrasted CT scan allows identifying the size of ventricles. Obstructive hydrocephalus is classically characterized by ventriculomegaly proximal to the site of obstruction and periventricular edema.

The treatment of acute hydrocephalus should be early and effective. Several procedures have been described such as emergency ventriculostomy, ventricular bypass, endoscopic ventriculostomy, aqueductoplasty (due to aqueduct stenosis), septostomy (in isolated lateral hydrocephalus), and in some cases tumor debunking. Radiotherapy and chemotherapy are options in patients with hydrocephalus secondary to leptomeningeal carcinomatosis or metastatic CSF seeding. Patients with nonsevere obstructive hydrocephalus could be treated with osmotic agents to reduce intracranial pressure (*e.g.*, manitol 20% or hypertonic sodium chloride) and/ or drug interfering with CSF production such as acetazolamide, furosemide, and glucocorticoids[179].

Table 10 Causes of cancer-related seizure and cancer-related acute hydrocephalus[158]

Causes	Comments
Cancer-related seizure	
Low-grade tumors	Glioma and oligodendroglioma have intrinsic epileptogenic activity as a result of their long survival and reduced seizure threshold
High-grade tumors	Usually secondary to necrosis, hemorrhage or edema
Brain metastases	Up to 40%
Tumor location	Cortical tumors and those on epileptogenic areas (*e.g.*, mesial temporal lobe and insula) are associated with intractable epilepsy
Stroke	Ischemic or hemorrhagic
Drug toxicity	Cytarabine, methotrexate, cisplatin, vincristine, cyclophosphamide, anthracyclines
Neoplastic meningitis	
Paraneoplastic encephalitis	
Central nervous system infections	
Electrolytic imbalance	Hyponatremia, hypocalcaemia
Metabolic disorders	Hypoglycemia
Liver or kidney failure	
Aggravated preexisting epilepsy	Withdrawal medication
Cancer-related acute hydrocephalus	
Stopped CSF flow by tumor obstruction of ventricular system	Colloid cysts, ependymoma, intraventricular meningioma, choroid plexus papilloma or posterior fossa tumor; in adults it is often due to leptomeningeal carcinomatosis and intra-ventricular extension of metastasis
Increased CSF content due to deficit in reabsorption	Venous sinus thrombosis, infectious meningitis, metastatic seeding or subarachnoid hemorrhage

CSF: Cerebrospinal fluid.

CHEMOTHERAPY IN ICU

Chemotherapy in ICU may be an option for patients with critical illness driven by the oncological disease, scheduled or ongoing chemotherapy in absence of contraindications, and requirement for monitoring or preventing potentially severe chemotherapy-side effects in high risk patients. Particularly, anticancer chemo or radiotherapy is necessary in cases of acute respiratory failure due to high grade non-Hodgkin lymphoma or hyperleukocytosis[5]. Antineoplastic drugs used by ICU team may be challenging due to little experience; indeed, associated sepsis or organ support methods at the time of chemotherapy onset are erroneously considered as a contraindication[6].

Organ support therapies accompanied by chemotherapy may be beneficial in critically ill patients with cancer-related organ dysfunction[180]. Patient's consent, comorbidities, performance status, cancer-related life expectancy, and life-span-expanding treatment are necessary to be evaluated to improve outcome. A close collaboration with the attending oncologist or hematologist is mandatory. Organizational issues should be assured for success, including clinical protocols, securing of the medication circuit, consultation with pharmacist and experienced nurses, and daily rounds with the attending oncologist or hematologist[181].

Studies identifying prognostic factors and outcomes of patients receiving chemotherapy in the ICU are scarce and have several limitations such as retrospective design, small sample size, and several nature of cancer[182-184]. Additionally, the following period and subgroup of analyzed patients may have an impact on clinical response (*e.g.*, solid tumor vs. hematological malignancy; traditional chemotherapy vs. targeted immunotherapy; urgent vs. maintenance chemotherapy), which need to be considered to state prognosis.

ICU and hospital mortality rates for patients with solid tumors who received chemotherapy in ICU range from 25% to 54%, and 58% to 77%, respectively[182-184]. One-year survival rates are as low as 7%-12%[182,183]. Lung cancer and acute respiratory failure due to airway compression or pulmonary infiltrates may explain the high

mortality rates[182-184]. In patients with hematological malignancy 25%-40% die in the ICU; 30-d, 6-mo and 1-year mortality rates is 40%, 51%-77% and 50%, respectively[10,185]. Risk factors for mortality are degree of organ dysfunction and life-support methods such as ventilatory support, vasopressors, and renal replacement therapy.

CONCLUSION

Patients with cancer and organ dysfunction need to be early admitted to ICU for improving survival. Clinical and pathophysiological condition, cancer status, and expected life-span must be collectively evaluated to decide full or time-limited organ support methods. Specific disorders require a specialized and well-trained medical staff to optimize diagnosis, enhance treatment, and improve outcomes.

REFERENCES

1 **Heron M**. Deaths: Leading Causes for 2016. *Natl Vital Stat Rep* 2018; **67**: 1-77 [PMID: 30248017]
2 **Jemal A**, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, Mariotto A, Lake AJ, Wilson R, Sherman RL, Anderson RN, Henley SJ, Kohler BA, Penberthy L, Feuer EJ, Weir HK. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *J Natl Cancer Inst* 2017; **109**: djx030 [PMID: 28376154 DOI: 10.1093/jnci/djx030]
3 **Yeh ET**, Chang HM. Oncocardiology-Past, Present, and Future: A Review. *JAMA Cardiol* 2016; **1**: 1066-1072 [PMID: 27541948 DOI: 10.1001/jamacardio.2016.2132]
4 **American Society of Clinical Oncology**. The State of Cancer Care in America, 2017: A Report by the American Society of Clinical Oncology. *J Oncol Pract* 2017; **13**: e353-e394 [PMID: 28326862 DOI: 10.1200/JOP.2016.020743]
5 **Kiehl MG**, Beutel G, Böll B, Buchheidt D, Forkert R, Fuhrmann V, Knöbl P, Kochanek M, Kroschinsky F, La Rosée P, Liebregts T, Lück C, Olgemoeller U, Schalk E, Shimabukuro-Vornhagen A, Sperr WR, Staudinger T, von Bergwelt Baildon M, Wohlfarth P, Zeremski V, Schellongowski P; Consensus of the German Society of Hematology and Medical Oncology (DGHO), Austrian Society of Hematology and Oncology (OeGHO), German Society for Medical Intensive Care Medicine and Emergency Medicine (DGIIN), and Austrian Society of Medical and General Intensive Care and Emergency Medicine (ÖGIAIN). Consensus statement for cancer patients requiring intensive care support. *Ann Hematol* 2018; **97**: 1271-1282 [PMID: 29704018 DOI: 10.1007/s00277-018-3312-y]
6 **Azoulay E**, Schellongowski P, Darmon M, Bauer PR, Benoit D, Depuydt P, Divatia JV, Lemiale V, van Vliet M, Meert AP, Mokart D, Pastores SM, Perner A, Pène F, Pickkers P, Puxty KA, Vincent F, Salluh J, Soubani AO, Antonelli M, Staudinger T, von Bergwelt-Baildon M, Soares M. The Intensive Care Medicine research agenda on critically ill oncology and hematology patients. *Intensive Care Med* 2017; **43**: 1366-1382 [PMID: 28725926 DOI: 10.1007/s00134-017-4884-z]
7 **Puxty K**, McLoone P, Quasim T, Sloan B, Kinsella J, Morrison DS. Risk of Critical Illness Among Patients With Solid Cancers: A Population-Based Observational Study. *JAMA Oncol* 2015; **1**: 1078-1085 [PMID: 26313462 DOI: 10.1001/jamaoncol.2015.2855]
8 **Shimabukuro-Vornhagen A**, Böll B, Kochanek M, Azoulay É, von Bergwelt-Baildon MS. Critical care of patients with cancer. *CA Cancer J Clin* 2016; **66**: 496-517 [PMID: 27348695 DOI: 10.3322/caac.21351]
9 **Bos MM**, Verburg IW, Dumaij I, Stouthard J, Nortier JW, Richel D, van der Zwan EP, de Keizer NF, de Jonge E. Intensive care admission of cancer patients: a comparative analysis. *Cancer Med* 2015; **4**: 966-976 [PMID: 25891471 DOI: 10.1002/cam4.430]
10 **Wigmore T**, Farquhar-Smith P. Outcomes for Critically Ill Cancer Patients in the ICU: Current Trends and Prediction. *Int Anesthesiol Clin* 2016; **54**: e62-e75 [PMID: 27623129 DOI: 10.1097/AIA.0000000000000121]
11 **Torres VB**, Vassalo J, Silva UV, Caruso P, Torelly AP, Silva E, Teles JM, Knibel M, Rezende E, Netto JJ, Piras C, Azevedo LC, Bozza FA, Spector N, Salluh JI, Soares M. Outcomes in Critically Ill Patients with Cancer-Related Complications. *PLoS One* 2016; **11**: e0164537 [PMID: 27764143 DOI: 10.1371/journal.pone.0164537]
12 **De la Hoz A**, Cortés JA. Bacterial and Atypical Infections in Critically Ill Cancer Patients. In: Nates JL, Price KJ, editors. Oncologic Critical Care. Cham: Springer, 2019: 1-22 [DOI: 10.1007/978-3-319-74698-2_123-1]
13 **Schellongowski P**, Kiehl M, Kochanek M, Staudinger T, Beutel G; Intensive Care in Hematologic-Oncologic Patients (iCHOP). Intensive care for cancer patients: An interdisciplinary challenge for cancer specialists and intensive care physicians. *Memo* 2016; **9**: 39-44 [PMID: 27069513 DOI: 10.1007/s12254-016-0256-6]
14 **Martos-Benítez FD**, Soto-García A, Gutiérrez-Noyola A. Clinical characteristics and outcomes of cancer patients requiring intensive care unit admission: a prospective study. *J Cancer Res Clin Oncol* 2018; **144**: 717-723 [PMID: 29362918 DOI: 10.1007/s00432-018-2581-0]
15 **Soubani AO**. Critical Care Prognosis and Outcomes in Patients with Cancer. *Clin Chest Med* 2017; **38**: 333-353 [PMID: 28477643 DOI: 10.1016/j.ccm.2016.12.011]
16 **Biskup E**, Cai F, Vetter M, Marsch S. Oncological patients in the intensive care unit: prognosis, decision-making, therapies and end-of-life care. *Swiss Med Wkly* 2017; **147**: w14481 [PMID: 28804862 DOI:

10.4414/smw.2017.14481]
17 **Azoulay E**, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J, Vincent F, Nyunga M, Bruneel F, Laisne LM, Rabbat A, Lebert C, Perez P, Chaize M, Renault A, Meert AP, Benoit D, Hamidfar R, Jourdain M, Darmon M, Schlemmer B, Chevret S, Lemiale V. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en réanimation onco-hématologique study. *J Clin Oncol* 2013; **31**: 2810-2818 [PMID: 23752112 DOI: 10.1200/JCO.2012.47.2365]
18 **Mokart D**, Lambert J, Schnell D, Fouché L, Rabbat A, Kouatchet A, Lemiale V, Vincent F, Lengliné E, Bruneel F, Pene F, Chevret S, Azoulay E. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. *Leuk Lymphoma* 2013; **54**: 1724-1729 [PMID: 23185988 DOI: 10.3109/10428194.2012.753446]
19 **Lengliné E**, Raffoux E, Lemiale V, Darmon M, Canet E, Boissel N, Schlemmer B, Dombret H, Azoulay E. Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure. *Leuk Lymphoma* 2012; **53**: 1352-1359 [PMID: 22233111 DOI: 10.3109/10428194.2011.649752]
20 **Hanzelka KM**, Yeung SC, Chisholm G, Merriman KW, Gaeta S, Malik I, Rice TW. Implementation of modified early-goal directed therapy for sepsis in the emergency center of a comprehensive cancer center. *Support Care Cancer* 2013; **21**: 727-734 [PMID: 22956191 DOI: 10.1007/s00520-012-1572-y]
21 **Song JU**, Suh GY, Park HY, Lim SY, Han SG, Kang YR, Kwon OJ, Woo S, Jeon K. Early intervention on the outcomes in critically ill cancer patients admitted to intensive care units. *Intensive Care Med* 2012; **38**: 1505-1513 [PMID: 22592633 DOI: 10.1007/s00134-012-2594-0]
22 **Ñamendys-Silva SA**, Plata-Menchaca EP, Rivero-Sigarroa E, Herrera-Gómez A. Opening the doors of the intensive care unit to cancer patients: A current perspective. *World J Crit Care Med* 2015; **4**: 159-162 [PMID: 26261768 DOI: 10.5492/wjccm.v4.i3.159]
23 **Shrime MG**, Ferket BS, Scott DJ, Lee J, Barragan-Bradford D, Pollard T, Arabi YM, Al-Dorzi HM, Baron RM, Hunink MG, Celi LA, Lai PS. Time-Limited Trials of Intensive Care for Critically Ill Patients With Cancer: How Long Is Long Enough? *JAMA Oncol* 2016; **2**: 76-83 [PMID: 26469222 DOI: 10.1001/jamaoncol.2015.3336]
24 **Azoulay E**, Pickkers P, Soares M, Perner A, Rello J, Bauer PR, van de Louw A, Hemelaar P, Lemiale V, Taccone FS, Martin Loeches I, Meyhoff TS, Salluh J, Schellongowski P, Rusinova K, Terzi N, Mehta S, Antonelli M, Kouatchet A, Barratt-Due A, Valkonen M, Landburg PP, Bruneel F, Bukan RB, Pène F, Metaxa V, Moreau AS, Souppart V, Burghi G, Girault C, Silva UVA, Montini L, Barbier F, Nielsen LB, Gaborit B, Mokart D, Chevret S; Efraim investigators and the Nine-I study group. Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. *Intensive Care Med* 2017; **43**: 1808-1819 [PMID: 28948369 DOI: 10.1007/s00134-017-4947-1]
25 **Azoulay E**, Mokart D, Kouatchet A, Demoule A, Lemiale V. Acute respiratory failure in immunocompromised adults. *Lancet Respir Med* 2019; **7**: 173-186 [PMID: 30529232 DOI: 10.1016/S2213-2600(18)30345-X]
26 **Bergeron A**, Chevret S, Peffault de Latour R, Chagnon K, de Margerie-Mellon C, Rivière F, Robin M, Mani J, Lorillon G, Socié G, Tazi A. Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. *Eur Respir J* 2018; **51**: 1702617 [PMID: 29650555 DOI: 10.1183/13993003.02617-2017]
27 **Mayer S**, Pastores SM, Riedel E, Maloy M, Jakubowski AA. Short- and long-term outcomes of adult allogeneic hematopoietic stem cell transplant patients admitted to the intensive care unit in the peritransplant period. *Leuk Lymphoma* 2017; **58**: 382-390 [PMID: 27347608 DOI: 10.1080/10428194.2016.1195499]
28 **Cupp J**, Culakova E, Poniewierski MS, Dale DC, Lyman GH, Crawford J. Analysis of Factors Associated With In-hospital Mortality in Lung Cancer Chemotherapy Patients With Neutropenia. *Clin Lung Cancer* 2018; **19**: e163-e169 [PMID: 29233611 DOI: 10.1016/j.cllc.2017.10.013]
29 **Gupta M**, Sahi MS, Bhargava AK, Talwar V. A Prospective Evaluation of Symptom Prevalence and Overall Symptom Burden Among Cohort of Critically Ill Cancer Patients. *Indian J Palliat Care* 2016; **22**: 118-124 [PMID: 27162420 DOI: 10.4103/0973-1075.179601]
30 **Yoo H**, Suh GY, Jeong BH, Lim SY, Chung MP, Kwon OJ, Jeon K. Etiologies, diagnostic strategies, and outcomes of diffuse pulmonary infiltrates causing acute respiratory failure in cancer patients: a retrospective observational study. *Crit Care* 2013; **17**: R150 [PMID: 23880212 DOI: 10.1186/cc12829]
31 **Almeida IC**, Soares M, Bozza FA, Shinotsuka CR, Bujokas R, Souza-Dantas VC, Ely EW, Salluh JI. The impact of acute brain dysfunction in the outcomes of mechanically ventilated cancer patients. *PLoS One* 2014; **9**: e85332 [PMID: 24465538 DOI: 10.1371/journal.pone.0085332]
32 **Azevedo LCP**, Caruso P, Silva UVA, Torelly AP, Silva E, Rezende E, Netto JJ, Piras C, Lobo SMA, Knibel MF, Teles JM, Lima RA, Ferreira BS, Friedman G, Rea-Neto A, Dal-Pizzol F, Bozza FA, Salluh JIF, Soares M; Brazilian Research in Intensive Care Network (BRICNet). Outcomes for patients with cancer admitted to the ICU requiring ventilatory support: results from a prospective multicenter study. *Chest* 2014; **146**: 257-266 [PMID: 24480886 DOI: 10.1378/chest.13-1870]
33 **Lamba TS**, Sharara RS, Singh AC, Balaan M. Pathophysiology and Classification of Respiratory Failure. *Crit Care Nurs Q* 2016; **39**: 85-93 [PMID: 26919670 DOI: 10.1097/CNQ.0000000000000102]
34 **Martos-Benítez FD**, Gutiérrez-Noyola A, Badal M, Dietrich NA. Risk factors and outcomes of severe acute respiratory failure requiring invasive mechanical ventilation in cancer patients: A retrospective cohort study. *Med Intensiva* 2018; **42**: 354-362 [PMID: 28966007 DOI: 10.1016/j.medin.2017.08.004]
35 **Pastores SM**, Voigt LP. Acute respiratory failure in the patient with cancer: diagnostic and management strategies. *Crit Care Clin* 2010; **26**: 21-40 [PMID: 19944274 DOI: 10.1016/j.ccc.2009.10.001]
36 **Zampieri FG**, Bozza FA, Moralez GM, Mazza DD, Scotti AV, Santino MS, Ribeiro RA, Rodrigues Filho EM, Cabral MM, Maia MO, D'Alessandro PS, Oliveira SV, Menezes MA, Caser EB, Lannes RS, Alencar Neto MS, Machado MM, Sousa MF, Salluh JI, Soares M. The effects of performance status one week before hospital admission on the outcomes of critically ill patients. *Intensive Care Med* 2017; **43**: 39-47 [PMID: 27686352 DOI: 10.1007/s00134-016-4563-5]

37 **Elicker BM**, Jones KT, Naeger DM, Frank JA. Imaging of Acute Lung Injury. *Radiol Clin North Am* 2016; **54**: 1119-1132 [PMID: 27719979 DOI: 10.1016/j.rcl.2016.05.006]

38 **Azoulay É**, Canet E, Raffoux E, Lengliné E, Lemiale V, Vincent F, de Labarthe A, Seguin A, Boissel N, Dombret H, Schlemmer B. Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. *Eur Respir J* 2012; **39**: 648-653 [PMID: 21828031 DOI: 10.1183/09031936.00057711]

39 **Schellongowski P**, Staudinger T, Kundi M, Laczika K, Locker GJ, Bojic A, Robak O, Fuhrmann V, Jäger U, Valent P, Sperr WR. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with de novo acute myeloid leukemia: a single center experience. *Haematologica* 2011; **96**: 231-237 [PMID: 21071501 DOI: 10.3324/haematol.2010.031583]

40 **Maschmeyer G**, Carratalà J, Buchheidt D, Hamprecht A, Heussel CP, Kahl C, Lorenz J, Neumann S, Rieger C, Ruhnke M, Salwender H, Schmidt-Hieber M, Azoulay E. Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Oncol* 2015; **26**: 21-33 [PMID: 24833776 DOI: 10.1093/annonc/mdu192]

41 **Wieruszewski PM**, Herasevich S, Gajic O, Yadav H. Respiratory failure in the hematopoietic stem cell transplant recipient. *World J Crit Care Med* 2018; **7**: 62-72 [PMID: 30370228 DOI: 10.5492/wjccm.v7.i5.62]

42 **White PL**, Backx M, Barnes RA. Diagnosis and management of Pneumocystis jirovecii infection. *Expert Rev Anti Infect Ther* 2017; **15**: 435-447 [PMID: 28287010 DOI: 10.1080/14787210.2017.1305887]

43 **Blanchard E**, Gabriel F, Jeanne-Leroyer C, Servant V, Dumas PY. [Invasive pulmonary aspergillosis]. *Rev Mal Respir* 2018; **35**: 171-187 [PMID: 29478757 DOI: 10.1016/j.rmr.2018.01.002]

44 **Koo HJ**, Lim S, Choe J, Choi SH, Sung H, Do KH. Radiographic and CT Features of Viral Pneumonia. *Radiographics* 2018; **38**: 719-739 [PMID: 29757717 DOI: 10.1148/rg.2018170048]

45 **Rochwerg B**, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P Members Of The Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; **50**: 1602426 [PMID: 28860265 DOI: 10.1183/13993003.02426-2016]

46 **Berbenetz N**, Wang Y, Brown J, Godfrey C, Ahmad M, Vital FM, Lambiase P, Banerjee A, Bakhai A, Chong M. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2019; **4**: CD005351 [PMID: 30950507 DOI: 10.1002/14651858.CD005351.pub4]

47 **Frat JP**, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M, Constantin JM, Tonnelier JM, Pierrot M, Mathonnet A, Béduneau G, Delétage-Métreau C, Richard JC, Brochard L, Robert R; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; **372**: 2185-2196 [PMID: 25981908 DOI: 10.1056/NEJMoa1503326]

48 **Lemiale V**, Mokart D, Mayaux J, Lambert J, Rabbat A, Demoule A, Azoulay E. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care* 2015; **19**: 380 [PMID: 26521922 DOI: 10.1186/s13054-015-1097-0]

49 **Mauri T**, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, Bottino N, Lissoni A, Spadaro S, Volta CA, Gattinoni L, Pesenti A, Grasselli G. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. *Intensive Care Med* 2017; **43**: 1453-1463 [PMID: 28762180 DOI: 10.1007/s00134-017-4890-1]

50 **Frat JP**, Ragot S, Girault C, Perbet S, Prat G, Boulain T, Demoule A, Ricard JD, Coudroy R, Robert R, Mercat A, Brochard L, Thille AW; REVA network. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *Lancet Respir Med* 2016; **4**: 646-652 [PMID: 27245914 DOI: 10.1016/S2213-2600(16)30093-5]

51 **Lemiale V**, Mokart D, Resche-Rigon M, Pène F, Mayaux J, Faucher E, Nyunga M, Girault C, Perez P, Guitton C, Ekpe K, Kouatchet A, Théodose I, Benoit D, Canet E, Barbier F, Rabbat A, Bruneel F, Vincent F, Klouche K, Loay K, Mariotte E, Bouadma L, Moreau AS, Seguin A, Meert AP, Reignier J, Papazian L, Mehzari I, Cohen Y, Schenck M, Hamidfar R, Darmon M, Demoule A, Chevret S, Azoulay E; Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH). Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2015; **314**: 1711-1719 [PMID: 26444879 DOI: 10.1001/jama.2015.12402]

52 **Cheng LC**, Chang SP, Wang JJ, Hsiao SY, Lai CC, Chao CM. The Impact of High-Flow Nasal Cannula on the Outcome of Immunocompromised Patients with Acute Respiratory Failure: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)* 2019; **55**: 693 [PMID: 31623276 DOI: 10.3390/medicina55100693]

53 **Coudroy R**, Frat JP, Ehrmann S, Pène F, Terzi N, Decavèle M, Prat G, Garret C, Contou D, Bourenne J, Gacouin A, Girault C, Dellamonica J, Malacrino D, Labro G, Quenot JP, Herbland A, Jochmans S, Devaquet J, Benzekri D, Vivier E, Nseir S, Colin G, Thévenin D, Grasselli G, Assefi M, Guerin C, Bougon D, Lherm T, Kouatchet A, Ragot S, Thille AW; REVA Network. High-flow nasal oxygen therapy alone or with non-invasive ventilation in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure: the randomised multicentre controlled FLORALI-IM protocol. *BMJ Open* 2019; **9**: e029798 [PMID: 31401603 DOI: 10.1136/bmjopen-2019-029798]

54 **Klemencic S**, Perkins J. Diagnosis and Management of Oncologic Emergencies. *West J Emerg Med* 2019; **20**: 316-322 [PMID: 30881552 DOI: 10.5811/westjem.2018.12.37335]

55 **Hansen BA**, Wendelbo Ø, Bruserud Ø, Hemsing AL, Mosevoll KA, Reikvam H. Febrile Neutropenia in Acute Leukemia. Epidemiology, Etiology, Pathophysiology and Treatment. *Mediterr J Hematol Infect Dis* 2020; **12**: e2020009 [PMID: 31934319 DOI: 10.4084/MJHID.2020.009]

56 **Stern A**, Carrara E, Bitterman R, Yahav D, Leibovici L, Paul M. Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer. *Cochrane Database Syst Rev* 2019; **1**: CD012184 [PMID: 30605229 DOI: 10.1002/14651858.CD012184.pub2]

57 **Mokart D**, Darmon M, Resche-Rigon M, Lemiale V, Pène F, Mayaux J, Rabbat A, Kouatchet A, Vincent F, Nyunga M, Bruneel F, Lebert C, Perez P, Renault A, Hamidfar R, Jourdain M, Meert AP, Benoit D, Chevret S, Azoulay E. Prognosis of neutropenic patients admitted to the intensive care unit. *Intensive Care Med* 2015; **41**: 296-303 [PMID: 25578678 DOI: 10.1007/s00134-014-3615-y]

58 **Georges Q**, Azoulay E, Mokart D, Soares M, Jeon K, Oeyen S, Rhee CK, Gruber P, Ostermann M, Hill QA, Depuydt P, Ferra C, Toffart AC, Schellongowski P, Müller A, Lemiale V, Tinquaut F, Bourmaud A, Darmon M. Influence of neutropenia on mortality of critically ill cancer patients: results of a meta-analysis on individual data. *Crit Care* 2018; **22**: 326 [PMID: 30514339 DOI: 10.1186/s13054-018-2076-z]

59 **Rivas-Ruiz R**, Villasis-Keever M, Miranda-Novales G, Castelán-Martínez OD, Rivas-Contreras S. Outpatient treatment for people with cancer who develop a low-risk febrile neutropaenic event. *Cochrane Database Syst Rev* 2019; **3**: CD009031 [PMID: 30887505 DOI: 10.1002/14651858.CD009031.pub2]

60 **Taj M**, Nadeem M, Maqsood S, Shah T, Farzana T, Shamsi TS. Validation of MASCC Score for Risk Stratification in Patients of Hematological Disorders with Febrile Neutropenia. *Indian J Hematol Blood Transfus* 2017; **33**: 355-360 [PMID: 28824237 DOI: 10.1007/s12288-016-0730-7]

61 **Coyne CJ**, Le V, Brennan JJ, Castillo EM, Shatsky RA, Ferran K, Brodine S, Vilke GM. Application of the MASCC and CISNE Risk-Stratification Scores to Identify Low-Risk Febrile Neutropenic Patients in the Emergency Department. *Ann Emerg Med* 2017; **69**: 755-764 [PMID: 28041827 DOI: 10.1016/j.annemergmed.2016.11.007]

62 **Ahn S**, Rice TW, Yeung SJ, Cooksley T. Comparison of the MASCC and CISNE scores for identifying low-risk neutropenic fever patients: analysis of data from three emergency departments of cancer centers in three continents. *Support Care Cancer* 2018; **26**: 1465-1470 [PMID: 29168032 DOI: 10.1007/s00520-017-3985-0]

63 **Gavelli F**, Teboul JL, Monnet X. How can CO_2-derived indices guide resuscitation in critically ill patients? *J Thorac Dis* 2019; **11**: S1528-S1537 [PMID: 31388457 DOI: 10.21037/jtd.2019.07.10]

64 **Poston JT**, Koyner JL. Sepsis associated acute kidney injury. *BMJ* 2019; **364**: k4891 [PMID: 30626586 DOI: 10.1136/bmj.k4891]

65 **Gotts JE**, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ* 2016; **353**: i1585 [PMID: 27217054 DOI: 10.1136/bmj.i1585]

66 **From the Immunocompromised Host Society**. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. *J Infect Dis* 1990; **161**: 397-401 [PMID: 2179421 DOI: 10.1093/infdis/161.3.397]

67 **Perdikouri EIA**, Arvaniti K, Lathyris D, Apostolidou Kiouti F, Siskou E, Haidich AB, Papandreou C. Infections Due to Multidrug-Resistant Bacteria in Oncological Patients: Insights from a Five-Year Epidemiological and Clinical Analysis. *Microorganisms* 2019; **7**: 277 [PMID: 31438593 DOI: 10.3390/microorganisms7090277]

68 **Jung SM**, Kim YJ, Ryoo SM, Sohn CH, Seo DW, Lim KS, Kim WY. Cancer patients with neutropenic septic shock: etiology and antimicrobial resistance. *Korean J Intern Med* 2020; **35**: 979-987 [PMID: 31648434 DOI: 10.3904/kjim.2018.306]

69 **Satlin MJ**, Walsh TJ. Multidrug-resistant Enterobacteriaceae, Pseudomonas aeruginosa, and vancomycin-resistant Enterococcus: Three major threats to hematopoietic stem cell transplant recipients. *Transpl Infect Dis* 2017; **19**: e12762 [PMID: 28815897 DOI: 10.1111/tid.12762]

70 **Ben-Chetrit E**, Eldaim MA, Bar-Meir M, Dodin M, Katz DE. Associated factors and clinical outcomes of bloodstream infection due to extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae during febrile neutropenia. *Int J Antimicrob Agents* 2019; **53**: 423-428 [PMID: 30572008 DOI: 10.1016/j.ijantimicag.2018.12.003]

71 **Torfoss D**, Fladhagen T, Holte H, Brinch L, Schjesvold FH, Fløisand Y, Nyquist E, Dalgaard J, Meyer P, Lehmann AK, Hammerstrøm J, Skjelbakken T, Høiby EA, Sandvik L, Kvaløy S. Benzylpenicillin plus an aminoglycoside versus meropenem in neutropenic lymphoma and leukaemia patients with a suspected bacterial infection: a randomized, controlled trial. *Clin Microbiol Infect* 2017; **23**: 179-187 [PMID: 27793737 DOI: 10.1016/j.cmi.2016.10.019]

72 **Gudiol C**, Royo-Cebrecos C, Tebe C, Abdala E, Akova M, Álvarez R, Maestro-de la Calle G, Cano A, Cervera C, Clemente WT, Martín-Dávila P, Freifeld A, Gómez L, Gottlieb T, Gurguí M, Herrera F, Manzur A, Maschmeyer G, Meije Y, Montejo M, Peghin M, Rodríguez-Baño J, Ruiz-Camps I, Sukiennik TC, Carratalà J; BICAR study group. Clinical efficacy of β-lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum β-lactamase-producing Enterobacteriaceae in haematological patients with neutropaenia: a study protocol for a retrospective observational study (BICAR). *BMJ Open* 2017; **7**: e013268 [PMID: 28115333 DOI: 10.1136/bmjopen-2016-013268]

73 **Gutiérrez-Gutiérrez B**, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, Venditti M, Tumbarello M, Daikos G, Cantón R, Doi Y, Tuon FF, Karaiskos I, Pérez-Nadales E, Schwaber MJ, Azap ÖK, Souli M, Roilides E, Pournaras S, Akova M, Pérez F, Bermejo J, Oliver A, Almela M, Lowman W, Almirante B, Bonomo RA, Carmeli Y, Paterson DL, Pascual A, Rodríguez-Baño J; REIPI/ESGBIS/INCREMENT Investigators. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis* 2017; **17**: 726-734 [PMID: 28442293 DOI: 10.1016/S1473-3099(17)30228-1]

74 **Gutiérrez-Gutiérrez B**, Pérez-Galera S, Salamanca E, de Cueto M, Calbo E, Almirante B, Viale P, Oliver A, Pintado V, Gasch O, Martínez-Martínez L, Pitout J, Akova M, Peña C, Molina J, Hernández A, Venditti M, Prim N, Origüen J, Bou G, Tacconelli E, Tumbarello M, Hamprecht A, Giamarellou H, Almela M, Pérez F, Schwaber MJ, Bermejo J, Lowman W, Hsueh PR, Mora-Rillo M, Natera C, Souli M, Bonomo RA, Carmeli Y, Paterson DL, Pascual A, Rodríguez-Baño J. A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-

Spectrum-β-Lactamase-Producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2016; **60**: 4159-4169 [PMID: 27139473 DOI: 10.1128/AAC.00365-16]

75 **Bassetti M**, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G, De Rosa FG, Giamarellos-Bourboulis EJ, Rossolini GM, Righi E, Karaiskos I, Tumbarello M, Nicolau DP, Viale PL, Poulakou G; Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Disease (ESCMID); Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA). Management of KPC-producing Klebsiella pneumoniae infections. *Clin Microbiol Infect* 2018; **24**: 133-144 [PMID: 28893689 DOI: 10.1016/j.cmi.2017.08.030]

76 **Kengkla K**, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. *J Antimicrob Chemother* 2018; **73**: 22-32 [PMID: 29069421 DOI: 10.1093/jac/dkx368]

77 **Hassoun A**, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacteremia across patient populations-a review of recent developments in MRSA management and treatment. *Crit Care* 2017; **21**: 211 [PMID: 28807042 DOI: 10.1186/s13054-017-1801-3]

78 **Schmiedel Y**, Zimmerli S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and Pneumocystis pneumonia. *Swiss Med Wkly* 2016; **146**: w14281 [PMID: 26901377 DOI: 10.4414/smw.2016.14281]

79 **Chen K**, Wang Q, Pleasants RA, Ge L, Liu W, Peng K, Zhai S. Empiric treatment against invasive fungal diseases in febrile neutropenic patients: a systematic review and network meta-analysis. *BMC Infect Dis* 2017; **17**: 159 [PMID: 28219330 DOI: 10.1186/s12879-017-2263-6]

80 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]

81 **Kochanek M**, Schalk E, von Bergwelt-Baildon M, Beutel G, Buchheidt D, Hentrich M, Henze L, Kiehl M, Liebregts T, von Lilienfeld-Toal M, Classen A, Mellinghoff S, Penack O, Piepel C, Böll B. Management of sepsis in neutropenic cancer patients: 2018 guidelines from the Infectious Diseases Working Party (AGIHO) and Intensive Care Working Party (iCHOP) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol* 2019; **98**: 1051-1069 [PMID: 30796468 DOI: 10.1007/s00277-019-03622-0]

82 **Averbuch D**, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, Pabst T, Özçelik T, Klyasova G, Donnini I, Wu D, Gülbas Z, Zuckerman T, Botelho de Sousa A, Beguin Y, Xhaard A, Bachy E, Ljungman P, de la Camara R, Rascon J, Ruiz Camps I, Vitek A, Patriarca F, Cudillo L, Vrhovac R, Shaw PJ, Wolfs T, O'Brien T, Avni B, Silling G, Al Sabty F, Graphakos S, Sankelo M, Sengeloev H, Pillai S, Matthes S, Melanthiou F, Iacobelli S, Styczynski J, Engelhard D, Cesaro S. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. *Clin Infect Dis* 2017; **65**: 1819-1828 [PMID: 29020364 DOI: 10.1093/cid/cix646]

83 **Kolonen A**, Sinisalo M, Huttunen R, Syrjänen J, Aittoniemi J, Huhtala H, Sankelo M, Rintala H, Räty R, Jantunen E, Nousiainen T, Säily M, Kauppila M, Itälä-Remes M, Ollikainen H, Rauhala A, Koistinen P, Elonen E; Finnish Leukemia Group. Bloodstream infections in acute myeloid leukemia patients treated according to the Finnish Leukemia Group AML-2003 protocol - a prospective nationwide study. *Infect Dis (Lond)* 2017; **49**: 799-808 [PMID: 28683646 DOI: 10.1080/23744235.2017.1347814]

84 **Wang Y**, Chen L, Liu F, Zhao N, Xu L, Fu B, Li Y. Efficacy and tolerability of granulocyte colony-stimulating factors in cancer patients after chemotherapy: A systematic review and Bayesian network meta-analysis. *Sci Rep* 2019; **9**: 15374 [PMID: 31653961 DOI: 10.1038/s41598-019-51982-4]

85 **Aguilar-Guisado M**, Espigado I, Martín-Peña A, Gudiol C, Royo-Cebrecos C, Falantes J, Vázquez-López L, Montero MI, Rosso-Fernández C, de la Luz Martino M, Parody R, González-Campos J, Garzón-López S, Calderón-Cabrera C, Barba P, Rodríguez N, Rovira M, Montero-Mateos E, Carratalá J, Pérez-Simón JA, Cisneros JM. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol* 2017; **4**: e573-e583 [PMID: 29153975 DOI: 10.1016/S2352-3026(17)30211-9]

86 **Huisman MV**, Barco S, Cannegieter SC, Le Gal G, Konstantinides SV, Reitsma PH, Rodger M, Vonk Noordegraaf A, Klok FA. Pulmonary embolism. *Nat Rev Dis Primers* 2018; **4**: 18028 [PMID: 29770793 DOI: 10.1038/nrdp.2018.28]

87 **Appleton C**, Gillam L, Koulogiannis K. Cardiac Tamponade. *Cardiol Clin* 2017; **35**: 525-537 [PMID: 29025544 DOI: 10.1016/j.ccl.2017.07.006]

88 **Cappetta D**, De Angelis A, Sapio L, Prezioso L, Illiano M, Quaini F, Rossi F, Berrino L, Naviglio S, Urbanek K. Oxidative Stress and Cellular Response to Doxorubicin: A Common Factor in the Complex Milieu of Anthracycline Cardiotoxicity. *Oxid Med Cell Longev* 2017; **2017**: 1521020 [PMID: 29181122 DOI: 10.1155/2017/1521020]

89 **Nebigil CG**, Désaubry L. Emergence of cardio-oncology. *Ann Pharm Fr* 2018; **76**: 504-506 [PMID: 30075937 DOI: 10.1016/j.pharma.2018.06.003]

90 **Bloom MW**, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan DJ, Gheorghiade M, Lyon AR, Butler J. Cancer Therapy-Related Cardiac Dysfunction and Heart Failure: Part 1: Definitions, Pathophysiology, Risk Factors, and Imaging. *Circ Heart Fail* 2016; **9**: e002661 [PMID: 26747861 DOI: 10.1161/CIRCHEARTFAILURE.115.002661]

91 **Totzeck M**, Schuler M, Stuschke M, Heusch G, Rassaf T. Cardio-oncology - strategies for management of cancer-therapy related cardiovascular disease. *Int J Cardiol* 2019; **280**: 163-175 [PMID: 30661849 DOI: 10.1016/j.ijcard.2019.01.038]

92 **Yeh ETH**, Ewer MS, Moslehi J, Dlugosz-Danecka M, Banchs J, Chang HM, Minotti G. Mechanisms and clinical course of cardiovascular toxicity of cancer treatment I. Oncology. *Semin Oncol* 2019; **46**: 397-402

[PMID: 31753424 DOI: 10.1053/j.seminoncol.2019.10.006]
93 **Michel L**, Rassaf T. Cardio-oncology: need for novel structures. *Eur J Med Res* 2019; **24**: 1 [PMID: 30606260 DOI: 10.1186/s40001-018-0359-0]
94 **Yeh ET**, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009; **53**: 2231-2247 [PMID: 19520246 DOI: 10.1016/j.jacc.2009.02.050]
95 **Wickramasinghe CD**, Nguyen KL, Watson KE, Vorobiof G, Yang EH. Concepts in cardio-oncology: definitions, mechanisms, diagnosis and treatment strategies of cancer therapy-induced cardiotoxicity. *Future Oncol* 2016; **12**: 855-870 [PMID: 26829050 DOI: 10.2217/fon.15.349]
96 **Plana JC**, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhães A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2014; **27**: 911-939 [PMID: 25172399 DOI: 10.1016/j.echo.2014.07.012]
97 **Kang Y**, Scherrer-Crosbie M. Echocardiography Imaging of Cardiotoxicity. *Cardiol Clin* 2019; **37**: 419-427 [PMID: 31587783 DOI: 10.1016/j.ccl.2019.07.006]
98 **Arciniegas Calle MC**, Sandhu NP, Xia H, Cha SS, Pellikka PA, Ye Z, Herrmann J, Villarraga HR. Two-dimensional speckle tracking echocardiography predicts early subclinical cardiotoxicity associated with anthracycline-trastuzumab chemotherapy in patients with breast cancer. *BMC Cancer* 2018; **18**: 1037 [PMID: 30359235 DOI: 10.1186/s12885-018-4935-z]
99 **Alvarez-Cardona J**, Lenihan DJ. Anthracycline Cardiotoxicity: It Is Possible to Teach an Old Dog Some New Tricks. *Cardiol Clin* 2019; **37**: 355-363 [PMID: 31587778 DOI: 10.1016/j.ccl.2019.08.001]
100 **Ye L**, Yang ZG, Selvanayagam JB, Luo H, Yang TZ, Perry R, Diao KY, Huang S, Yang MX, Yang P, Jin Y, Guo YK. Myocardial Strain Imaging by Echocardiography for the Prediction of Cardiotoxicity in Chemotherapy-Treated Patients: A Meta-Analysis. *JACC Cardiovasc Imaging* 2020; **13**: 881-882 [PMID: 31734206 DOI: 10.1016/j.jcmg.2019.09.013]
101 **Simões R**, Silva LM, Cruz ALVM, Fraga VG, de Paula Sabino A, Gomes KB. Troponin as a cardiotoxicity marker in breast cancer patients receiving anthracycline-based chemotherapy: A narrative review. *Biomed Pharmacother* 2018; **107**: 989-996 [PMID: 30257411 DOI: 10.1016/j.biopha.2018.08.035]
102 **Ryan TD**, Nagarajan R, Godown J. Cardiovascular Toxicities in Pediatric Cancer Survivors. *Cardiol Clin* 2019; **37**: 533-544 [PMID: 31587793 DOI: 10.1016/j.ccl.2019.07.002]
103 **von Minckwitz G**, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, Baselga J; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017; **377**: 122-131 [PMID: 28581356 DOI: 10.1056/NEJMoa1703643]
104 **Cardinale D**, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M, Cucchi G, Menatti E, Mangiavacchi M, Cavina R, Barbieri E, Gori S, Colombo A, Curigliano G, Salvatici M, Rizzo A, Ghisoni F, Bianchi A, Falci C, Aquilina M, Rocca A, Monopoli A, Milandri C, Rossetti G, Bregni M, Sicuro M, Malossi A, Nassiacos D, Verusio C, Giordano M, Staszewsky L, Barlera S, Nicolis EB, Magnoli M, Masson S, Cipolla CM; ICOS-ONE Study Investigators. Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial. *Eur J Cancer* 2018; **94**: 126-137 [PMID: 29567630 DOI: 10.1016/j.ejca.2018.02.005]
105 **Avila MS**, Ayub-Ferreira SM, de Barros Wanderley MR Jr, das Dores Cruz F, Gonçalves Brandão SM, Rigaud VOC, Higuchi-Dos-Santos MH, Hajjar LA, Kalil Filho R, Hoff PM, Sahade M, Ferrari MSM, de Paula Costa RL, Mano MS, Bittencourt Viana Cruz CB, Abduch MC, Lofrano Alves MS, Guimaraes GV, Issa VS, Bittencourt MS, Bocchi EA. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. *J Am Coll Cardiol* 2018; **71**: 2281-2290 [PMID: 29540327 DOI: 10.1016/j.jacc.2018.02.049]
106 **Shah P**, Garris R, Abboud R, Vasudev R, Patel H, Doshi R, Shamoon F, Bikkina M. Meta-Analysis Comparing Usefulness of Beta Blockers to Preserve Left Ventricular Function During Anthracycline Therapy. *Am J Cardiol* 2019; **124**: 789-794 [PMID: 31307662 DOI: 10.1016/j.amjcard.2019.05.046]
107 **Montoya A**, Amaya CN, Belmont A, Diab N, Trevino R, Villanueva G, Rains S, Sanchez LA, Badri N, Otoukesh S, Khammanivong A, Liss D, Baca ST, Aguilera RJ, Dickerson EB, Torabi A, Dwivedi AK, Abbas A, Chambers K, Bryan BA, Nahleh Z. Use of non-selective β-blockers is associated with decreased tumor proliferative indices in early stage breast cancer. *Oncotarget* 2017; **8**: 6446-6460 [PMID: 28031536 DOI: 10.18632/oncotarget.14119]
108 **Montoya A**, Varela-Ramirez A, Dickerson E, Pasquier E, Torabi A, Aguilera R, Nahleh Z, Bryan B. The beta adrenergic receptor antagonist propranolol alters mitogenic and apoptotic signaling in late stage breast cancer. *Biomed J* 2019; **42**: 155-165 [PMID: 31466709 DOI: 10.1016/j.bj.2019.02.003]
109 **Baek MH**, Kim DY, Kim SO, Kim YJ, Park YH. Impact of beta blockers on survival outcomes in ovarian cancer: a nationwide population-based cohort study. *J Gynecol Oncol* 2018; **29**: e82 [PMID: 30207092 DOI: 10.3802/jgo.2018.29.e82]
110 **Mullen PJ**, Yu R, Longo J, Archer MC, Penn LZ. The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer* 2016; **16**: 718-731 [PMID: 27562463 DOI: 10.1038/nrc.2016.76]
111 **Collins R**, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; **388**: 2532-2561 [PMID: 27616593 DOI: 10.1016/S0140-6736(16)31357-5]
112 **El-Hamamsy M**, Elwakil H, Saad AS, Shawki MA. A Randomized Controlled Open-Label Pilot Study of

Simvastatin Addition to Whole-Brain Radiation Therapy in Patients With Brain Metastases. *Oncol Res* 2016; **24**: 521-528 [PMID: 28281972 DOI: 10.3727/096504016X14719078133528]

113 **Xia DK**, Hu ZG, Tian YF, Zeng FJ. Statin use and prognosis of lung cancer: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Drug Des Devel Ther* 2019; **13**: 405-422 [PMID: 30774306 DOI: 10.2147/DDDT.S187690]

114 **Farooqi MAM**, Malhotra N, Mukherjee SD, Sanger S, Dhesy-Thind SK, Ellis P, Leong DP. Statin therapy in the treatment of active cancer: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2018; **13**: e0209486 [PMID: 30571754 DOI: 10.1371/journal.pone.0209486]

115 **van Diepen S**, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation* 2017; **136**: e232-e268 [PMID: 28923988 DOI: 10.1161/CIR.0000000000000525]

116 **Chakravarthy M**, Tsukashita M, Murali S. A Targeted Management Approach to Cardiogenic Shock. *Crit Care Clin* 2018; **34**: 423-437 [PMID: 29907274 DOI: 10.1016/j.ccc.2018.03.009]

117 **Lenneman CG**, Sawyer DB. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. *Circ Res* 2016; **118**: 1008-1020 [PMID: 26987914 DOI: 10.1161/CIRCRESAHA.115.303633]

118 **Nhola LF**, Villarraga HR. Rationale for Cardio-Oncology Units. *Rev Esp Cardiol (Engl Ed)* 2017; **70**: 583-589 [PMID: 28330611 DOI: 10.1016/j.rec.2017.02.006]

119 **Mitroi C**, Martín-García A, Mazón Ramos P, Virizuela Echaburu JA, Arenas-Prat M, García-Sanz R, Arrarte Esteban V, García-Pinilla JM, Cosín-Sales J, López-Fernández T. Current functioning of cardio-oncology units in Spain. *Clin Transl Oncol* 2020; **22**: 1418-1422 [PMID: 31863353 DOI: 10.1007/s12094-019-02250-4]

120 **Noone J**, Barclay C. Head and Neck Cancer Patients – Information for the General Dental Practitioner. *Dent Update* 2017; **44**: 209-210, 213-215 [PMID: 29172327 DOI: 10.12968/denu.2017.44.3.209]

121 **Fantoni D**, Shih AC. Perioperative Fluid Therapy. *Vet Clin North Am Small Anim Pract* 2017; **47**: 423-434 [PMID: 28164837 DOI: 10.1016/j.cvsm.2016.11.004]

122 **Heming N**, Moine P, Coscas R, Annane D. Perioperative fluid management for major elective surgery. *Br J Surg* 2020; **107**: e56-e62 [PMID: 31903587 DOI: 10.1002/bjs.11457]

123 **Necchi A**, Miceli R, Oualla K, Sonpavde G, Giannatempo P, Raggi D, Nicolai N, Boffi R, Busia A, Mariani L, Salvioni R. Effect of Bleomycin Administration on the Development of Pulmonary Toxicity in Patients With Metastatic Germ Cell Tumors Receiving First-Line Chemotherapy: A Meta-Analysis of Randomized Studies. *Clin Genitourin Cancer* 2017; **15**: 213-220.e5 [PMID: 27692810 DOI: 10.1016/j.clgc.2016.08.021]

124 **Aakre BM**, Efem RI, Wilson GA, Kor DJ, Eisenach JH. Postoperative acute respiratory distress syndrome in patients with previous exposure to bleomycin. *Mayo Clin Proc* 2014; **89**: 181-189 [PMID: 24485131 DOI: 10.1016/j.mayocp.2013.11.007]

125 **Remy KE**, Hall MW, Cholette J, Juffermans NP, Nicol K, Doctor A, Blumberg N, Spinella PC, Norris PJ, Dahmer MK, Muszynski JA; Pediatric Critical Care Blood Research Network (Blood Net). Mechanisms of red blood cell transfusion-related immunomodulation. *Transfusion* 2018; **58**: 804-815 [PMID: 29383722 DOI: 10.1111/trf.14488]

126 **Connor JP**, O'Shea A, McCool K, Sampene E, Barroilhet LM. Peri-operative allogeneic blood transfusion is associated with poor overall survival in advanced epithelial ovarian Cancer; potential impact of patient blood management on Cancer outcomes. *Gynecol Oncol* 2018; **151**: 294-298 [PMID: 30201233 DOI: 10.1016/j.ygyno.2018.08.040]

127 **Manning-Geist BL**, Alimena S, Del Carmen MG, Goodman A, Clark RM, Growdon WB, Horowitz NS, Berkowitz RS, Muto MG, Worley MJ Jr. Infection, thrombosis, and oncologic outcome after interval debulking surgery: Does perioperative blood transfusion matter? *Gynecol Oncol* 2019; **153**: 63-67 [PMID: 30635213 DOI: 10.1016/j.ygyno.2019.01.001]

128 **Torella MC**, Duarte B, Villarroel M, Lasa J, Zubiaurre I. Increased Risk of Synchronous Colorectal Lesions in Patients Referred for Endoscopic Mucosal Resection of Lateral Spreading Tumors. *Arq Gastroenterol* 2019; **56**: 276-279 [PMID: 31633725 DOI: 10.1590/S0004-2803.201900000-52]

129 **Byrne K**, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? *Can J Anaesth* 2016; **63**: 184-192 [PMID: 26497721 DOI: 10.1007/s12630-015-0523-8]

130 **Wall T**, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. *Br J Anaesth* 2019; **123**: 135-150 [PMID: 31255291 DOI: 10.1016/j.bja.2019.04.062]

131 **Luo X**, Zhao H, Hennah L, Ning J, Liu J, Tu H, Ma D. Impact of isoflurane on malignant capability of ovarian cancer in vitro. *Br J Anaesth* 2015; **114**: 831-839 [PMID: 25501719 DOI: 10.1093/bja/aeu408]

132 **Buckley A**, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. *Br J Anaesth* 2014; **113** Suppl 1: i56-i62 [PMID: 25009196 DOI: 10.1093/bja/aeu200]

133 **Hong B**, Lee S, Kim Y, Lee M, Youn AM, Rhim H, Hong SH, Kim YH, Yoon SH, Lim C. Anesthetics and long-term survival after cancer surgery-total intravenous versus volatile anesthesia: a retrospective study. *BMC Anesthesiol* 2019; **19**: 233 [PMID: 31852445 DOI: 10.1186/s12871-019-0914-4]

134 **Myles PS**, Leslie K, Chan MT, Forbes A, Peyton PJ, Paech MJ, Beattie WS, Sessler DI, Devereaux PJ, Silbert B, Schricker T, Wallace S; ANZCA Trials Group for the ENIGMA-II investigators. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. *Lancet* 2014; **384**: 1446-1454 [PMID: 25142708 DOI: 10.1016/S0140-6736(14)60893-X]

135 **Kim SY**, Kim NK, Baik SH, Min BS, Hur H, Lee J, Noh HY, Lee JH, Koo BN. Effects of Postoperative Pain Management on Immune Function After Laparoscopic Resection of Colorectal Cancer: A Randomized

Study. *Medicine (Baltimore)* 2016; **95**: e3602 [PMID: 27175664 DOI: 10.1097/MD.0000000000003602]
136 **Shao YJ**, Liu WS, Guan BQ, Hao JL, Ji K, Cheng XJ, Wang K. Contribution of Opiate Analgesics to the Development of Infections in Advanced Cancer Patients. *Clin J Pain* 2017; **33**: 295-299 [PMID: 27526334 DOI: 10.1097/AJP.0000000000000405]
137 **Boland JW**, Pockley AG. Influence of opioids on immune function in patients with cancer pain: from bench to bedside. *Br J Pharmacol* 2018; **175**: 2726-2736 [PMID: 28593737 DOI: 10.1111/bph.13903]
138 **Xie N**, Gomes FP, Deora V, Gregory K, Vithanage T, Nassar ZD, Cabot PJ, Sturgess D, Shaw PN, Parat MO. Activation of μ-opioid receptor and Toll-like receptor 4 by plasma from morphine-treated mice. *Brain Behav Immun* 2017; **61**: 244-258 [PMID: 27939249 DOI: 10.1016/j.bbi.2016.12.002]
139 **Liang X**, Liu R, Chen C, Ji F, Li T. Opioid System Modulates the Immune Function: A Review. *Transl Perioper Pain Med* 2016; **1**: 5-13 [PMID: 26985446]
140 **Plein LM**, Rittner HL. Opioids and the immune system - friend or foe. *Br J Pharmacol* 2018; **175**: 2717-2725 [PMID: 28213891 DOI: 10.1111/bph.13750]
141 **Gong L**, Qin Q, Zhou L, Ouyang W, Li Y, Wu Y, Li Y. Effects of fentanyl anesthesia and sufentanil anesthesia on regulatory T cells frequencies. *Int J Clin Exp Pathol* 2014; **7**: 7708-7716 [PMID: 25550807]
142 **Sacerdote P**, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* 2000; **90**: 1411-1414 [PMID: 10825330 DOI: 10.1097/00000539-200006000-00028]
143 **Lai HC**, Lee MS, Lin C, Lin KT, Huang YH, Wong CS, Chan SM, Wu ZF. Propofol-based total intravenous anaesthesia is associated with better survival than desflurane anaesthesia in hepatectomy for hepatocellular carcinoma: a retrospective cohort study. *Br J Anaesth* 2019; **123**: 151-160 [PMID: 31171343 DOI: 10.1016/j.bja.2019.04.057]
144 **Wu ZF**, Lee MS, Wong CS, Lu CH, Huang YS, Lin KT, Lou YS, Lin C, Chang YC, Lai HC. Propofol-based Total Intravenous Anesthesia Is Associated with Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery. *Anesthesiology* 2018; **129**: 932-941 [PMID: 30028726 DOI: 10.1097/ALN.0000000000002357]
145 **Huang YH**, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, Wong CS, Wu ZF. Propofol-based total intravenous anesthesia did not improve survival compared to desflurane anesthesia in breast cancer surgery. *PLoS One* 2019; **14**: e0224728 [PMID: 31697743 DOI: 10.1371/journal.pone.0224728]
146 **Hakeam HA**, Arab A, Azzam A, Alyahya Z, Eldali AM, Amin T. Incidence of leukopenia and thrombocytopenia with cisplatin plus mitomycin-c versus melphalan in patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Cancer Chemother Pharmacol* 2018; **81**: 697-704 [PMID: 29429054 DOI: 10.1007/s00280-018-3537-4]
147 **Abel ML**, Kokosis G, Blazer DG. Pulmonary toxicity after intraperitoneal mitomycin C: a case report of a rare complication of HIPEC. *World J Surg Oncol* 2017; **15**: 49 [PMID: 28219391 DOI: 10.1186/s12957-016-1047-6]
148 **Segelman J**, Nygren J. Best practice in major elective rectal/pelvic surgery: enhanced recovery after surgery (ERAS). *Updates Surg* 2017; **69**: 435-439 [PMID: 29067634 DOI: 10.1007/s13304-017-0492-2]
149 **Pędziwiatr M**, Mavrikis J, Witowski J, Adamos A, Major P, Nowakowski M, Budzyński A. Current status of enhanced recovery after surgery (ERAS) protocol in gastrointestinal surgery. *Med Oncol* 2018; **35**: 95 [PMID: 29744679 DOI: 10.1007/s12032-018-1153-0]
150 **Lohsiriwat V**, Jitmungngan R. Enhanced recovery after surgery in emergency colorectal surgery: Review of literature and current practices. *World J Gastrointest Surg* 2019; **11**: 41-52 [PMID: 30842811 DOI: 10.4240/wjgs.v11.i2.41]
151 **Aarts MA**, Rotstein OD, Pearsall EA, Victor JC, Okrainec A, McKenzie M, McCluskey SA, Conn LG, McLeod RS; iERAS group. Postoperative ERAS Interventions Have the Greatest Impact on Optimal Recovery: Experience With Implementation of ERAS Across Multiple Hospitals. *Ann Surg* 2018; **267**: 992-997 [PMID: 29303803 DOI: 10.1097/SLA.0000000000002632]
152 **Ljungqvist O**, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg* 2017; **152**: 292-298 [PMID: 28097305 DOI: 10.1001/jamasurg.2016.4952]
153 **Mingjie X**, Luyao Z, Ze T, YinQuan Z, Quan W. Laparoscopic Radical Gastrectomy for Resectable Advanced Gastric Cancer Within Enhanced Recovery Programs: A Prospective Randomized Controlled Trial. *J Laparoendosc Adv Surg Tech A* 2017; **27**: 959-964 [PMID: 27875094 DOI: 10.1089/lap.2016.0057]
154 **Liu G**, Jian F, Wang X, Chen L. Fast-track surgery protocol in elderly patients undergoing laparoscopic radical gastrectomy for gastric cancer: a randomized controlled trial. *Onco Targets Ther* 2016; **9**: 3345-3351 [PMID: 27330314 DOI: 10.2147/OTT.S107443]
155 **Wang LH**, Zhu RF, Gao C, Wang SL, Shen LZ. Application of enhanced recovery after gastric cancer surgery: An updated meta-analysis. *World J Gastroenterol* 2018; **24**: 1562-1578 [PMID: 29662294 DOI: 10.3748/wjg.v24.i14.1562]
156 **Thandra K**, Salah Z, Chawla S. Oncologic Emergencies-The Old, the New, and the Deadly. *J Intensive Care Med* 2020; **35**: 3-13 [PMID: 30411648 DOI: 10.1177/0885066618803863]
157 **Todd KH**, Thomas CR Jr. An Inflection Point in the Evolution of Oncologic Emergency Medicine. *Ann Emerg Med* 2016; **68**: 712-716 [PMID: 27038693 DOI: 10.1016/j.annemergmed.2016.03.008]
158 **Baldwin KJ**, Zivković SA, Lieberman FS. Neurologic emergencies in patients who have cancer: diagnosis and management. *Neurol Clin* 2012; **30**: 101-128, viii [PMID: 22284057 DOI: 10.1016/j.ncl.2011.09.004]
159 **Achrol AS**, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, Peters S, Arvold ND, Harsh GR, Steeg PS, Chang SD. Brain metastases. *Nat Rev Dis Primers* 2019; **5**: 5 [PMID: 30655533 DOI: 10.1038/s41572-018-0055-y]
160 **Halfdanarson TR**, Hogan WJ, Madsen BE. Emergencies in Hematology and Oncology. *Mayo Clin Proc* 2017; **92**: 609-641 [PMID: 28385197 DOI: 10.1016/j.mayocp.2017.02.008]
161 **Stea B**, Skrepnik T, Hsu CC, Abendroth R. The role of radiation therapy in the treatment of metastatic cancer. *Clin Exp Metastasis* 2018; **35**: 535-546 [PMID: 30062507 DOI: 10.1007/s10585-018-9926-6]
162 **Kemmerer E**, Shah S. Update on Radiotherapy for Central Nervous System Malignancies. *Surg Oncol Clin*

N Am 2017; **26**: 347-355 [PMID: 28576175 DOI: 10.1016/j.soc.2017.01.003]
163 **Xu Y**, Ma P, Xu Y, Dai J. Selection of prescription isodose line for brain metastases treated with volumetric modulated arc radiotherapy. *J Appl Clin Med Phys* 2019; **20**: 63-69 [PMID: 31833642 DOI: 10.1002/acm2.12761]
164 **Kotecha R**, Gondi V, Ahluwalia MS, Brastianos PK, Mehta MP. Recent advances in managing brain metastasis. *F1000Res* 2018; **7**: 1772 [PMID: 30473769 DOI: 10.12688/f1000research.15903.1]
165 **Niranjan A**, Monaco E, Flickinger J, Lunsford LD. Guidelines for Multiple Brain Metastases Radiosurgery. *Prog Neurol Surg* 2019; **34**: 100-109 [PMID: 31096242 DOI: 10.1159/000493055]
166 **Mayer SA**, Solimando DA, Waddell JA. Cancer Chemotherapy Update: Bevacizumab, Etoposide, and Cisplatin Regimen for Refractory Brain Metastases. *Hosp Pharm* 2017; **52**: 394-399 [PMID: 29276261 DOI: 10.1177/0018578717717622]
167 **Kalra M**, Adra N, Hanna N, Abonour R, Einhorn LH. High-dose chemotherapy plus peripheral blood stem cell transplantation for patients with relapsed germ cell tumors and active brain metastases. *Cancer* 2020; **126**: 1202-1207 [PMID: 31743434 DOI: 10.1002/cncr.32628]
168 **Wu YL**, Ahn MJ, Garassino MC, Han JY, Katakami N, Kim HR, Hodge R, Kaur P, Brown AP, Ghiorghiu D, Papadimitrakopoulou VA, Mok TSK. CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non-Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3). *J Clin Oncol* 2018; **36**: 2702-2709 [PMID: 30059262 DOI: 10.1200/JCO.2018.77.9363]
169 **Economopoulou P**, Mountzios G. Non-small cell lung cancer (NSCLC) and central nervous system (CNS) metastases: role of tyrosine kinase inhibitors (TKIs) and evidence in favor or against their use with concurrent cranial radiotherapy. *Transl Lung Cancer Res* 2016; **5**: 588-598 [PMID: 28149754 DOI: 10.21037/tlcr.2016.12.06]
170 **Venur VA**, Leone JP. Targeted Therapies for Brain Metastases from Breast Cancer. *Int J Mol Sci* 2016; **17**: 1543 [PMID: 27649142 DOI: 10.3390/ijms17091543]
171 **McArthur GA**, Maio M, Arance A, Nathan P, Blank C, Avril MF, Garbe C, Hauschild A, Schadendorf D, Hamid O, Fluck M, Thebeau M, Schachter J, Kefford R, Chamberlain M, Makrutzki M, Robson S, Gonzalez R, Margolin K. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. *Ann Oncol* 2017; **28**: 634-641 [PMID: 27993793 DOI: 10.1093/annonc/mdw641]
172 **Berghoff AS**, Venur VA, Preusser M, Ahluwalia MS. Immune Checkpoint Inhibitors in Brain Metastases: From Biology to Treatment. *Am Soc Clin Oncol Educ Book* 2016; **35**: e116-e122 [PMID: 27249713 DOI: 10.1200/EDBK_100005]
173 **King T**, Faiman B. Steroid-Associated Side Effects: A Symptom Management Update on Multiple Myeloma Treatment. *Clin J Oncol Nurs* 2017; **21**: 240-249 [PMID: 28315528 DOI: 10.1188/17.CJON.240-249]
174 **Carney N**, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**: 6-15 [PMID: 27654000 DOI: 10.1227/NEU.0000000000001432]
175 **Claassen J**, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M; Neurointensive Care Section of the European Society of Intensive Care Medicine. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. *Intensive Care Med* 2013; **39**: 1337-1351 [PMID: 23653183 DOI: 10.1007/s00134-013-2938-4]
176 **Wychowski T**, Wang H, Buniak L, Henry JC, Mohile N. Considerations in prophylaxis for tumor-associated epilepsy: prevention of status epilepticus and tolerability of newer generation AEDs. *Clin Neurol Neurosurg* 2013; **115**: 2365-2369 [PMID: 24054994 DOI: 10.1016/j.clineuro.2013.08.023]
177 **Billington M**, Kandalaft OR, Aisiku IP. Adult Status Epilepticus: A Review of the Prehospital and Emergency Department Management. *J Clin Med* 2016; **5**: 74 [PMID: 27563928 DOI: 10.3390/jcm5090074]
178 **Farrokh S**, Tahsili-Fahadan P, Ritzl EK, Lewin JJ 3rd, Mirski MA. Antiepileptic drugs in critically ill patients. *Crit Care* 2018; **22**: 153 [PMID: 29880020 DOI: 10.1186/s13054-018-2066-1]
179 **Del Bigio MR**, Di Curzio DL. Nonsurgical therapy for hydrocephalus: a comprehensive and critical review. *Fluids Barriers CNS* 2016; **13**: 3 [PMID: 26846184 DOI: 10.1186/s12987-016-0025-2]
180 **Barth C**, Soares M, Toffart AC, Timsit JF, Burghi G, Irrazabal C, Pattison N, Tobar E, Almeida BF, Silva UV, Azevedo LC, Rabbat A, Lamer C, Parrot A, Souza-Dantas VC, Wallet F, Blot F, Bourdin G, Piras C, Delemazure J, Durand M, Salluh J, Azoulay E, Lemiale V; Lung Cancer in Critical Care (LUCCA) Study Investigators. Characteristics and outcome of patients with newly diagnosed advanced or metastatic lung cancer admitted to intensive care units (ICUs). *Ann Intensive Care* 2018; **8**: 80 [PMID: 30076547 DOI: 10.1186/s13613-018-0426-2]
181 **Soares M**, Bozza FA, Azevedo LC, Silva UV, Corrêa TD, Colombari F, Torelly AP, Varaschin P, Viana WN, Knibel MF, Damasceno M, Espinoza R, Ferez M, Silveira JG, Lobo SA, Moraes AP, Lima RA, de Carvalho AG, do Brasil PE, Kahn JM, Angus DC, Salluh JI. Effects of Organizational Characteristics on Outcomes and Resource Use in Patients With Cancer Admitted to Intensive Care Units. *J Clin Oncol* 2016; **34**: 3315-3324 [PMID: 27432921 DOI: 10.1200/JCO.2016.66.9549]
182 **Zerbib Y**, Rabbat A, Fartoukh M, Bigé N, Andréjak C, Mayaux J, De Prost N, Misset B, Lemiale V, Bruneel F, Maizel J, Ricome S, Jacobs F, Bornstain C, Dupont H, Baudin F, Azoulay E, Pène F; Groupe de Recherche sur la Réanimation Respiratoire en Onco-Hématologie (GRRR-OH). Urgent Chemotherapy for Life-Threatening Complications Related to Solid Neoplasms. *Crit Care Med* 2017; **45**: e640-e648 [PMID: 28398925 DOI: 10.1097/CCM.0000000000002331]
183 **de Oliveira MCF**, Ferreira JC, Nassar Junior AP, Dettino ALA, Caruso P. Impact of Urgent Chemotherapy in Critically Ill Patients. *J Intensive Care Med* 2020; **35**: 347-353 [PMID: 29258386 DOI: 10.1177/0885066617748602]
184 **Chen YF**, Lin JW, Ho CC, Yang CY, Chang CH, Huang TM, Chen CY, Chen KY, Shih JY, Yu CJ. Outcomes of cancer therapy administered to treatment-naïve lung cancer patients in the intensive care unit.

J Cancer 2017; **8**: 1995-2003 [PMID: 28819399 DOI: 10.7150/jca.18178]

185 **Pastores SM**, Goldman DA, Shaz DJ, Kostelecky N, Daley RJ, Peterson TJ, Tan KS, Halpern NA. Characteristics and outcomes of patients with hematologic malignancies receiving chemotherapy in the intensive care unit. *Cancer* 2018; **124**: 3025-3036 [PMID: 29727916 DOI: 10.1002/cncr.31409]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 October 24; 11(10): 836-843

DOI: 10.5306/wjco.v11.i10.836

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Primary small cell oesophageal carcinoma: A retrospective study of different treatment modalities

Mohammad Alfayez

ORCID number: Mohammad Alfayez 0000-0002-4190-0270.

Author contributions: Alfayez M collected and analyzed the data, wrote the manuscript, read and approve the final manuscript.

Institutional review board statement: NHS Greater Glasgow and Clyde Ethics Committee has reviewed the research proposal for the study title primary small oesophageal cancer: A retrospective study of different modalities of treatment. The study is a historical cohort which was looking at the outcomes of patients with small cell of oesophagus who were treated at the Beatson West of Scotland Cancer Centre. There was no requirement to obtain ethical approval for such historical study.

Informed consent statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

Conflict-of-interest statement: The author has no conflict of interest related to the manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at malfayez@nhs.net. No additional data are available.

Mohammad Alfayez, Faculty of Medicine, Umm Al-Qura University, Makkah 21514, Saudi Arabia

Mohammad Alfayez, King Abdullah Medical City, Makkah 21514, Saudi Arabia

Mohammad Alfayez, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, United Kingdom

Corresponding author: Mohammad Alfayez, MD, PhD, Assistant Professor, Faculty of Medicine, Umm Al-Qura University, Alabdeh campus, Makkah-Taif Road, Makkah 21514, Saudi Arabia. malfayez@nhs.net

Abstract

BACKGROUND

Primary small cell of esophageal carcinoma is an aggressive tumor with no established treatment guidelines. A treatment strategy was adopted based on small cell carcinoma of the lung because of many similar clinicopathological features. Here, we report one of the largest case series in a western population.

AIM

To review the practice of treating small cell oesophageal cancer (SCOC) with different treatment modalities treated at our institution between 2001 and 2014.

METHODS

A total of 28 cases of SCOC have been identified. All cases were identified with a ten-digit code known as the CHI number. Data was collected using a combination of an electronic database, case notes and the chemotherapy electronic prescribing system (chemocare). We collected information on age, gender, performance status, staging of the disease (limited stage *vs* extensive stage).

RESULTS

The results showed 17 patients (61%) were diagnosed with limited stage small cell oesophageal cancer (LS-SCOC), while 11 patients (39%) were diagnosed with extensive stage small cell oesophageal cancer (ES-SCOC). The median age at diagnosis of SCOC was 72 years (range 52-86). The median survival for patients with ES-SCOC was 7 mo (95%CI: 1-12) *vs* LS-SCOC [median 23 mo (95%CI: 14-40)], $P < 0.0001$. Subgroup analysis of those who received treatment showed the median survival for patients who received palliative chemotherapy was 7 mo

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Manuscript source: Unsolicited manuscript

Received: June 16, 2020
Peer-review started: June 16, 2020
First decision: July 25, 2020
Revised: July 29, 2020
Accepted: September 11, 2020
Article in press: September 11, 2020
Published online: October 24, 2020

P-Reviewer: Que J
S-Editor: Huang P
L-Editor: A
P-Editor: Wang LL

(95%CI: 1.5-12), concurrent chemoradiation 45 mo (95%CI: 38-) and sequential chemoradiation 20 mo (95%CI: 17-25), $P < 0.0001$.

CONCLUSION
Our data strongly support the use of concurrent chemoradiation in the treatment of LS-SCOC in patients who are fit with no significant comorbidity.

Key Words: Chemotherapy; Chemoradiotherapy; Small cell carcinoma; Oesophageal cancer; Pallaitive chemotherapy; Radiotherapy

Core Tip: Primary small cell oesophageal carcinoma is rare, prognosis is poor and there is no established optimum treatment strategy. Here, we report largest case series in western world. Our data strongly support the use of concurrent chemoradiation in the treatment of limited stage of small cell carcinoma of the oesophagous in patients who are fit with no significant comorbidity.

Citation: Alfayez M. Primary small cell oesophageal carcinoma: A retrospective study of different treatment modalities. *World J Clin Oncol* 2020; 11(10): 836-843
URL: https://www.wjgnet.com/2218-4333/full/v11/i10/836.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i10.836

INTRODUCTION

Small cell cancer is a disease characterised by aggressive clinical features, dramatic but often short-lived sensitivity to anti-cancer therapy, and rapid dissemination. The gastrointestinal (GI) tract is one of the more common sites of extra-pulmonary small cell cancer[1], and within the GI tract the oesophagus is the organ most frequently affected[2]. Since its first description in 1952[3], only a few hundred cases have been reported, and because of its rarity, consensus on treatment is lacking. Furthermore, no randomised controlled trials have been conducted, however, retrospective cohort studies are reported in the literature. Treatment strategy for small cell carcinoma of the lung has been adopted for oesophageal cancer, as both share many clinical and pathological features. For patients with primary oesophageal small cell cancer in whom there is no evidence of metastatic spread, treatment options include resection[4,5], radiotherapy[6], chemotherapy[7-9] and combination modality treatment[2]. Here, we review the practice of treating small cell oesophageal cancer (SCOC) with different treatment modalities at out institution.

MATERIALS AND METHODS

We analysed all cases of SCOC treated at our institution between 2001 and 2014. A total of 28 cases of SCOC have been identified. All cases were identified with a ten-digit code known as the CHI number. Data was collected using a combination of an electronic database, case notes and the chemotherapy electronic prescribing system (chemocare). We collected information on age, gender, performance status, staging of the disease [limited stage (LS) *vs* extensive stage (ES)]. Further data on treatment modality was also collected. This including palliative chemotherapy, sequential chemoradiation (chemotherapy followed by consolidation radiotherapy), or concurrent chemoradiation. None of the patients had surgical resection as primary modality of treatment. Staging was used similar to the staging used in small cell lung cancer. LS is defined as when the tumour is encompassed within a safe and a tolerable radiation field. ES is when the disease is too widespread to be treated within one safe and tolerable radiation field. All patients had a confirmed histological diagnosis of SCOC from an upper gastrointestinal endoscopic biopsy as well as staging with a computed tomography (CT) for chest, abdomen and pelvis. The middle oesophageal tumour is defined endoscopically between 24 cm to 32 cm from incisors while lower oesophageal tumour is defined 32-40 cm from incisors.

None of the patients underwent a CT head scan as part of the staging process. None of the patients had positron emission tomography/computed tomography (PET/CT). The diagnosis of SCOC was made based on classical cellular morphology as well as immunohistochemistry staining. All cases were discussed at regional multidisciplinary team meeting before starting their treatment. Information on date of death was obtained *via* survival analysis undertaken by the Information Service Division of NHS Scotland. Death records were complete until 1 February 2015, which served as the censor date for those alive.

RESULTS

Seventeen patients (61%) were diagnosed with limited stage small cell oesophageal cancer (LS-SCOC), while 11 patients (39%) were diagnosed with extensive stage small cell oesophageal cancer (ES-SCOC). Four patients diagnosed with LS-SCOC had mixed pathology, three of them diagnosed with small cell carcinoma and adenocarcinoma, while one patient had LS-SCOC mixed with squamous cell carcinoma.

The median age at diagnosis of SCOC was 72 years (range 52-86), and it appeared to be more common in men (57%) than in women. The tumour is more likely to be located in the lower part of the oesophagus (82%) than in the middle (Table 1). No upper oesophageal SCOC has been recorded.

Two patients (7%) diagnosed with ES-SCOC did not receive any treatment, while eight patients received platinum-based palliative chemotherapy (Table 2). The overall median survival for ES-SCOC was 7 mo (95%CI: 1-12, Figure 1). Three patients with ES-SCOC were found to have brain metastasis, two them did not receive chemotherapy. Four patients who were treated with palliative chemotherapy went onto have a palliative dose of radiotherapy to the oesophagus of 20 Gray (Gy) in five fractions (Table 2).

Four patients with LS-small cell of esophageal carcinoma received platinum-based chemotherapy. One patient with mixed pathology of SCOC and squamous cell carcinoma had three cycles of ECX (epirubicin, cisplatin, and capecitabine) followed by three cycles of platinum-based chemotherapy. The median survival for that patient was 13.3 mo (Table 2).

Five patients received concurrent chemoradiation. Five weeks of radiotherapy, as part of the concurrent chemoradiation regimen, was provided after two cycles of induction platinum-based chemotherapy. This was delivered concurrently with one to two cycles of platinum-based chemotherapy. The dose of radiotherapy was 4000-5000 cGy.

Eight patients received sequential chemoradiotherapy. Radiotherapy as part of sequential chemoradiotherapy was administered three to five weeks after the last cycle of chemotherapy, with the dose given being 4005-5000 cGy. No prophylactic cranial irradiation (PCI) was given to any patients. None of the patients who were treated radically were found to have any brain metastases (Table 3).

The overall median survival of the LS-SCOC patients was 23 mo (95%CI: 14-40, Figure 1). Subgroup analysis showed survival of patients who received sequential chemoradiotherapy, and those who received concurrent chemoradiation, was 20 mo (95%CI: 17-25) and 45 mo (95%CI: 39-) respectively (Figure 2).

Two patients with ES-SCOC who progressed shortly after first line chemotherapy were determined fit enough and managed to receive two to three cycles of second line chemotherapy with a combination of the chemotherapy drugs cyclophosphamide, doxorubicin, and vincristine (CAV). Both patients progressed on while receiving CAV chemotherapy (two to three cycles). The experience with second-line chemotherapy in patients diagnosed with LS-SCOC was variable. Among those that received sequential chemoradiation, only three out of five patients who received second line chemotherapy were re-challenged with platinum-based chemotherapy (Table 4). None of the patients who had been treated with concurrent chemoradiotherapy had received second-line chemotherapy.

DISCUSSION

Primary SCOC is an uncommon cancer, and here we report one of the largest case studies in a Western population. The clinical features of our patients with SCOC and its distribution are similar to most studies in the literature[10]. Specifically, we describe a male: Female ratio of 1.33:1, with all tumours arising from the mid- to lower-

Table 1 Demographics of the patients and the tumours

Characteristic	All patients (28)	Palliative chemotherapy (15)	Concurrent chemoradiotherapy (5)	Sequential chemoradiotherapy (8)
Age (yr)				
Median	72	72	79	70
Range	52-86	53-86	58-83	52-78
Performance status of 0 or 1 (%)	82	67	100	100
Sex				
Male (%)	57	53	100	38
Female (%)	43	47	None	62
Tumour Stage				
Limited (%)	60	27	100	100
Extensive (%)	40	73	None	None
Location of the tumour				
Mid-oesophagus (%)	18	27	None	13
Low-oesophagus (%)	82	73	100	87

Table 2 Clinical and treatment details of the 15 patients who received palliative chemotherapy

Patient	Age	Sex	PS	Stage	Site	CT	Cycles (*n*)	Palliative RT	Response	Survival (mo)
1	80	M	1	ES	Low	PE	6	No	PR	16
2	58	M	1	ES	Low	PE	6	No	PR	12
3	67	F	2	ES	Mid	P	4	No	PR	9
4	80	M	3	ES	Mid	P	2	No	UK	1.5
5	59	M	1	ES	Mid	PE	2	Yes	UK	2
6	70	F	1	ES	Low	PE	4	Yes	PR	12
7	53	F	0	ES	Low	CE	6	No	PR	10
8	62	F	2	ES	Mid	P	4	No	PR	7
9	65	M	0	ES	Low	PE	4	No	PR	3.5
10	81	F	3	ES	Low	None	0	No	NA	1
11	84	F	2	ES	Low	None	0	Yes	NA	1
12	86	M	1	LS	Low	P	2	Yes	SD	14
13	75	M	1	LS	Low	PE	4	No	PR	3
14	72	M	0	LS	Low[1]	ECX/CE	3/3	No	SD	13
15	75	F	1	LS	Low	PE	2	No	PR	5.5

[1]Mixed pathology of small cell oesophageal cancer and squamous cell carcinoma. CE: Cisplatin and etoposide; CT: Chemotherapy; ED: Extensive stage; ECX: Epirubicin, cisplatin and capecitabine; F: Female; LD: Limited disease; M: Male; Mid: Middle; NA: Not applicable; Low: Lower; PE: Carboplatin and etoposide; PS: Performance status; PR: Partial response; RT: Radiotherapy; SD: Stable disease; UK: Unknown.

oesophagus.

Four cases out of 28 (14%) had mixed pathology with the reminder 24 (86%) cases having a pure variant of small cell carcinoma. Comparable findings were reported in a recent meta-analysis[11]. Whilst the prognosis for many patients with the more typical oesophageal squamous or adenocarcinoma is often poor, small cell cancers are particularly associated with rapid growth, early dissemination, and a resultant poor prognosis with a typical median overall survival of 12 mo in the recent published

Table 3 Clinical and treatment details of the five patients who received concurrent chemoradiotherapy

Patient	Age	Sex	PS	Site	CT	Cycles (*n*)	RT dose	Response	Relapse	Alive[1]	Survival (mo)
1	83	M	0	Low	PE	4	50 Gy in 25 Fr	PR	Local	1	45
2	79	M	1	Low[2]	CE	4	45 Gy in 25 Fr	CR	Liver	1	38
3	73	M	1	Low	PE	3	45 Gy in 25 Fr	CR	None	0	92
4	58	M	1	Low	CE	4	50 Gy in 25 Fr	CR	Local[3]	0	110
5	79	M	0	Low	CE	4	45 Gy in 25 Fr	PR	Liver	1	40

[1]1 = Died, 0 = Otherwise.
[2]Mixed pathology initially, biopsy confirmed recurrence of squamous cell carcinoma only.
[3]New primary with adenocarcinoma; patient had salvage surgery. CE: Cisplatin and etoposide; CT: Chemotherapy; Fr: Fractions; M: Male; PE: Carboplatin and etoposide; PS: Performance status; PR: Partial response; RT: Radiotherapy.

Table 4 Clinical and treatment details of the 8 patients who received sequential chemoradiotherapy

Patient	Age	Sex	PS	Site	CT	Cycles (*n*)	RT dose	Response	Site of relapse	2nd Line CT	Survival (mo)
1	52	F	0	Mid	CE	6	50 Gy in 20 Fr	CR	Liver	2 Top	25
2	78	F	0	Low	PE	1	50 Gy in 20 Fr	CR	UK	None	25
3	71	M	0	Low	CE/PE	3	50 Gy in 20 Fr	CR	Local	6 PE	23
4	70	M	1	Low[1]	PE	5	50 Gy in 20 Fr	PR	Local	2 PE	20
5	67	F	1	Low	CE	4	45 Gy in 25 Fr	PR	Local[2]	3 ECX	65.5
6	70	F	1	Low	CE	4	50 Gy in 20 Fr	UK	UK	None	19
7	73	F	1	Low	PE	4	4005 cGy in 15 Fr	PR	UK	None	17
8	69	M	1	Low[1]	PE	5	50 Gy in 25 Fr	PR	UK	2 PE	20

[1]Mixed pathology of small cell oesophageal cancer and adenocarcinoma.
[2]New primary with adenocarcinoma, patient had palliative chemotherapy. CE: Cisplatin and etoposide; CR: Complete response; CT: Chemotherapy; Fr: Fractions; M: Male; Mid: Middle; PE: Carboplatin and etoposide; Low: Lower; PS: Performance status; PR: Partial response; RT: Radiotherapy; Top: Topotecan; UK: Unknown; 2nd Line CT: Second line chemotherapy.

meta-analysis[11].

The role of surgical resection in patients with SCOC is still not proven with outcomes remaining unfavourable. Primary surgery with or without adjuvant treatment has elicited poor outcomes[12-14] with a median survival in a number of surgical resection series is less than 12 mo[12].

There is a general consensus that systemic chemotherapy should also be used in the treatment of small cell carcinoma of any primary site because of the high likelihood of early dissemination. It may be appropriate to extrapolate the data from small cell carcinoma of the lung to SCOC. In our case series, patients with ES-SCOC treated with systemic treatment had only a median survival time of nine months. Similar findings have been reported from a case series in the United Kingdom[15]. The treatment of choice in the first-line setting is platinum-based chemotherapy. The treatment choice for second-line chemotherapy is variable. However, extrapolating from small cell

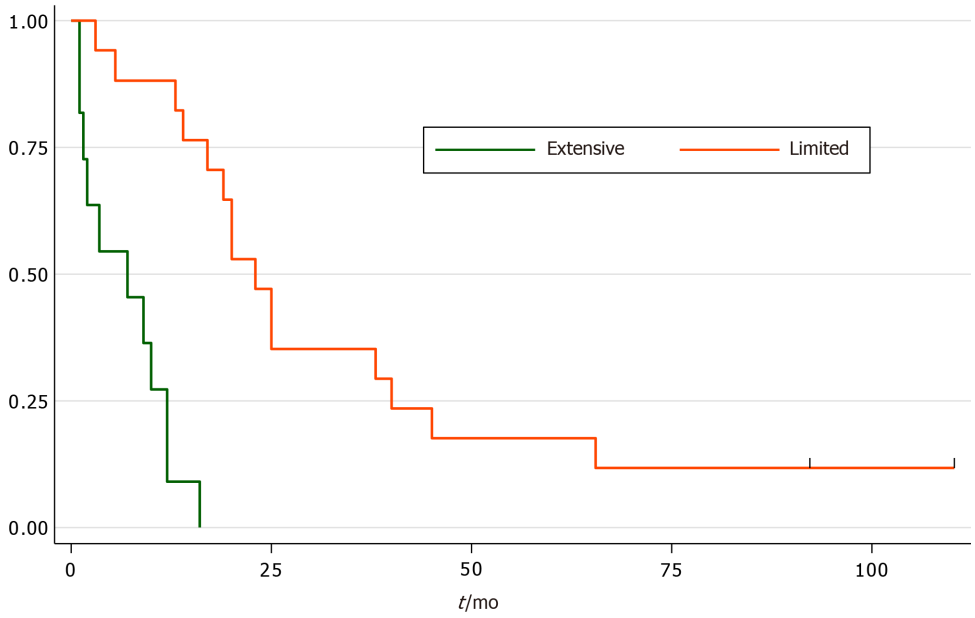

Figure 1 Kaplan Meier survival curves of extensive stage small cell oesophageal cancer [median 7 mo (95%CI: 1-12)] *vs* limited stage small cell oesophageal cancer [median 23 mo (95%CI: 14-40)]. Log-rank test $P < 0.0001$.

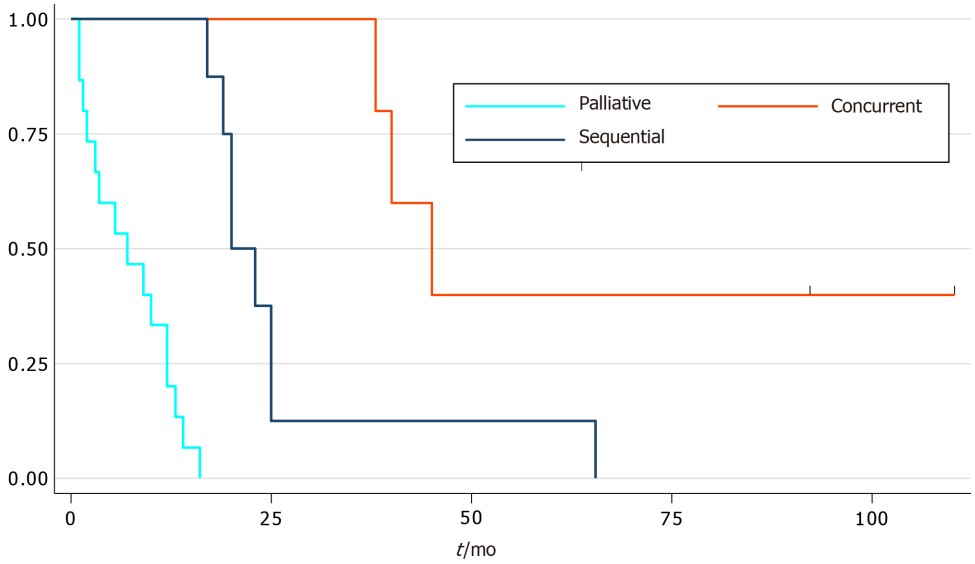

Figure 2 Kaplan Meier survival curves for palliative chemotherapy (median survival 7 mo (95%CI: 1.5-12), concurrent chemoradiation 45 mo (95%CI: 38-) and sequential chemoradiotherapy 20 mo (95%CI: 17-25). Overall Log-rank test $P < 0.0001$. Concurrent

carcinoma of the lung, for late relapse (> 6 mo), it is reasonable to consider retreatment with platinum-based chemotherapy[16]. In our case series, all patients received platinum based chemotherapy as their first line chemotherapy here, such chemotherapy was administered to all patients that received active treatment. Only eight out of 25 patients (32%) were given second-line chemotherapy.

In contrast to systemic treatment, radiotherapy alone has not been widely used[15]. None of the patients presented in our series had primary radiotherapy as the sole treatment. However, radiotherapy has been used previously either to consolidate the primary site sequentially after systemic treatment or concurrently with chemotherapy. In our series sequential chemoradiotherapy has a median survival time of 23 mo (95%CI: 17.5-27.8). This is compatible with Hudson *et al*[15]'s case series.

There have recently been favourable reports of chemoradiotherapy as the sole treatment of SCOC[13]. Unfortunately, there are no randomised controlled trials to support its use. The results presented in our case series suggest that treating patients with LS-SCOC with concurrent chemoradiation yields the longest median survival

time of 45 mo (95%CI: 34.5-55.3). Although we recognise it is difficult to draw conclusions from this given there were so few patients involved. Furthermore, our data suggested re-biopsy of the local recurrence is warranted as a new primary tumour at the local site is a possibility.

In our cohort, one patient treated with concurrent chemoradiation had an initial biopsy that was compatible with a carcinoma demonstrating mixed squamous and small cell features. Upon completion of treatment, repeat endoscopic and radiologic assessment revealed no evidence of residual tumour or metastatic disease. The patient remained well for three years before presenting with fatigue, weight loss, and abdominal pain. Investigations at this time demonstrated liver metastases. Fine-needle aspiration cytology of one of the liver lesions uncovered features of recurrent squamous cancer with no evidence of a residual neuroendocrine element. No further treatment was provided and the patient subsequently died two months later, 38 mo after diagnosis.

Another patient who diagnosed with pure SCOC treated with concurrent chemoradiation, remained well (with negative endoscopic/histological findings) until the development of symptoms of gastro-oesophageal reflux 21 mo after completion of CRT. Endoscopy demonstrated minor oesophagitis with no macroscopic tumour evident, through biopsies of this area revealed the presence of a moderately differentiated adenocarcinoma. The patient underwent salvage oesophagostomy and recovered very well from the operation, continuing to be alive today.

PCI has been shown to improve survival, as well as local control, in small cell carcinomas of the lung[17,18]. The role of PCI in patients with SCOC is unclear. None of the patients presented in this series with LS had a relapse in the brain. We think It is therefore reasonable to omit PCI in patients with SCOC, consistent with a previous case series report[15]. One of the drawback of the study is no robust collection of treatment toxicity.

CONCLUSION

In conclusion, tumours such as SCOC provide treatment challenges because of the lack of RCT evidence. However, our data strongly support the use of concurrent chemoradiation in the treatment of LS-SCOC in patients who are fit with no significant comorbidity. Those patients have a better survival compared to the rest of the other groups. Further, PCI can be safely omitted in this group.

ARTICLE HIGHLIGHTS

Research background

Small cell oesophageal cancer (SCOC) is rare. Until now, there was no general consensus of optimal treatment in this group of patients.

Research motivation

Future RCT involving this small group population is a priority to determine best modality of treatment.

Research objectives

The main objective was to determine the best modality of treatment for patients diagnosed with SCOC.

Research methods

This is a retrospective analysis of different treatment modalities on this highly poor prognosis as well as a rare group of esophageal carcinoma.

Research results

The finding of this study will add to growing body of literature on the benefit of CCRT in the treatment of limited stage (LS) small cell cancer of esophagus.

Research conclusions

Patient with LS of oesophageal cancer with good performance status should be treated with Concurrent chemoradiation.

Research perspectives

The future research will involve prospective studies.

REFERENCES

1 **Haider K**, Shahid RK, Finch D, Sami A, Ahmad I, Yadav S, Alvi R, Popkin D, Ahmed S. Extrapulmonary small cell cancer: a Canadian province's experience. *Cancer* 2006; **107**: 2262-2269 [PMID: 16998932 DOI: 10.1002/cncr.22235]

2 **Huncharek M**, Muscat J. Small cell carcinoma of the esophagus. The Massachusetts General Hospital experience, 1978 to 1993. *Chest* 1995; **107**: 179-181 [PMID: 7813272 DOI: 10.1378/chest.107.1.179]

3 **Mckeown F**. Oat-cell carcinoma of the oesophagus. *J Pathol Bacteriol* 1952; **64**: 889-891 [PMID: 13000600 DOI: 10.1002/path.1700640420]

4 **Yachida S**, Matsushita K, Usuki H, Wanibuchi H, Maeba T, Maeta H. Long-term survival after resection for small cell carcinoma of the esophagus. *Ann Thorac Surg* 2001; **72**: 596-597 [PMID: 11515903 DOI: 10.1016/s0003-4975(00)02528-5]

5 **Nishimaki T**, Suzuki T, Nakagawa S, Watanabe K, Aizawa K, Hatakeyama K. Tumor spread and outcome of treatment in primary esophageal small cell carcinoma. *J Surg Oncol* 1997; **64**: 130-134 [PMID: 9047250 DOI: 10.1002/(sici)1096-9098(199702)64:2<130::aid-jso8>3.0.co;2-c]

6 **Nemoto K**, Zhao HJ, Goto T, Ogawa Y, Takai Y, Matsushita H, Takeda K, Takahashi C, Saito H, Yamada S. Radiation therapy for limited-stage small-cell esophageal cancer. *Am J Clin Oncol* 2002; **25**: 404-407 [PMID: 12151974 DOI: 10.1097/00000421-200208000-00017]

7 **Kelsen DP**, Weston E, Kurtz R, Cvitkovic E, Lieberman P, Golbey RB. Small-cell carcinoma of the esophagus: treatment by chemotherapy alone. *Cancer* 1980; **45**: 1558-1561 [PMID: 7189441 DOI: 10.1002/1097-0142(19800401)45:7<1558::aid-cncr2820450708>3.0.co;2-2]

8 **Tanabe G**, Kajisa T, Shimazu H, Yoshida A. Effective chemotherapy for small cell carcinoma of the esophagus. *Cancer* 1987; **60**: 2613-2616 [PMID: 2824012 DOI: 10.1002/1097-0142(19871201)60:11<2613::aid-cncr2820601106>3.0.co;2-s]

9 **Okuma HS**, Iwasa S, Shoji H, Takashima A, Okita N, Honma Y, Kato K, Hamaguchi T, Yamada Y, Shimada Y. Irinotecan plus cisplatin in patients with extensive-disease poorly differentiated neuroendocrine carcinoma of the esophagus. *Anticancer Res* 2014; **34**: 5037-5041 [PMID: 25202088]

10 **Casas F**, Ferrer F, Farrús B, Casals J, Biete A. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. *Cancer* 1997; **80**: 1366-1372 [PMID: 9338459 DOI: 10.1002/(SICI)1097-0142(19971015)80:8<1366::AID-CNCR2>3.0.CO;2-D]

11 **Al Mansoor S**, Ziske C, Schmidt-Wolf IG. Primary small cell carcinoma of the esophagus: patient data metaanalysis and review of the literature. *Ger Med Sci* 2013; **11**: Doc12 [PMID: 23983673 DOI: 10.3205/000180]

12 **Law SY**, Fok M, Lam KY, Loke SL, Ma LT, Wong J. Small cell carcinoma of the esophagus. *Cancer* 1994; **73**: 2894-2899 [PMID: 8199985 DOI: 10.1002/1097-0142(19940615)73:12<2894::AID-CNCR2820731204>3.0.CO;2-M]

13 **Wang HH**, Zaorsky NG, Meng MB, Wu ZQ, Zeng XL, Jiang B, Jiang C, Zhao LJ, Yuan ZY, Wang P. Multimodality therapy is recommended for limited-stage combined small cell esophageal carcinoma. *Onco Targets Ther* 2015; **8**: 437-444 [PMID: 25709477 DOI: 10.2147/OTT.S76048]

14 **Hosokawa A**, Shimada Y, Matsumura Y, Yamada Y, Muro K, Hamaguchi T, Igaki H, Tachimori Y, Kato H, Shirao K. Small cell carcinoma of the esophagus. Analysis of 14 cases and literature review. *Hepatogastroenterology* 2005; **52**: 1738-1741 [PMID: 16334769]

15 **Hudson E**, Powell J, Mukherjee S, Crosby TD, Brewster AE, Maughan TS, Bailey H, Lester JF. Small cell oesophageal carcinoma: an institutional experience and review of the literature. *Br J Cancer* 2007; **96**: 708-711 [PMID: 17299393 DOI: 10.1038/sj.bjc.6603611]

16 **Postmus PE**, Berendsen HH, van Zandwijk N, Splinter TA, Burghouts JT, Bakker W. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *Eur J Cancer Clin Oncol* 1987; **23**: 1409-1411 [PMID: 2824211 DOI: 10.1016/0277-5379(87)90128-3]

17 **Slotman B**, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, Postmus P, Collette L, Musat E, Senan S; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; **357**: 664-672 [PMID: 17699816 DOI: 10.1056/NEJMoa071780]

18 **Aupérin A**, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PE, Johnson BE, Ueoka H, Wagner H, Aisner J. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; **341**: 476-484 [PMID: 10441603 DOI: 10.1056/NEJM199908123410703]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 October 24; 11(10): 844-853

DOI: 10.5306/wjco.v11.i10.844

ISSN 2218-4333 (online)

CASE REPORT

Albumin-bound paclitaxel as new treatment for metastatic cholangiocarcinoma: A case report

Roberto Martin Huertas, Raquel Fuentes-Mateos, Juan Jose Serrano Domingo, Elena Corral de la Fuente, Mercedes Rodríguez-Garrote

ORCID number: Roberto Martin Huertas 0000-0002-4623-7236; Raquel Fuentes-Mateos 0000-0003-4338-8976; Juan Jose Serrano Domingo 0000-0003-4126-7150; Elena Corral de la Fuente 0000-0002-7030-2413; Mercedes Rodríguez-Garrote 0000-0003-0486-6760.

Author contributions: All authors contributed equally to this case report and all of them gave final approval for its publication.

Informed consent statement: The patient gave informed consent and the identifiers have been removed prior to submission for publication.

Conflict-of-interest statement: The authors declare no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Roberto Martin Huertas, Raquel Fuentes-Mateos, Juan Jose Serrano Domingo, Elena Corral de la Fuente, Mercedes Rodríguez-Garrote, Medical Oncology Department, Hospital Universitario Ramon y Cajal, Madrid 28034, Spain

Corresponding author: Roberto Martin Huertas, MD, Medical Oncology Department, Hospital Universitario Ramon y Cajal, Ctra. de Colmenar Viejo km. 9100, Madrid 28034, Spain. robertomartinhuertas@outlook.com

Abstract

BACKGROUND

Cholangiocarcinomas are rare and very aggressive tumors. Most patients have advanced-stage or unresectable disease at presentation, and the systemic therapies have limited efficacy. Albumin-bound paclitaxel (nab-paclitaxel) is a solvent-free taxane that has been approved for the treatment of some cancers such as breast, non-small cell lung and pancreatic cancer, however it has not been applied to treat cholangiocarcinoma. We have both preclinical and clinical evidence of the efficacy of nab-paclitaxel in cholangiocarcinoma, yet no phase 3 trials have been made.

CASE SUMMARY

A 63-year-old man was diagnosed in December 2016 with stage III B intrahepatic cholangiocarcinoma. Surgery was performed, followed by adjuvant chemotherapy treatment with capecitabine and gemcitabine; although, the gemcitabine was suspended due to allergic reaction after two cycles. In April 2019, metastatic cholangiocarcinoma relapse was diagnosed, and a first-line treatment with FOLFOX scheme was started. Eight cycles were administered, producing an initial clinical improvement and decrease in blood tumor marker levels. Radiological and serological progression was noted in September 2019. As a second-line treatment, FOLFIRI was not recommended due to risk of worsening the patient's tumor-related diarrhea. A combination therapy with gemcitabine was not feasible, as the patient had previously suffered from an allergic reaction to this treatment. We decided to use nab-paclitaxel as a second-line treatment, and four cycles were administered. Both clinical and serological responses were observed, and a radiological mixed response was also noted.

CONCLUSION

Advanced cholangiocarcinoma could be treated with nab-paclitaxel monotherapy,

Manuscript source: Unsolicited manuscript

Received: May 4, 2020
Peer-review started: May 4, 2020
First decision: July 25, 2020
Revised: July 31, 2020
Accepted: September 8, 2020
Article in press: September 8, 2020
Published online: October 24, 2020

P-Reviewer: Donadon M, Fu TL, Perini M
S-Editor: Huang P
L-Editor: A
P-Editor: Wang LL

which should be studied in combination with other types of treatment (chemotherapy, fibroblast growth factor receptor inhibitors).

Key Words: Cholangiocarcinoma; Chemotherapy; Albumin-bound paclitaxel; Case report; Metastatic; Clinical trial

Core Tip: Cholangiocarcinomas are very aggressive tumors. Most patients have advanced-stage disease at presentation and the efficacy of systemic therapies for this setting is limited. Albumin bound paclitaxel (nab-paclitaxel) has been approved in some cancers but not in cholangiocarcinoma. We present a clinical case of metastatic cholangiocarcinoma treatment with second-line nab-paclitaxel and we review the preclinical and clinical evidence about its useful in these tumors.

Citation: Martin Huertas R, Fuentes-Mateos R, Serrano Domingo JJ, Corral de la Fuente E, Rodríguez-Garrote M. Albumin-bound paclitaxel as new treatment for metastatic cholangiocarcinoma: A case report. *World J Clin Oncol* 2020; 11(10): 844-853
URL: https://www.wjgnet.com/2218-4333/full/v11/i10/844.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i10.844

INTRODUCTION

Cholangiocarcinoma (CC) is a tumor that arises from epithelial bile duct cells. Intrahepatic CC originates above second-order bile ducts, whereas the cystic duct is the anatomical point of distinction between perihilar and distal (extrahepatic) CC[1].

This tumor type accounts for less than 3% of all gastrointestinal cancers[2]. Considering its location, intrahepatic disease is less frequent (between 10%-20% of cases), whereas distal disease is more common (40% of total cases) and perihilar disease is most common (50% of cases)[3]. However, the international classification (*i.e.*, the ICD) of CC does not distinguish between perihilar and distal CC[4]. Also, the American Cancer Society groups intrahepatic bile duct cancers together with primary liver cancers, while placing extrahepatic biliary cancers in a separate category that includes gallbladder cancer. Thus, incidence data on CC subtypes according to location are difficult to interpret[5].

The incidence of intrahepatic CC is rising in the United States and Europe[6-8], although the proportion of early stage or smaller size lesions remains low without an observed increase[7]. The increasing incidence of intrahepatic CC may be due to new diagnostic methods for obstructive jaundice, or may be related to a concomitant increase in certain risk factors (cirrhosis, alcoholic liver disease, hepatitis C virus infection). Extrahepatic CC incidence is declining, and some of these differences may be due to changes in the ICD[9].

CCs are aggressive tumors, and only a minority of patients (approximately 35%) have early-stage disease that is amenable to surgical resection with curative intent. Most patients have advanced-stage disease at presentation[10], and the available systemic therapies for these patients have demonstrated limited efficacy; the median overall survival time with the current standard-of-care first-line chemotherapy (cisplatin and gemcitabine) is less than 1 year[11]. The development of new therapies is therefore essential.

Albumin-bound paclitaxel (nab-paclitaxel), a solvent-free taxane, has been demonstrated to produce higher response rates and improved tolerability than solvent-based formulations in patients with advanced metastatic breast cancer or non-small-cell lung cancer, among others tumor types. Additionally, it has not yet been proven to be efficacious in CC-based phase 3 clinical trials[12].

In this study, we present what is, to our knowledge, one of the first published cases in the literature on the use of nab-paclitaxel as treatment for metastatic CC. We demonstrate that this therapy achieves a significant clinical and serological response, and we thus encourage studying this drug as a new treatment option for patients with poor CC prognoses.

CASE PRESENTATION

Chief complaints

In December 2016, a 63-year-old male underwent a magnetic resonance cholangiography as an assessment for cholecystectomy surgery. A possible cholangiocarcinoma was reported, appearing as a 20 mm hypodense intrahepatic mass at the right liver lobe. Confluence of the hepatic ducts was observed (Figure 1).

History of present illness

In August 2018, a significant elevation of CA19-9 (294.4 IU/mL, Figure 2) was reported, although no relapse was observed in the computed tomography (CT) scan. The patient was asymptomatic, and the liver blood test results were similar to those presented after surgery [aspartate aminotransferase (AST) 56 U/L, alanine aminotransferase (ALT) 97 U/L, gamma-glutamyltransferase (GGT) 455 U/L, alkaline phosphatase (FA) 187 U/L]. Close monitoring was implemented.

In September 2018, CA19-9 continued to increase (513.2 IU/mL, Figure 2). However, the CT scan did not reveal disease relapse. In January 2019, the patient was admitted for cholangitis. A magnetic resonance cholangiography was performed, and no changes were observed in the liver. After discharge in February 2019, close follow-up was continued.

During the following months, the patient experienced clinical deterioration, which included stomach-ache, dyspepsia, and loss of 4 kg of weight. A slight deterioration in the liver blood test was seen (AST 83 U/L, ALT 125 U/L, GGT 1580 U/L, FA 308 U/L) and a progressive rise in CA19-9 was also observed (from 671.3 IU/mL in February 2019 to 3220.9 IU/mL at the end of April 2019, Figure 2). A thorax-abdomen-pelvis computerized tomography (TAP-CT) scan was requested, and no disease relapse was observed. Given the high suspicion of relapse, a positron emission tomography-CT was performed in April 2019. Multiple supraclavicular, mediastinal, and bilateral hilar lymphadenopathies, as well as segment IVa liver nodes and increased soft tissue in the celiac trunk region; all showed increased metabolic activity (Figure 3).

After 25 mo without signs of radiological disease, a relapse of stage IV intrahepatic cholangiocarcinoma was diagnosed. We recommended that the patient begin a first-line chemotherapy with cisplatin and gemcitabine at the usual doses. However, since a poor tolerance to gemcitabine was previously presented, we decided to instead begin with the FOLFOX6 treatment scheme.

The FOLFOX6 treatment began in April 2019. Initial clinical improvement in cancer-related asthenia was observed, as well as a significant decrease in CA19-9 blood levels (from 3592 IU/mL in May 2019, after two cycles of FOLFOX, to 1138.8 IU/mL in August 2019, after eight cycles of FOLFOX, Figure 2). Grade 1 neurotoxicity and grade 1 rectal bleeding from hemorrhoids were the principal clinical chemotherapy-related toxicities that occurred. After cycle 4, grade 1 thrombopenia was presented, and cycles 5, 6, and 7 were scheduled without a 5-fluorouracil bolus. Grade 2 thrombopenia was then observed, and the administration of cycle 8 was delayed for 1 wk. In July 2019, CT scans were performed (prior to cycle 8) and segment IV liver nodes were not identified, as reported in the previous study (Figure 4). However, a small amount of free fluid in the pelvis, as well as a thickening of the peritoneal leaves, appeared. A mixed response was also considered. Given the improving clinical status of the patient, the same treatment was continued, and cycle 8 was administered with a 10% decrease in oxaliplatin dose.

History of past illness

The patient was referred to our center for surgical evaluation. A TAP-CT scan and blood tests were performed. Distant metastases were not observed, and CA19-9 tumor markers were found to be elevated (3494 IU/mL, Figure 2).

In March 2017, after a right portal embolization was performed that caused compensatory hypertrophy in the left liver lobe, the patient underwent surgery. A hilar tumor with right portal involvement was found. Resection of the extrahepatic bile duct with right trisegmentectomy extended to segment 1 and portal resection were both performed.

The pathology report revealed a moderately differentiated intrahepatic hilar cholangiocarcinoma infiltrating the liver parenchyma, perihilar adipose tissue, cystic duct, and gallbladder neck. Frequent perineural infiltration and vascular invasion were also observed. The tumor had metastasized in one of the four lymph nodes that were isolated from the hilum, which affected the resection margin of the surgical piece.

Stage III B (pT3N1M0) intrahepatic cholangiocarcinoma, a R1 resection, was

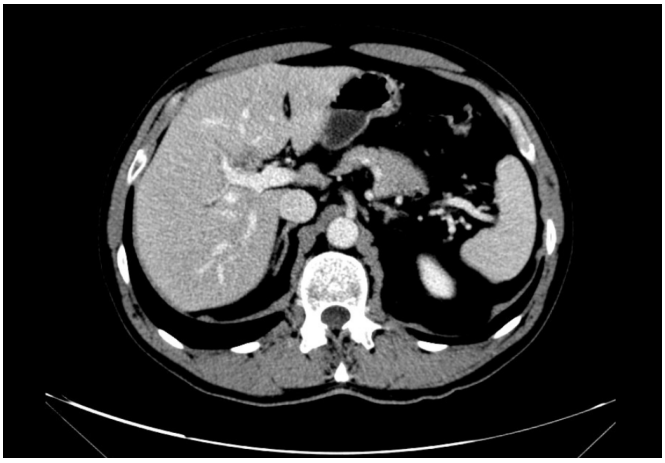

Figure 1 Computed tomography scan performed in December 2016. A 20 mm hypodense intrahepatic mass at the right lobe, possible cholangiocarcinoma, was reported.

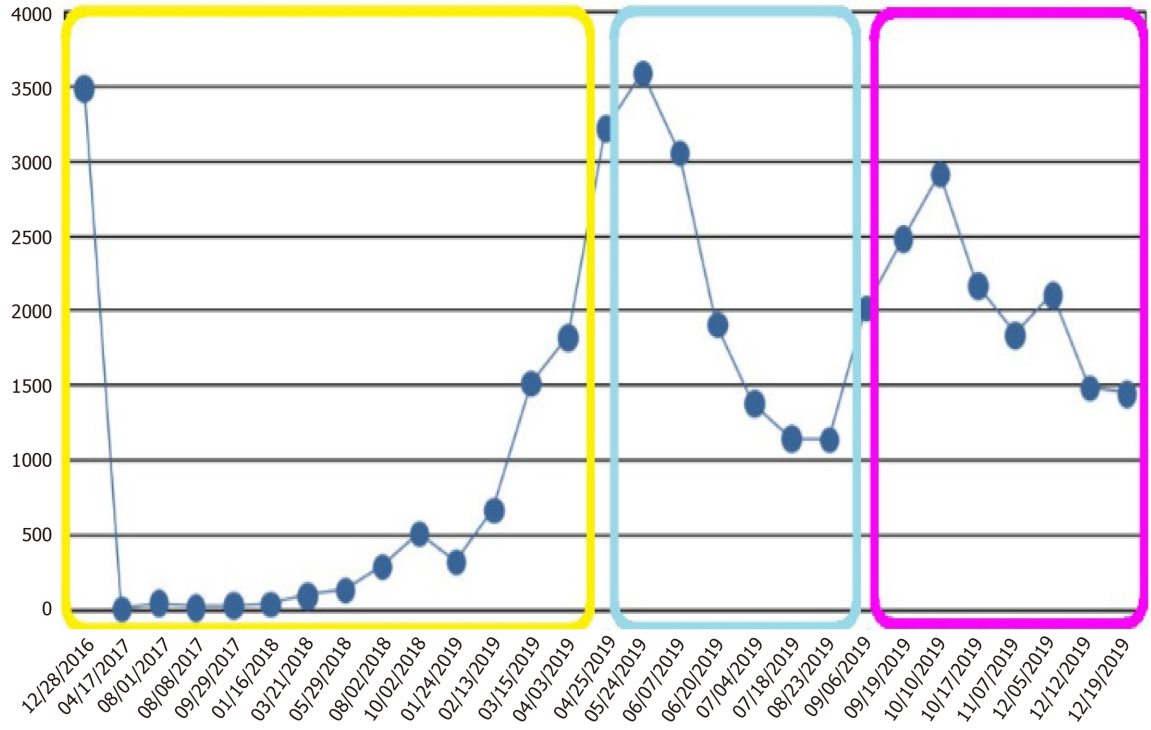

Figure 2 Evolution of CA19-9 blood levels (IU/mL). Yellow: CA19-9 levels of localized cholangiocarcinoma at diagnosis, after surgery, and during follow-up; Cyan: CA19-9 levels during FOLFOX treatment; Magenta: CA19-9 levels during albumin-bound paclitaxel treatment.

diagnosed and the patient was referred to the Medical Oncology Department. Adjuvant chemotherapy treatment with capecitabine 1660 mg/m^2 on days 1 to 21 and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 every 28 d, given for six cycles, was started. The patient received this treatment between May and November 2017. However, gemcitabine was suspended in July 2017 due to an allergic reaction. After completion of the adjuvant treatment, the follow-up period began.

Physical examination

Despite initial clinical improvement, a progressive clinical deterioration was then presented, with an increase in asthenia. Grade 2 diarrhea (Table 1) and minimal effort dyspnea also appeared. Abdominal examination was normal, and hypoventilation in the right lower lung lobe was auscultated. Cycle 9 was not prescribed, due to grade 1 thrombopenia and persistent grade 2 neutropenia.

Table 1 Diarrhea lab work

Diarrhea lab work	
Hormonal and enzymatic study	Normal range
Thyrotropin, TSH	0.888 μIU/mL
Free T4	1.10 ng/dL
Free T3	2.57 pg/mL
Serum cortisol	16.50 μg/dL
ACTH	34.38 pg/mL
Pancreatic elastase E1	More than 437 μg/g of dry stool
Microbiology study	No pathogenic microorganisms identified
Stool culture	Usual bacterial flora in the sample
Clostridium difficile toxin/glutamate dehydrogenase	Negative
Autoimmunity study	Negative for celiac disease
Anti-transglutaminase immunoglobulin-A antibodies	3.63 UA/mL

We carried out a detailed study of diarrhea to rule out non-cancer-related causes. We confirmed that diarrhea was a symptom of the patient's cancer (peritoneal carcinomatosis). ACTH: Adrenocorticotropic hormone; TSH: Thyroid-stimulating hormone.

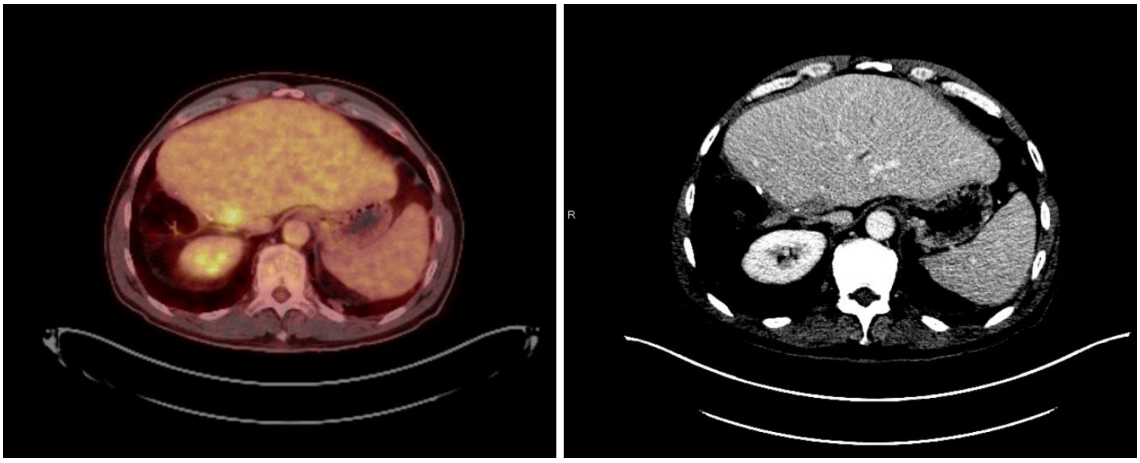

Figure 3 Positron emission tomography-computed tomography performed in April 2019. Cholangiocarcinoma relapse in segment IVa liver node (before FOLFOX6 treatment).

Laboratory examinations

Serological progression was observed: CA19-9 blood levels rose to 2023 IU/mL (with a previous rise in August 2019 of 1138.8 IU/mL, Figure 2) and carcinoembryonic antigen (CEA) blood levels also rose to 5 IU/mL (high CEA levels had not previously occurred). Regarding liver blood testing, AST levels were 74 U/L, ALT levels were 70 U/L, GGT levels were 849 U/L, and FA levels were 440 U/L. The remaining biochemistry parameters were normal, with the exception of grade 1 hypoalbuminemia.

Imaging examinations

Given the suspicion of disease progression, a new CT scan was performed in early September 2019. Both peritoneal carcinomatosis (Figure 5) and pleural involvement were confirmed by one last cytological study (Table 2).

Genetic testing

Massive genetic analysis of the tumor using next-generation sequencing (NGS) was requested. Several alterations could be identified in some genes, such as *RNF43*, *PTCH1*, *ATM* and *ARID1A*, as well as in variants of unknown significance.

Table 2 Pleural effusion study

Pleural effusion study	
Pleural effusion biochemistry	
Glucose	92 mg/dL
Total proteins	4.1 g/dL
Albumin	2.7 g/dL
Lactate dehydrogenase	137 IU/L
Cholesterol	12 mg/dL
Triglycerides	182 mg/dL
Adenosine deaminase	Not available
Pleural effusion hemogram	
Hemoglobin	0.2 g/dL
Platelets	2600/μL
White blood cells	850/μL
Neutrophils	0
Lymphocytes	800/μL
Blood test biochemistry	
Glucose	86 mg/dL
Total proteins	6 g/dL
Albumin	3.5 g/dL
Lactate dehydrogenase	208 IU/L
Cholesterol	195 mg/dL
Triglycerides	122 mg/dL
Microbiology study	No pathogenic microorganisms identified
Light's criteria	The pleural effusion meets two of three of Light's criteria for exudate, and is compatible with cancer
Ratio pleural/serum proteins	0.68 (> 0.5)
Ratio pleural/serum proteins	0.65 (> 0.6)
Pleural effusion lactate dehydrogenase > 2/3 upper limit of normal	No

We conducted an extensive study of pleural fluid to rule out non-cancer-related causes. The presence of cancer cells in the pleural effusion was confirmed by cytology.

Microsatellite instability was not found. Given the clinical deterioration, we decided to begin chemotherapy prior to obtaining these test results.

FINAL DIAGNOSIS

Massive genetic analysis of the tumor using NGS was requested. Several alterations could be identified in some genes, such as *RNF43*, *PTCH1*, *ATM* and *ARID1A*, as well as in variants of unknown significance. Microsatellite instability was not found. Given the clinical deterioration, we decided to begin chemotherapy prior to obtaining these test results.

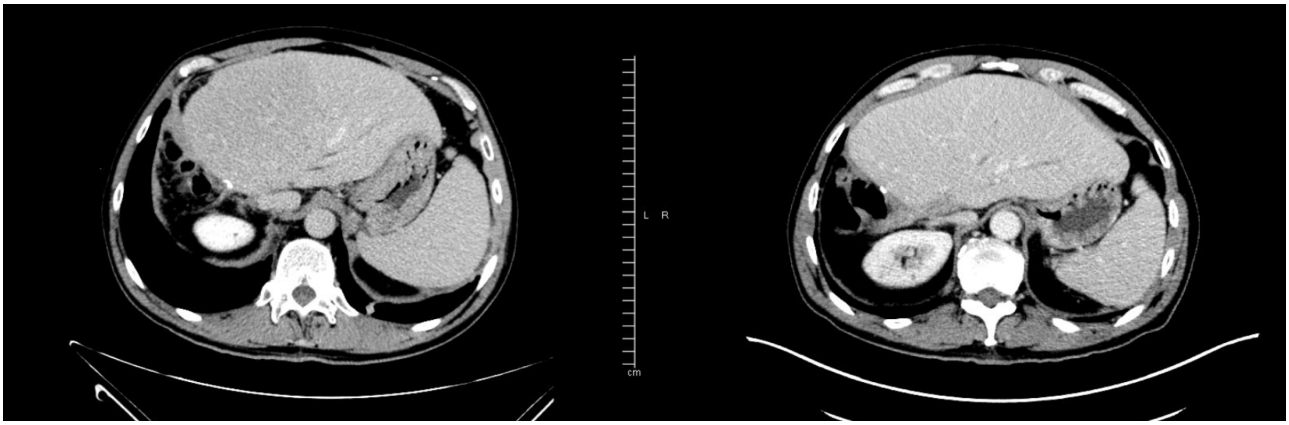

Figure 4 Computed tomography scans performed in July 2019 (left, after seven cycles of FOLFOX6 treatment, where a complete response of disease in segment IV liver is shown) and April 2019 (right, before FOLFOX6 treatment, where segment IV liver node metastasis is seen).

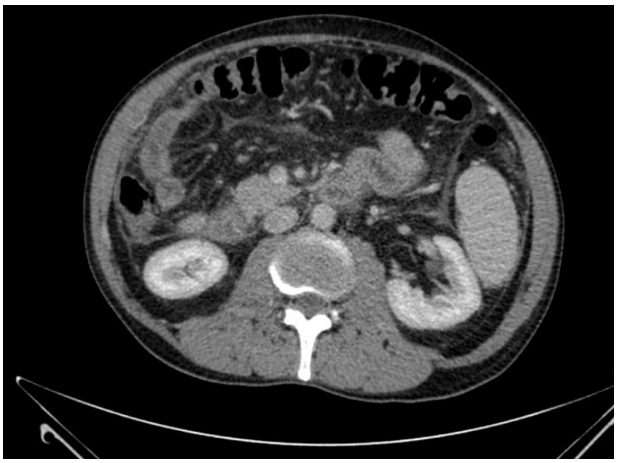

Figure 5 Computed tomography scan performed in September 2019. Peritoneal carcinomatosis (before albumin-bound paclitaxel treatment).

TREATMENT

Stage IV cholangiocarcinoma with peritoneal and pleural progression to FOLFOX is presented. There are limited therapeutic options available. We decided to use nab-paclitaxel in the place of other options for specific reasons. On the one hand, we did not recommend that the patient receive FOLFIRI because of the potential risk of worsening his diarrhea. On the other hand, a combination treatment with gemcitabine was not feasible due to his previous allergic reaction to gemcitabine.

OUTCOME AND FOLLOW-UP

Second-line treatment with nab-paclitaxel at the same doses as used for pancreatic cancer (125 mg/m^2 on days 1, 8 and 15 every 28 d) was started, although without the associated gemcitabine.

On cycle 1 day 8, grade 3 neutropenia (910 neutrophils/mL) and grade 1 thrombopenia (97500 platelets/mL) were observed, and so the treatment with a reduction of one dose level (100 mg/m^2) was prescribed. On cycle 1 day 15, platelets had recovered (150000 platelets/mL) but neutrophils had declined (630 neutrophils/mL). We decided to prescribe a treatment with the same dose level (100 mg/m^2), however we also prescribed two injected doses of granulocyte colony-stimulating factor (GCSF).

On cycle 2 day 1, the patient reported clinical improvements with less asthenia, a 1 kg increase in weight, diarrheal improvements, and slight dyspnea improvements. CA19-9 blood levels rose to 2917.6 IU/mL (CA19-9 levels prior to the start of nab-

paclitaxel were 2023.1 IU/mL, Figure 2), and neutrophil and platelet levels were normal. Given the clinical improvements observed, we decided to continue the treatment. Cycle 2 days 1, 8 and 15 at 100 mg/m^2, without GCSF, were scheduled.

Four cycles of nab-paclitaxel at 100 mg/m^2 doses were administered (except for cycle 1 day 1). GCSF treatment was not needed (except cycle 1 day 15). Neutropenia below 1500 neutrophils/mL and thrombopenia below 10000 platelets/mL were not detected by blood tests prior to cycles 2, 3 and 4, so the hematological tolerance was considered to be excellent (Figure 6).

DISCUSSION

This clinical case is one of the first published concerning cholangiocarcinoma treatment using nab-paclitaxel monotherapy. Nab-paclitaxel has only been approved as a monotherapy for breast cancer[13,14]. In addition, it has proven to be useful when scheduled weekly[15,16]. In the remaining settings, a combination with other drugs (gemcitabine, carboplatin) was always required.

The only data on the efficacy of nab-paclitaxel in metastatic cholangiocarcinoma was phase 2 clinical trials but was part of a combination treatment in this case[17,18]. In addition, a retrospective registry of cases[19] and preclinical studies have also been performed[20,21]. However, no prospective evidence from phase 3 clinical trials has been found.

A combination of nab-paclitaxel with gemcitabine, as used in pancreatic cancer, is potentially more effective in cholangiocarcinoma in terms of disease control than nab-paclitaxel alone. In the phase 2 trials of first-line nab-paclitaxel combinations, the disease control rate is higher than 50% and ranges from 66% (in combination with gemcitabine)[17] to 84% (in combination with gemcitabine and cisplatin)[18]. However, our patient received nab-paclitaxel as a monotherapy and second-line treatment after platinum-containing chemotherapy, which can explain the reduced efficacy of nab-paclitaxel in this context. We decided to use weekly nab-paclitaxel based on data from the combination of weekly nab-paclitaxel and gemcitabine regimens for pancreatic cancer, and also from data showing the efficacy of weekly nab-paclitaxel monotherapy for breast cancer.

Achievement of a clinical and serological response was shown by a decrease in CA19-9 as well as improved liver function tests. There was also a mixed radiological response observed after four cycles of nab-paclitaxel. Therefore, we can consider that, although a new lesion appeared, the disease is controlled due to the shrinking or stabilization of most lesions. In a highly aggressive disease such as cholangiocarcinoma, a clinical response can be considered to be a clinical benefit and, therefore, a justification to continue treatment, despite the fact that a strict radiological response was not achieved. The objective of treatment for this patient was improving his quality of life, which was observed. Therefore, while we have evidence of the biological activity of nab-paclitaxel in cholangiocarcinoma, a partial radiological response was not observed.

We also have preclinical evidence of the efficacy of nab-paclitaxel in cholangiocarcinoma. In one study[20], primary cultures prepared from human mixed and mucin intrahepatic cholangiocarcinoma specimens were evaluated for cell proliferation and apoptosis after incubation with increasing concentrations of different drugs. Nab-paclitaxel showed an inhibitory effect on cell proliferation in both mixed- and mucin intrahepatic cholangiocarcinoma primary cultures. Additionally, nab-paclitaxel induced a significant increase in apoptotic activity in only mucin-intrahepatic cholangiocarcinoma. In another study[21], the inhibitory effect of paclitaxel and nab-paclitaxel in different cholangiocarcinoma cell lines was studied, revealing that both drugs induced anti-proliferative effects. Furthermore, a toxin-induced intrahepatic cholangiocarcinoma rat model was used to evaluate the *in vivo* tumor activity of paclitaxel, nab-paclitaxel and gemcitabine plus oxaliplatin regimen. Only nab-paclitaxel and gemcitabine plus oxaliplatin induced antitumor effect in the rat model. Compared with paclitaxel, nab-paclitaxel demonstrated increased effectiveness in reducing *in vivo* tumor formation by disrupting the desmoplastic stroma.

The genomic alterations identified in our patient's tumor by NGS do not appear to be related to nab-paclitaxel efficacy. In addition, we have no molecular markers that predict nab-paclitaxel activity in metastatic cholangiocarcinoma, as we do for other tumor types.

In a study evaluating the response of breast cancer to neoadjuvant chemotherapy in the GeparSepto trial according to the genomic alterations revealed by NGS, there was

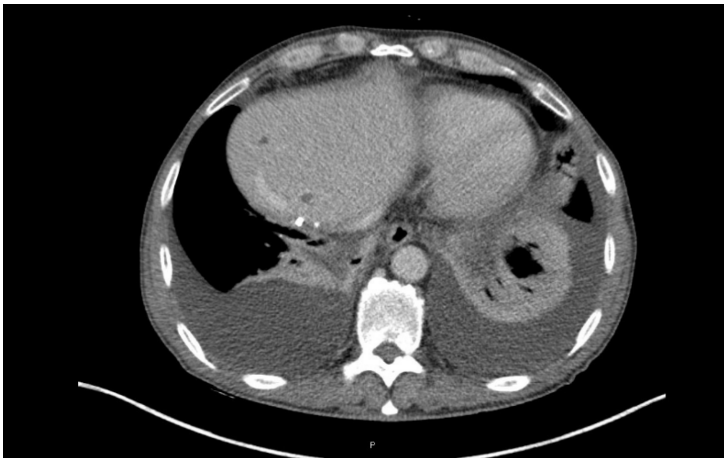

Figure 6 Computed tomography scan performed after four cycles of albumin-bound paclitaxel, where a mixed response was observed.

an increased response to nab-paclitaxel that was only observed in PIK3CA wild-type breast cancer patients[22]. The presence or absence of fibroblast growth factor receptor (FGFR) amplifications, a pathway that is aberrantly activated in 15%-20% of intrahepatic cholangiocarcinomas[23], was not related to the nab-paclitaxel response in this study. In non-small cell lung cancer, nintedanib is the only approved agent that targets the FGFR axis. This agent is limited to adenocarcinoma and is used in combination with docetaxel, according to the results of LUME-Lung 1 trial[24]. Based on this trial, a combination of a taxane, such as nab-paclitaxel, and an FGFR inhibitor in patients with FGFR amplifications would be a viable option for future use in metastatic cholangiocarcinoma patients.

CONCLUSION

Nab-paclitaxel monotherapy could be a viable treatment option for patients with advanced cholangiocarcinoma in later lines of treatment, after they have already progressed to standard therapies. This therapy has demonstrated preliminary efficacy in preclinical models. In addition, according to phase 2 clinical trial results, nab-paclitaxel is a potential first-line treatment in combination with either gemcitabine or gemcitabine plus cisplatin. Nab-paclitaxel should be studied as a potential treatment for metastatic cholangiocarcinoma in combination with not only chemotherapy but also with FGFR inhibitors. This is based on available efficacy data for a combination of taxane and FGFR inhibitor that has been used in other cancers. This approach could therefore be an interesting alternative to be explored over the next years.

ACKNOWLEDGEMENTS

The authors thank the patient and his family for their collaboration.

REFERENCES

1 **Rizvi S**, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 2013; **145**: 1215-1229 [PMID: 24140396 DOI: 10.1053/j.gastro.2013.10.013]
2 **Vauthey JN**, Blumgart LH. Recent advances in the management of cholangiocarcinomas. *Semin Liver Dis* 1994; **14**: 109-114 [PMID: 8047893 DOI: 10.1055/s-2007-1007302]
3 **DeOliveira ML**, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schulick RD. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**: 755-762 [PMID: 17457168 DOI: 10.1097/01.sla.0000251366.62632.d3]
4 **Nakeeb A**, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD, Yeo CJ, Cameron JL. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996; **224**: 463-473; discussion 473-475 [PMID: 8857851 DOI: 10.1097/00000658-199610000-00005]
5 **American Cancer Society**. Cancer Statics Center. 2020. Available from: https://cancerstatisticscenter.cancer.org

6 **Patel T**. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 2001; **33**: 1353-1357 [PMID: 11391522 DOI: 10.1053/jhep.2001.25087]

7 **Shaib YH**, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol* 2004; **40**: 472-477 [PMID: 15123362 DOI: 10.1016/j.jhep.2003.11.030]

8 **Patel T**. Worldwide trends in mortality from biliary tract malignancies. *BMC Cancer* 2002; **2**: 10 [PMID: 11991810 DOI: 10.1186/1471-2407-2-10]

9 **Welzel TM**, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. *J Natl Cancer Inst* 2006; **98**: 873-875 [PMID: 16788161 DOI: 10.1093/jnci/djj234]

10 **Jarnagin WR**, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, Youssef BA M, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; **234**: 507-517; discussion 517-519 [PMID: 11573044 DOI: 10.1097/00000658-200110000-00010]

11 **Valle J**, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine *versus* gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]

12 **Yardley DA**. nab-Paclitaxel mechanisms of action and delivery. *J Control Release* 2013; **170**: 365-372 [PMID: 23770008 DOI: 10.1016/j.jconrel.2013.05.041]

13 **Gradishar WJ**, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, O'Shaughnessy J. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005; **23**: 7794-7803 [PMID: 16172456 DOI: 10.1200/JCO.2005.04.937]

14 **Aigner J**, Marmé F, Smetanay K, Schuetz F, Jaeger D, Schneeweiss A. Nab-Paclitaxel monotherapy as a treatment of patients with metastatic breast cancer in routine clinical practice. *Anticancer Res* 2013; **33**: 3407-3413 [PMID: 23898112]

15 **Gradishar WJ**, Krasnojon D, Cheporov S, Makhson AN, Manikhas GM, Clawson A, Bhar P. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol* 2009; **27**: 3611-3619 [PMID: 19470941 DOI: 10.1200/JCO.2008.18.5397]

16 **Gradishar WJ**, Krasnojon D, Cheporov S, Makhson AN, Manikhas GM, Clawson A, Bhar P, McGuire JR, Iglesias J. Phase II trial of nab-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer: final analysis of overall survival. *Clin Breast Cancer* 2012; **12**: 313-321 [PMID: 22728026 DOI: 10.1016/j.clbc.2012.05.001]

17 **Sahai V**, Catalano PJ, Zalupski MM, Lubner SJ, Menge MR, Nimeiri HS, Munshi HG, Benson AB 3rd, O'Dwyer PJ. Nab-Paclitaxel and Gemcitabine as First-line Treatment of Advanced or Metastatic Cholangiocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol* 2018; **4**: 1707-1712 [PMID: 30178032 DOI: 10.1001/jamaoncol.2018.3277]

18 **Shroff RT**, Javle MM, Xiao L, Kaseb AO, Varadhachary GR, Wolff RA, Raghav KPS, Iwasaki M, Masci P, Ramanathan RK, Ahn DH, Bekaii-Saab TS, Borad MJ. Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. *JAMA Oncol* 2019; **5**: 824-830 [PMID: 30998813 DOI: 10.1001/jamaoncol.2019.0270]

19 **Unseld M**, Scheithauer W, Weigl R, Kornek G, Stranzl N, Bianconi D, Brunauer G, Steger G, Zielinski CC, Prager GW. Nab-paclitaxel as alternative treatment regimen in advanced cholangiocellular carcinoma. *J Gastrointest Oncol* 2016; **7**: 588-594 [PMID: 27563449 DOI: 10.21037/jgo.2016.05.01]

20 **Fraveto A**, Cardinale V, Bragazzi MC, Giuliante F, De Rose AM, Grazi GL, Napoletano C, Semeraro R, Lustri AM, Costantini D, Nevi L, Di Matteo S, Renzi A, Carpino G, Gaudio E, Alvaro D. Sensitivity of Human Intrahepatic Cholangiocarcinoma Subtypes to Chemotherapeutics and Molecular Targeted Agents: A Study on Primary Cell Cultures. *PLoS One* 2015; **10**: e0142124 [PMID: 26571380 DOI: 10.1371/journal.pone.0142124]

21 **Chang PM**, Cheng CT, Wu RC, Chung YH, Chiang KC, Yeh TS, Liu CY, Chen MH, Chen MH, Yeh CN. Nab-paclitaxel is effective against intrahepatic cholangiocarcinoma *via* disruption of desmoplastic stroma. *Oncol Lett* 2018; **16**: 566-572 [PMID: 29963132 DOI: 10.3892/ol.2018.8690]

22 **Loibl S**, Treue D, Budczies J, Weber K, Stenzinger A, Schmitt WD, Weichert W, Jank P, Furlanetto J, Klauschen F, Karn T, Pfarr N, von Minckwitz G, Möbs M, Jackisch C, Sers C, Schneeweiss A, Fasching PA, Schem C, Hummel M, van Mackelenbergh M, Nekljudova V, Untch M, Denkert C. Mutational Diversity and Therapy Response in Breast Cancer: A Sequencing Analysis in the Neoadjuvant GeparSepto Trial. *Clin Cancer Res* 2019; **25**: 3986-3995 [PMID: 30979740 DOI: 10.1158/1078-0432.CCR-18-3258]

23 **Krook MA**, Lenyo A, Wilberding M, Barker H, Dantuono M, Bailey KM, Chen HZ, Reeser JW, Wing MR, Miya J, Samorodnitsky E, Smith AM, Dao T, Martin DM, Ciombor KK, Hays J, Freud AG, Roychowdhury S. Efficacy of FGFR Inhibitors and Combination Therapies for Acquired Resistance in FGFR2-Fusion Cholangiocarcinoma. *Mol Cancer Ther* 2020; **19**: 847-857 [PMID: 31911531 DOI: 10.1158/1535-7163.MCT-19-0631]

24 **Tsironis G**, Ziogas DC, Kyriazoglou A, Lykka M, Koutsoukos K, Bamias A, Dimopoulos MA. Breakthroughs in the treatment of advanced squamous-cell NSCLC: not the neglected sibling anymore? *Ann Transl Med* 2018; **6**: 143 [PMID: 29862232 DOI: 10.21037/atm.2018.02.18]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com