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GUIDELINES

GOECP/SEOR radiotheraphy guidelines for non-small-cell lung cancer

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Abstract

Non-small cell lung cancer (NSCLC) is a heterogeneous disease accounting for approximately 85% of all lung cancers. Only 17% of patients are diagnosed at an early stage. Treatment is multidisciplinary and radiotherapy plays a key role in all stages of the disease. More than 50% of patients with NSCLC are treated with radiotherapy (curative-intent or palliative). Technological advances-including highly conformal radiotherapy techniques, new immobilization and respiratory control systems, and precision image verification systems-allow clinicians to individualize treatment to maximize tumor control while minimizing treatment-related toxicity. Novel therapeutic regimens such as moderate hypofractionation and advanced techniques such as stereotactic body radiotherapy (SBRT) have reduced the number of radiotherapy sessions. The integration of SBRT into routine clinical practice has radically altered treatment of early-stage disease. SBRT also plays an increasingly important role in oligometastatic disease. The aim of the present guidelines is to review the role of radiotherapy in the treatment of localized, locally-advanced, and metastatic NSCLC. We review the main radiotherapy techniques and clarify the role of radiotherapy in routine clinical practice. These guidelines are based on the best available evidence. The level and grade of evidence supporting each recommendation is provided.

Key Words: Radiotherapy; Non-small cell lung cancer; Guidelines; Stereotactic radiation therapy; Hypofractionated radiation; Oligometastasis

Core Tip: Radiotherapy is a critical component of multi-modality treatment of non-small-cell lung cancer (NSCLC). This guideline provides recommendations on the use of radiation therapy to treat patients with different stages of NSCLC. Our goal is to promote medical knowledge among physicians and improve health-care quality on these patients. These guidelines are based on the best available evidence. The level and grade of evidence supporting each recommendation is provided.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in both men and women. In 2018, there were more than 1.7 million cancer-related deaths worldwide. In that same year, more than 2 million people were newly-diagnosed with lung cancer. At diagnosis, approximately 57% of lung cancers are metastatic, 22% present lymph node involvement, and only 17% of cases are diagnosed at early stages [1]. Various environmental and lifestyle factors have been associated with the development of lung cancer. The main risk factor is tobacco use, accounting for 85%-90% of cases[2]. Non-small cell cancer (NSCLC) comprises more than 85% of all lung cancer diagnoses. Despite important treatment advances in recent years, 5-year overall survival (OS) rates remain low, ranging from to 0%-10% in stage IVA-IVB disease to as high as 68% in early stage[3,4].

Advances in treatment and diagnosis include minimally-invasive diagnostic/therapeutic techniques such as endobronchial ultrasound (EBUS) and video-assisted thoracic surgery[5]. In addition, determination of the histological subtypes has become standard practice to assess eligibility-based on tumor

histology and molecular status-for systemic therapy[6,7].

Radiotherapy (RT) is one of the three pillars of the multidisciplinary treatment of lung cancer. In recent years, technological advances have greatly improved this treatment modality. It is estimated that more than half of all cancer patients will require curative or palliative-intent RT at some point in the course of the disease[8]. A series of important advances-including simulation with four-dimensional computed tomography (4D-CT), three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), cone beam CT (CBCT) image verification systems, and control of respiratory movement-have made it possible to maximize tumor control while minimizing toxicity to adjacent healthy organs and tissues[9]. As a result, the radiation dose can be precisely delivered to the target and adapted to the patient's individual characteristics [anatomy and tumor location, TNM stage, comorbidities, and general performance status (PS)].

In the present guidelines, we review the clinical indications for RT in NSCLC according to disease stage, with a discussion of fractionation schedules, treatment volumes, and organs at risk (OAR). We also discuss the management of the main clinical scenarios seen in routine practice, establishing the grades of recommendation for each treatment according to the strength of evidence.

METHODS

These guidelines are based on the most relevant studies published in peer reviewed journals. A comprehensive review of the clinical literature in the following databases was performed: MEDLINE (Pubmed), EMBASE (Ovid), Web of science (Web of Knowledge). Article selection was undertaken by the expert authors. The Infectious Diseases Society of America grading system[10] was used to assign levels of evidence and grades of recommendation (Table 1). Statements without grading were considered justified standard clinical practice by the authors.

Diagnosis

The clinical manifestations of lung cancer are frequently nonspecific. If NSCLC is suspected, the patient should be referred to the pulmonologist and/or the rapid diagnosis unit and be evaluated by a multidisciplinary team (II, C)[11,12]. The evaluation begins with CT[13,14] and positron emission tomography (PET), which are essential for diagnosis, staging, and treatment planning (I, A). Brain magnetic resonance imaging (MRI) is also essential[15]. All nodes > 1.5 cm on the CT scan should be biopsied, even if the PET scan is negative (I, C). A positive PET scan should be further evaluated, regardless of lesion size[16,17], through EBUS or digestive endoscopic ultrasonography[18-20] (I, A). In uncertain cases, conventional mediastinoscopy or video-assisted mediastinoscopy and video-assisted thoracoscopy are surgical alternatives to obtain samples for subsequent analysis[21,22]. Peripheral lesions can be evaluated by CT-guided transthoracic fine-needle aspiration biopsy[14,23]. Pathologic confirmation is required in patients with a single metastatic lesion and uptake on PET[24].

Pathologic diagnosis of NSCLC should be based on the criteria established in the World Health Organization classification system[6]. It is important to differentiate between the histological subtype: Squamous cell carcinoma, adenocarcinoma (the most common), large cell carcinoma, and neuroendocrine tumors (I, B). The International Association for the Study of Lung Cancer (IASLC) has developed a classification system for adenocarcinoma with prognostic implications[25]. Immunohistochemical studies and determination of molecular alterations such as epidermal growth factor receptor (EGFR), Kirsten rat sarcoma, and anaplastic lymphoma kinase (ALK) mutations should be performed, as these alterations can predict sensitivity to certain drugs and/or targeted therapies[26] (I, B). Classification of NSCLC or not otherwise specified histology should be avoided. Staging is based on the IASLC TNM classification system (8th edition), which is used to classify patients according to disease stage to determine the prognosis and appropriate treatment[27].

CLINICAL INDICATIONS BY TNM STAGE

Early stages: Stereotactic body radiation therapy

Indications: Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative body radiation, consists of delivery of high dose radiation to a very specific target volume, with a high dose gradient in all directions[28]. The indication for this technique is based on the patient's surgical risk category: Inoperable, high-risk, or standard-risk[29]. As follows: (1) Inoperable: Approximately 25% of patients with early-stage NSCLC (ES-NSCLC) are inoperable due to age or comorbidities[30]. In this population, prospective studies of SBRT have reported local control (LC) rates of 90% at 5 years[31] and 91.9% at 7 years[32] and, with a ≥ grade (G)3 toxicity rate under 10%. The well-designed phase II TROG 09.02 CHISEL trial[33] compared SBRT to conventional 3D-RT. SBRT was superior to conventional 3D-RT in terms of LC [hazard ratio (HR) = 0.32, 95% confidence interval (CI): 0.13-0.77, P = 0.0077] with no increase in treatment-related adverse events (AEs). SBRT is therefore the treatment of choice in

Table 1 Level of evidence and grades of recommendation

Level of evidence	
I	Evidence from at least one large randomised controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control groups; case reports; expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, *etc.*), optional
D	Moderate evidence against efficacy or for adverse outcomes, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

inoperable patients (III, A); (2) Operable NSCLC: Only one prospective study (a pooled analysis of the ROSEL and STARS trials) has (indirectly) compared SBRT to 3D-CRT in operable patients[34,36]. The findings of that study, published in 2015, were criticised for the underpowered statistical analyses and the poor surgical quality in the two trials[35]. Several non-comparative prospective studies of SBRT have been conducted, most notably the phase II RTOG 0618 trial[36]. In that trial, 33 operable patients received SBRT, with a 4-year LC rate of 96% and ≥ G3 toxicity of only 8%. The findings of retrospective series comparing SBRT to surgery through matched pair analysis are inconclusive[37,38]. However, a recent meta-analysis[39] suggested that surgery may provide better outcomes on various survival parameters, including OS, cancer-specific survival, and disease-free survival (DFS). Prospective phase III trials are needed to confirm these findings. Currently, four prospective trials are underway to compare surgery to SBRT. Of these trials, the only non-randomised study is the Canadian RAXSIA trial (NCT03431415). The POSTILV trial (NCT01753414) is comparing SBRT to surgery in operable patients while the STABLE-MATES trial (NCT02468024) is comparing sublobar resection to SBRT. Although the VALUE trial (NCT02984761) was activated in 2016, they are still recruiting patients as of the last update (December 2020). Therefore, at present, there is no evidence to support SBRT *vs* surgery in operable patients, unless the patient refuses surgery (III, C); and (3) High-risk patients or patients > 75 years of age. The American Society of Clinical Oncology and the American Society of Radiation Oncology (ASTRO) recommend offering SBRT as an alternative treatment in high-risk patients[40,41] (III, A).

Fractionation: In order to select the appropriate fractionation schedule in SBRT, it is essential to carefully weigh the risks and benefits. LC is poor when the biological equivalent dose (BED) is < 100 Gy [42]. Consequently, the dose should be determined according to the location of the target lesion and, therefore, to the tolerance of adjacent organs. Tumor are classified as central, peripheral, or "safe" (> 2 cm from mediastinal structures and > 1 cm from the chest wall) depending on their location within the thoracic cavity.

Central tumors: Central tumor fractionations as defined by the IASLC[42]: The most important prospective phase I/II trial for central tumors was the RTOG 0813 trial[43], a dose escalation study comparing 50 Gy to 60 Gy, both administered in 5 daily fractions (fx), with an escalation schedule of 0.5 Gy per fraction/arm. The maximum tolerated dose was 12.0 Gy/fx, with a ≥ G3 toxicity rate of 7.2%. Two-year LC rates in patients who received the lowest dose fraction (10 Gy/fx) was 87.5% *vs* 87.9% in the 12 Gy/fx regimen, with 2-year progression free survival (PFS) rates of 50% *vs* 54.5%, respectively.

The dose-escalated SUNSET[44] trial (dose level 1:60 Gy/7 fr-dose level 3 60 Gy/5 fr) and the Hilus [45] trial (56 Gy/8 fr to 65%-70% isodose line) were both performed to assess high-dose SBRT in central/ultracentral tumors. The recently published, Hilus trial showed that this fraccionation regimen in tumors located ≤ 1 cm from the main bronchus and trachea had a high risk of G3 to G5 toxicity (33.8%) with 10 patients experiencing G5 toxicity. These regimens contrast with the more conservative Dutch regimen (60 Gy/8 fx)[46], which obtained a 3-year LC rate of 92.6% and ≥ G3 toxicity of 7.9%.

Based on the available evidence, the optimal fractionation in central tumors appears to be 50 to 60 Gy delivered in five fractions. The dose per fraction should be adjusted to OAR tolerances, and can range from 10-12 Gy/fraction with a total dose of 50-60 Gy administered in 5 daily fractions or 8 fx of 7.5 Gy each to a total of 60 Gy.

Lesions adjacent to the chest wall: In patients with tumors located adjacent to or in contact with the chest wall, European guidelines[47] recommend a total dose of 48 Gy in four fractions. Prospective studies[48] have shown that this fractionation schedule yields 3-year LC rates ranging from 85.4% to 87.3%, with a ≥ G3 toxicity rate (rib fracture) of 3%. Other fractionation schedules have been proposed in this location. For example, Haasbeek *et al*[46] proposed 60 Gy in five fractions, with a 3-year LC rate of 89.3% and a late ≥ G3 toxicity rate (chest wall pain) of 2.1%[46]. Nyman *et al*[49] proposed 45 Gy in three fractions, which achieved a LC rate of 80% with late toxicity (rib fracture) in 4%.

Tumors located in the "safe" zone: Lesions located in the "safe" zone can be considered non-central tumors located > 2 cm from the chest wall. Evidence from two prospective phase II trials - Singh *et al*[50] and RTOG 0915[31]-support extreme hypofractionation (single 30-34 Gy fraction). Singh *et al*[50] found that a single 30 Gy fraction yielded a 2-year LC rate of 94.9%, with G3 toxicity in 17%, and no ≥ G4 toxicity. In RTOG 0915, which evaluated a single 34 Gy dose, the one-year LC rate was 97.0%, with ≥ G3 toxicity rate of 10.3%. Timmerman *et al*[51] conducted a prospective phase II trial to evaluate SBRT in inoperable ES-NSCLC, the findings of that trial supported the classical Timmerman fractionation scheme, with a 3-year LC rate in peripheral tumors ranging from 90.6%-94% and ≥ G3 AEs ranging from 10% to 16.3% (Table 2).

Locally-advanced, inoperable disease

Radical chemoradiotherapy: Concomitant *vs* sequential: At diagnosis, approximately 35% of patients with NSCLC present locally-advanced disease, for which the standard treatment is CRT. The recommended RT dose is 60-66 Gy (I, A). Increasing the radiation dose in combination with chemotherapy (ChT) does not improve outcomes but does increase toxicity rates[52].

In patients with good PS, the recommended treatment is concomitant chemoradiotherapy, which has been shown to improve OS *vs* sequential chemoradiotherapy by 5.7% at 3 years and 4.5% at 5 years, with a mean survival time of 22-25 mo and 5-year OS of 20%[53], probably due to better locoregional control (2.9% at 3 years and 2.2% at 5 years) (I, A). However, concomitant chemoradiotherapy also has a higher incidence of acute non-hematological toxicity[54], mainly G3-G4 esophagitis (range: 4%-18%), but no effect on acute pulmonary toxicity[55]. To date, no differences in treatment outcomes have been observed for the following variables: Type or ChT scheme, age, sex, PS, histology, or disease stage. Neither induction nor consolidation ChT are indicated, although data from the phase III PACIFIC trial showed that consolidation therapy with durvalumab improves both PFS and OS in patients with programmed death ligand 1 > 1% who do not progress after concomitant chemoradiotherapy[56].

Neoadjuvant chemoradiotherapy: Several studies, including the SAKK Lung Cancer Project Group trial [57] and the Lung Intergroup Trial 0139[58], have evaluated the role of neoadjuvant chemoradiotherapy, finding this approach improves PFS in patients who receive trimodal treatment, but without any benefit for OS. This lack of benefit in the surgical arm may be due to higher early mortality rates, especially in patients undergoing right pneumonectomy. A subanalysis found a significant improvement in survival in patients treated with induction chemoradiotherapy followed by lobectomy *vs* those who received concomitant chemoradiotherapy [58].

Induction chemoradiotherapy has been shown to achieve a greater reduction in nodal downstaging than ChT alone, but with no benefit in OS[53] except for potentially resectable superior sulcus tumors, for which the treatment of choice is concomitant chemoradiotherapy (45-54 Gy, 1.8-2 Gy/d) (III, A). However, it is important to plan radical dose RT in case surgery is ultimately not performed[59].

Adjuvant RT: Adjuvant RT is indicated when complete resection (R0) has not been achieved and salvage surgery is not feasible (I, A). In these cases, sequential chemoradiotherapy (ChT followed by RT) should be offered, although with a less aggressive ChT scheme. Concomitant chemoradiotherapy should be limited to patients with macroscopic residual disease (V, C).

The role of adjuvant RT has long been controversial, especially after a meta-analysis published in 1998 showed higher mortality rates after postoperative RT (PORT) in patients with N0-N1 disease[60]. However, the increased mortality was probably due to the excessive toxicity associated with older radiation therapy techniques. By contrast, no deleterious effects of adjuvant RT have been observed in N2 disease. A recent meta-analysis concluded that adjuvant RT is associated with better OS and PFS rates in these patients[61].

The role of PORT was evaluated in two recent phase III trials. In the phase III Lung-ART trial (definitive results still pending publication) patients with N2 involvement were randomized to receive PORT (54 Gy) or observation after complete tumor resection. The initial results showed that PORT did not improve DFS or OS, although fewer thoracic relapses were observed in the group treated with PORT (25% *vs* 46.1%). The lack of improvement in survival outcomes (DFS and OS) could be due to higher rates of cardiopulmonary toxicity ≥ G3 (10.8% *vs* 4.9%). In this regard, it should be noted that 89% of the patients were treated with 3D-CRT and only 11% with IMRT[62].

The second recently-published phase III trial was a single-center study involving 394 patients with stage IIIA-pN2 disease randomized to receive PORT (50 Gy) or observation after complete resection and four cycles of adjuvant chemotherapy. Most of the patients (89.3%) were treated with IMRT (10.7%

Table 2 Recommended stereotactic body radiation therapy dose in early-stage disease

Localization	Dose	Ref.	Evidence level
Central tumour	50/5 fx-60/5 fx	Bezjak *et al*[43], 2019	II, B
	60 Gy/8 fx	Haasbeek *et al*[46], 2011	
Chest wall	48 Gy/4 fx	Guckenberger *et al*[47], 2017	II, B
	60 Gy/5 fx	Nagata *et al*[48], 2015	
	45 Gy/3 fx	Nyman *et al*[49], 2006	
Safe zone	30 Gy/1 fx	Singh *et al*[50], 2019	II, B
	34 Gy/1 fx	Videtic *et al*[31], 2019	
	54 Gy/3 fx	Timmerman *et al*[36], 2018	

SBRT: Stereotactic body radiation therapy; fx: Fractions.

received 3D-CRT). In the intention-to-treat analysis, PORT did not improve DFS, although it did improve DFS in the per-protocol analysis. The results of a pre-planned exploratory analysis in which patients were stratified according to the number of resected nodes (20 *vs* > 20) and involved nodes [(1-3) *vs* ≥ 4] revealed a significant improvement in DFS (HR = 0.75; 95%CI: 0.58-0.98; *P* = 0.04). PORT had no impact on OS. Toxicity rates were lower than observed in the Lung-ART trial, probably due to the high proportion of patients treated with IMRT, stricter dose limits to the OARs, and the exclusion of the contralateral mediastinal nodes from the treatment volume[63].

Despite the significant improvement in LC achieved in both trials, this did not lead to better survival outcomes. For this reason, PORT is not currently recommended as part of standard treatment in patients with N2 involvement and R0 resection. However, stage IIIA-N2 patients are a heterogeneous group and some of these patients could benefit from PORT, as suggested by data from previous studies as well as the recently published findings of the Lung-ART trial (ESMO 2021), which show that a mediastinal nodal involvement ratio (nodes involved/nodes evaluated) ≥ 25% is a prognostic factor for DFS, suggesting that the extent of nodal involvement could help to select patients who may benefit from PORT. Nonetheless, more studies are needed to better determine, through a comprehensive analysis of clinical and molecular characteristics, the patients most likely to benefit from PORT. Based on the postoperative pathologic findings, the recommended PORT doses are as follows: (1) R0: 50-54 Gy, 1.8-2 Gy/fx; (2) Involved margins or microscopic disease: 54-60 Gy; and (3) Macroscopic residual disease: ≥ 60 Gy[59,64].

Altered fractionation schemes: Various dose-intensification strategies have been explored, including accelerated hyperfractionation and other hypofractionated schemes.

Accelerated fractionation and hyperfractionation: Three phase III trials compared different hyperfractionated schemes to conventional RT, demonstrating that hyperfractionated RT yields positive results when administered alone or after induction ChT (I, A). Those trials include the Continuous Hyperfractionated Accelerated Radiotherapy Trial (CHART)[65,66], HART[67], and Continuous Hyperfractionated Accelerated Radiotherapy Weekend Less (CHARTWEL)[68]. The findings of these trials were recently confirmed in a large retrospective series[69].

A meta-analysis evaluated the results of nine trials (2000 patients) - including the CHART, HART, and CHARTWEL trials - comparing conventional RT to various hyperfractionated and accelerated RT schemes. All of the altered fractionation schemes improved OS, although without any significant between-group differences in PFS. The administration or not of ChT did not impact OS. The modified fractionation schemes, particularly very accelerated RT, increased the risk of acute severe esophagitis in Table 3[70].

Moderate hypofractionation: Some patients - due to advanced age, the presence of comorbidities, and/or travel-related difficulties - are poor candidates for conventional (60-66 Gy, 30-36 daily fractions) or hyperfractionated RT. In recent months, due to the coronavirus disease 2019 (COVID-19) pandemic and the consequent need to reduce the number of hospital visits, the use of moderately hypofractionated RT has become more common in patients eligible for radical RT.

The available evidence suggests that dose escalation with standard fractionation techniques (achieved by extending treatment duration) does not improve outcomes[52]. However, radiobiological models show that each 1% increase in the radiation dose improves LC by 1% to 2%[71]. A systematic review of clinical data from dose escalation studies[72] found a BED_{10} dose-response relationship for NSCLC. That review evaluated studies that applied various fractionation schemes, including standard fractionation, hyperfractionation, and hypofractionation. Although the best results were obtained with hypofrac-

Table 3 Accelerated fractionation-hyperfractionation studies

Ref.	Study type	Number of patients	Radiotherapy	Chemotherapy	Results	Toxicity
[65, 66]	Phase III RCT	*n* = 563: Stage I (29%), II (7%), IIIA (38%), IIIB (23%). Similar in both arms	[cRT: 60 Gy, 2 Gy/d (6 wk). INP 44 Gy + boost 16 Gy tumour and involved nodes] *vs* (CHART: 54 Gy, 1.5 Gy/3 times/d, 6 h apart, on 12 consecutive days). INP 37.5 Gy in 25 fx + boost 16.5 Gy in 11 Gy to tumour and involved nodes	No	Absolute 2-yr survival improvement of 9%: 20% cRT *vs* 29% CHART. 21% relative risk reduction for PL. Major improvement in squamous cell disease: 13% 2-yr survival: 20% cRT *vs* 33% CHART. 25% relative risk reduction of PL	Clinical pneumonitis 19% cRT and 10% CHART
[67]	Phase III RCT	*n* = 141: Stage III A-B unresectable. ECOG 0-1	[cRT: 64 Gy, 2 Gy/d (6 ½ wk)] *vs* [HART: 57.6 Gy, 1.5 Gy 2 times/d (2.5 wk)]	Induction: Carboplatin AUC 6 + paclitaxel 225 mg/m^2 2 cycles prior to RT	2-yr OS: 44% HART *vs* 24% cRT; 3 yr: 34% *vs* 14%. Non-significant trend towards better survival with HART. Feasible treatment. Trial close early due to slow recruitment	Esophagitis ≥ G3: 23% HART *vs* 15% cRT. Pneumonitis ≥ G3: 0 HART *vs* 10% cRT
[68]	Phase III RCT	*n* = 406: Stage I 10%, II 5%, IIIA 38%, IIIB 46%. Similar in both arms	(CHARTWEL: 60 Gy, 1.5 Gy 2 times/d in 2.5 wk) *vs* (cRT: 66 Gy, 2 Gy/d, 6.5 wk)	Neoadjuvant 27%. Similar in both arms	Better LC in CHARTWEL. No difference between arms in OS at 2, 3, 5 yr. Better LC CHARTWEL trend in advanced stages and after neoadjuvant ChT	Greater acute dysphagia CHARTWEL. Greater radiological pneumonitis CHARTWEL, no differences in clinical pneumonitis
[69]	Retrospective	*n* = 849, 9 United Kingdom centres. Stage I 33%, II 13%, IIIA 24%, IIIB 24%, IV 1%	CHART: 54 Gy, 1.5 Gy/3 times/d, 6 h apart, in 12 d	Induction: 27% patients, 82% stage III (96% platinum doublets: Cisplatin or carboplatin with vinorelbine, gemcitabine or paclitaxel)	OS 2 and 3 yr: 47% and 32%. OS 3 yr: 38% stage I and 27% stage III. Tendency to better survival in stage III after ChT	Esophagitis, pneumonitis ≥ G3 5%

RCT: Randomised controlled trial; cRT: Conventional radiotherapy; ENI: Elective nodal irradiation; CHART: Continuous Hyperfractionated Accelerated Radiotherapy Trial; OS: Overall survival; RT: Radiotherapy; LC: Local control; CHARTWEL: Continuous Hyperfractionated Accelerated Radiotherapy Weekend Less.

tionated RT, the differences were not significant.

Phase I dose escalation trials of hypofractionated RT have evaluated various regimens[73-75]. Prospective and retrospective series[76-80] have found that accelerated RT is both feasible and well-tolerated when administered alone or concurrently/sequentially with ChT, a finding that was also confirmed in the interim analysis of a phase III trial (Iyengar *et al*[81]) comparing accelerated hypofractionated RT to conventional RT.

The phase III EORTC 08972-22973 trial[82] and the randomised phase II SOCCAR trial[83] compared concurrent to sequential CRT in patients receiving hypofractionated RT. Based on the excellent results obtained with concomitant CRT in the SOCCAR trial[83], this scheme is now widely used in routine practice in the United Kingdom. Iqbal *et al*[84] showed that modifying the ChT dose, incorporating advanced imaging techniques such as PET-CT for staging, and the use of IMRT and VMAT improved survival outcomes at 2-years (58%), with acceptable rates of acute toxicity (Table 4).

A systematic review evaluated 33 studies (1902 patients) involving radical-intent hypofractionated RT for the treatment of stage III NSCLC. The number of fractions in those studies ranged from 15 to 35, with dose fractions ranging from 2.3 Gy to 3.5 Gy, and total doses from 45.0 to 85.5 Gy. Nearly half of those studies (15/33) included concurrent ChT with radiation schemes ranging from 52.5 to 75 Gy at 2.24-3.5 Gy/dose in 15-30 fx. The other studies included neoadjuvant, adjuvant, or no ChT, at RT doses ranging from 45-85.5 Gy (2.25-3.42 Gy/fx, 15-35 fx). There was a linear relationship between BED_{10} and OS: Every 1 Gy increase in BED_{10} yielded an absolute survival benefit of 0.36% to 0.70%. Compared to non-concurrent schemes, concurrent CRT was associated with better OS, albeit with higher - but still acceptable - rates of esophageal toxicity[85].

A single-centre study evaluated 563 patients; 43% received CHART and 57% hypofractionated RT (55 Gy in 20 fx of 2.75 Gy). Both treatment regimens yielded comparable results in terms of survival and treatment-related AEs[86]. Based on their findings, the authors concluded that moderately hypofractionated RT with concurrent ChT is safe when delivered with modern RT techniques and may improve treatment outcomes. However, these findings need to be confirmed in phase III trials.

The ongoing COVID-19 pandemic has led to an increase in the use of hypofractionated RT. To address the challenges presented by the pandemic, a group in the United Kingdom[87] and the ESTRO-

Table 4 Studies of moderate hypofractionated radiotherapy

Ref.	Type of study	Number of patients	Radiotherapy	Chemotherapy	Results	Toxicity
[76]	Prospective	30, stage III-IVA. ECOG ≥ 2	60 Gy (20 fx 3 Gy); (BED_{10} 79.4 Gy)	Sequential (80% patients)	LR 37%. OS 2-yr 38.1%. LR 37%. Distant relapse 57%	Acute esophagitis G3 7%. Acute pneumonitis G3 3%. No chronic toxicity
[77]	Prospective	83 (32 stage III)	66 Gy (24 fx 2.75 Gy); (BED_{10} 84 Gy)	Sequential 90.6% stage III (platinum + vinorelbine)	OS 2 yr 37.5%. SCE 2 yr 41.5%	No toxicity ≥ G3
[78]	Retrospective	300, stage III, inoperable, MEG	3 arms: 45 Gy (15 fx 3 Gy); 60-63 Gy (6 wk); > 63 Gy (6 wk)		No significant differences in LC, distant control, or OS. > DFS in 60-63 Gy	Lower in hypofractionated arm
[79]	Retrospective	609 (9 centres). Stage IA (18%), IB (30.7%), II (14.8%), IIIA (16.4%), IIIB (19.2%). Unresectable or inoperable	55 Gy (20 fx 2.75 Gy)	ChT 28% (83% stage III). Platinum doublets. Most neoadjuvant	OS at 2, 3 and 5 yr: 50%, 36% and 20%. 2 yr OS: stage IA, 72%, stage Ib 51%, stage IIIA 40%. Adenocarcinoma better median survival (31 m) *vs* squamous (20.4 m). No difference in OS between ChT *vs* no ChT. Stage III, trend towards better OS with ChT	No toxicity ≥ G3. Pneumonitis G1-2, 15%
[80, 82]	Retrospective	31, stage I (15), II (15), IIIA (57), IIIB (43). Medically inoperable or unresectable	3 arms: 66 Gy (24 fx 2.75 Gy) + daily cisplatin (6 mg/m^2); same sequential RT after 2 cycles cisplatin/gemcitabine; RT alone 66 Gy (24 fx 2.75 Gy) or 60 Gy (20 fx 3 Gy)	Concurrent: Cisplatin daily (6 mg/m^2). Sequential: (2 cycles cisplatin/gemcitabine) prior to RT	LR 36%, DM 46%. Better RT + ChT than RT alone. 5 yr OS: Concurrent CRT, 23%. No significant difference between concurrent and sequential CRT. LR 36%, DM 46%	Severe late toxicity greater in CRT (27% concurrent, 23% sequential) than in RT alone (8%)
[81]	Phase III RCT[1]	60, stage II/III (11.6%/88.3%). ECOG ≥ 2. Not candidates for ChT/RT	cRT 60-66 Gy/30-33 fx *vs* accelerated hypofx 60 Gy/15 fx 4 Gy	Non-concurrent ChT. Possible neoadjuvant or adjuvant	OS and PFS without significant differences between cRT and hypofx	No G4 toxicity. G3 toxicity: 35% cRT and 18.75% hypofx
[82]	Phase III RCT	158, stage I (3% sequential, 1% concurrent), II (4% sequential, 5% concurrent), IIIA (45% sequential, 30% concurrent), IIIB (47% sequential, 64% concurrent). Inoperable ECOG 0-1	66 Gy (24 fx 2.75 Gy)	Concurrent: Daily cisplatin (6 mg/m^2) + RT 66 Gy (24 fx 2.75 Gy) *vs* sequential: 2 cycles gemcitabine 1250 mg/m^2 days 1, 8 and cisplatin (75 mg/m^2 day 2, prior to RT 66 Gy (24 fx 2.75 Gy)	No significant differences between the 2 groups in DM, OS, PFS. OS 2 and 3 yr: 39%-34% concurrent and 34%-22% sequential. Both schemes well tolerated. Due to early closure, no conclusions drawn	Acute esophagitis G3/4 more common in concurrent (14% *vs* 5%). Late esophagitis G3 = 4% in both arms. Pneumonitis G3/4 = 18% concurrent and 14% sequential
[83]	Phase II RCT	130, stage III inoperable. ECOG 0-1	55 Gy (20 fx 2.75 Gy)	Concurrent: Cisplatin 20 mg/m^2 days 1-4 and 16-19 and vinorelbine 15 mg/m^2 days 1, 6, 15 and 20 RT and 1 or 2 post ChT cycles (CDDP) 80 mg/m^2 day 1 and vinorelbine 25 mg/m^2 days 1 and 8). Sequential: Cisplatin 80 mg/m^2 day 1 and vinorelbine 25 mg/m^2 days 1 and 8, x 3-4 cycles before RT	No significant differences. OS 1 yr: 70% concurrent *vs* 83% sequential and 2 yr: 50% concurrent *vs* 46% sequential. PFS 1 yr: 74% concurrent *vs* 85% sequential; 2 yr: 47% concurrent *vs* 45% sequential. Both safe and effective treatments. Non-significant trend towards better survival with concurrent RT/ChT	Similar esophagitis ≥ G3 in both arms (8.8% concurrent and 8.5% sequential. Pneumonitis ≥ G3: 3.1% concurrent *vs* 5.2% sequential. No grade 4/5 esophagitis. G3 neutropenia lower in concurrent (37%) *vs* sequential (55%)
[84]	Retrospective	100, stages IIIA-B 95%, II 5%. ECOG 0/1	55 Gy (20 fx 2.75 Gy)	Concurrent: Cisplatin 20 mg/m^2 days 1-4 and 16-19 RT and vinorelbine 15 mg/m^2 days 1, 6, 15, 20 and 2 cycles post RT/ChT	OS 2 yr 58%. PFS 2 yr 49%	Esophagitis G3/4 14%. Pneumonitis G3/4 4%

[1]Interim analysis of NCT01459497 with 226 patients: Arm A (experimental), 60 Gy in 15 fractions (3 wk) with image-guided radiotherapy versus arm B,

conventional radiotherapy 60-66 Gy in 30-33 fractions (6 wk) with optional concurrent carboplatin/taxol. Final data expected in December 2021 and December 2022.

RT: Radiotherapy; cRT: Conventional radiotherapy; LR: Local recurrence; DM: Distant metastases; LC: Local control; G: Grade; ChT: Chemotherapy; PFS: Progression-free survival; MFS: Metastasis-free survival; OS: Overall survival; CDDP: Concurrent cisplatin.

ASTRO[88] have both published recommendations for hypofractionated schemes during this period. The United Kingdom group recommends 55 Gy in 20 fx of 2.75 Gy with concurrent ChT in patients with good PS. In patients unable to tolerate concurrent CRT, those guidelines recommend either sequential CRT or RT alone. If ChT is not administered, then hypofractionated RT schemes (*e.g.*, 50-58 Gy in 15 fx) can be considered[87]. The ESTRO-ASTRO practice guidelines, developed through a modified Delphi consensus process, proposed recommendations for two different scenarios: (1) Early pandemic phase, focused on risk mitigation; and (2) A later phase (severe pandemic scenario) in which RT resources may be limited. In the first scenario, there was strong support (97% of the expert panel) for hypofractionated RT (60 Gy in 15 fx, 60 Gy in 20 fx, 60-66 Gy in 24-30 fx, or 55 Gy in 20 fx) if treatment was limited to RT alone. For sequential CRT, there was also strong support (97%) for the same fractionation and dose schemes, although with a clear preference for the 55 Gy (20 fx) or 60-66 Gy (24-30 fx at 2.2-2.75 Gy/d) schemes (II, A). There was no consensus to support concomitant hypofractionated CRT. An alternative would be 55-60 Gy in 20 fx[88] (II, B).

RT in advanced NSCLC

RT in oligometastatic patients: Approximately two-thirds (60%-70%) of patients with NSCLC are diagnosed with stage IV disease. Of these, 20% - or more if PET-CT imaging is used for staging - are oligometastatic at diagnosis[89]. Oligometastasis may present in one of two ways: (1) "*De novo*" oligometastasis: Patient with 3-5 lesions at diagnosis (synchronous) or after 3-6 mo of treatment of the primary tumor (metachronous); and (2) Induced oligometastatic: Polymetastatic patient with metastatic disease in 3-5 locations after systemic therapy.

This recently described concept of oligometastatic disease[90,91] can be further subdivided as follows: (1) Oligopersistence: Persistent disease that is stable on imaging studies, with < 5 lesions after systemic treatment; (2) Oligoprogression: Progression (new lesions or growth of known lesions) in 3 to 5 sites after systemic treatment; and (3) Oligorecurrence: Recurrent disease in 3-5 sites in patients not receiving active systemic therapy.

In these patients, a prior with disseminated disease, the use of local treatments has been shown to improve OS[92] (II, B). In this regard, three prospective[93-95] studies involving patients with oligometastasis at diagnosis have been published (Table 5). Those trials demonstrated that the patients most likely to benefit from local treatments are those whose disease remains stable or responds to systemic therapy, which is why the National Comprehensive Cancer Network guidelines for oligoprogression recommend mutation-directed therapies (EGFR, ALK). However, it is important to keep in mind that patients in the experimental arms of those trials did not receive immunotherapy, an approach that has altered the treatment paradigm in metastatic disease. In this regard, several studies are currently evaluating radioimmunotherapy, which combines local RT with immunotherapy[96].

Multiple studies have sought to identify the characteristics of the "true" oligometastatic patient and those with the best prognosis based on predictors identified in retrospective series (Table 6), as well as other predictive variables currently under investigation[97,98]. These patients are candidates for radical RT, with the dose adjusted for the lesion location and size. The most common metastatic sites in patients with stage IV NSCLC are the brain, lungs, liver, bone, and adrenal glands.

RT in metastatic patients: In metastatic disease, the main objective of RT is symptom relief and better quality of life (QoL). Prior to RT, it is important to assess the patient's functional status, social and family situation, and systemic treatment. Thanks for the important advances in targeted therapies and immunotherapy in recent years, survival in this subgroup has substantially improved[99]. The specific symptoms will depend on the tumor location; symptom relief is the main indication for RT in this setting.

Based on currently available data[100], symptom control appears to be similar regardless of the specific palliative RT scheme (I, A). Short course RT is associated with a higher risk of reirradiation, which is why it is recommended only in patients with poor PS or short life expectancy[101,102] (II, A). Higher doses (20-30 Gy in 5-10 fx) have been shown to improve OS by 5% in selected patients[103], which is why this RT scheme is recommended for thoracic lesions (II, B). Another option is endobronchial brachytherapy, which until recently was reserved for the treatment of airway obstruction in previously-irradiated patients. However, a systematic review published in 2012 comparing endobronchial brachytherapy + external beam RT (EBRT) to EBRT alone reported better symptom control in the EBRT group[104] (II, B).

The optimal management of brain metastases is increasingly controversial. In patients ineligible for stereotactic radiosurgery (SRS) and patients with multiple diffuse brain metastases, the treatment of choice is whole-brain RT (WBRT). However, the findings of the QUARTZ trial, a randomised phase III

Table 5 Radiation therapy in patients with oligometastatic non-small cell lung cancer

Ref.	Type	Design	Palliative treatment	Histology	Presentation	No. of metastases/location	RT type	Follow-up (mo)	PFS (mo)	MFS (mo)	OS (mo)
Gomez *et al* [93], 2019	Phase II RCT. Multicentre	Induct. ChT: (RT + MT) *vs* MT	49	NSCLC (No EGFR, ALK)	Synchronous. Metachronous	≤ 3 (1%:65%)/lung, CNS, bone, liver SSRR, nodes	SABR/SBRT (MTX) hypofra. RT (primary)	38.8	14.2 (SABR/SBRT + MT) *vs* 4.4 (MT)	11.9 (SABR/SBRT + MT) *vs* 5.7	41 (SABR/SBRT + MT) *vs* 17
Iyengar *et al*[95], 2018	Phase II RCT. Multicentre	Induct. ChT: (SBRT + mChT) *vs* mChT	29	NSCLC (No GFR, ALK)	Synchronous	≤ 5 (1%:21%, 2%-3%:76%)/lung, lymph, bone, SSRR	SABR/SBRT (MTX) hypofra. RT (primary)	9.6[1]	9.7 (SABR/SBRT + MT) *vs* 3.5 (MT)	NR	NR (SABR/SBRT + MT) *vs* 17
Palma *et al* [94], 2020	Phase II RCT. Multicentre	(ChT + PT) *vs* (ChT + SABR/SBRT)	99	Lung (18/99)	Synchronous. Metachronous	≤ 5 (1%-3%:93%)/lung, bone, CNS, liver, SSRR	SABR/SBRT	51	11.6 (SABR/SBRT + MT) *vs* 5.4 (TP-MT)	NR	50 (SABR/SBRT + MT) *vs* 22

[1]Study stopped early due to significant difference in progression-free survival between the two arms.

RT: Radiotherapy; MT: Maintenance treatment; mChT: Maintenance chemotherapy; SABR: Stereotactic ablative radiotherapy; SBRT: Stereotactic body radiotherapy; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; MTX: Metastasis; NR: Not reported; PFS: Progression-free survival; MFS: Metastasis-free survival; OS: Overall survival; PT: Palliative treatment; NSCLC: Non-small cell lung cancer.

trial comparing WBRT to supportive treatment in patients unsuitable for SRS, which found no benefit for WBRT in terms of OS or QoL, called this indication into question[105] (I, A).

In patients with asymptomatic brain metastases who have not yet started systemic therapy - and could potentially benefit from targeted therapy due to the presence of oncogenic driver mutations (*e.g.*, ALK mutation) - the start of RT can be considered given the intra- and extra-cranial effects of RT[106] (III, B).

At present, there are no clear recommendations on how to best combine RT and immunotherapy. However, two phase II studies (one randomised)[107,108] found that combined treatment was safe and provided adequate symptom control without negatively affecting QoL (III, B).

DEFINITION OF VOLUMES AND RISK ORGANS, CONSTRAINTS

Definition of tumour volumes

Systematic errors (inaccurate contouring of the target volume, OARs, and/or margins) reduce the likelihood of LC while increasing treatment-related toxicity. In 2018, the ESTRO published consensus guidelines for target volume definition in the treatment (radical and PORT) of locally-advanced NSCLC, with four grades of recommendation[109].

According to those guidelines, contrast-enhanced CT should be used for treatment planning. If possible, a recent PET-CT scan in the treatment position is recommended[110]. Respiratory motion should be quantified by 4D-CT, particularly in lower lobe tumours or treatments involving SBRT (IV, A). Treatment volumes[111]: (1) Gross tumour volume (GTV): The primary tumor GTV (GTV-P) and lymph nodes (GTV-N) should be delineated separately. It is important to select the correct window on CT (lung window: W = 1600, l = 600 for lesions surrounded by the lung; mediastinum window: W = 400,

Table 6 Prognostic factors associated with better survival in oligometastatic patients with non-small cell lung cancer

Factor	Comments
Gender	Female > male
Histology	Adenocarcinoma > squamous cell carcinoma
Presentation	Metachronous > synchronous
Karnofsky index - ECOG	80% < - ≤ 100%
Number of lesions	1 > 2-3 > 4-10
Size	< 3 cm
Location	Lung, bone > adrenal glands, lymph nodes > liver, brain

ECOG: Eastern Cooperative Oncology Group.

l = 20, for lymph nodes and tumors invading the mediastinum/chest wall) (III, A); (2) GTV-P: Areas of atelectasis should be excluded[112], which is why PET-CT imaging is particular valuable. If neoadjuvant ChT is administered, the initial volume based on the current CT scan should be used for contouring (III, B); and (3) GTV-N[113-115]: Lymph nodes that are positive on biopsy or pathologic by PET-CT or CT (≥ 1 cm) should be included. Nodes that are highly suspicious on PET-CT imaging but with negative findings on EBUS should be included due to the risk of false negatives (III, A).

If neoadjuvant ChT has been performed, include the lymph nodes or nodal stations involved prior to ChT, regardless of the response. Contouring atlases should be used for nodal station delineation[116-118]. Clinical target volume (CTV): The CTV includes the GTV plus adjacent subclinical disease. It is generally not contoured in SBRT (III, B). CTV-P[119]: For the CTV-P, the GTV should be expanded by 5-8 mm and manually edited to account for surrounding anatomy. CTV-N: The CTV-N can be created in two ways: Either by including the involved nodal station with a margin ≥ 5 mm around the GTV-N[109] or through geometric expansion of the GTV-N (5-8 mm), adapted to anatomical barriers. Elective or prophylactic nodal radiation is not recommended since it does not improve locoregional control but does increase toxicity. PORT[120]: The following areas should be irradiated: Involved lymph nodes, bronchial stump, ipsilateral hilum, and lymph node stations 4 and 7. In left lung cancers, levels 5 and 6 should also be irradiated.

Internal target volume: The internal target volume (ITV) takes into account the internal motion of the tumor. Various systems are available to estimate this motion, which can be limited to reduce the ITV, or monitored with 4D-CT or target lesion tracking[121,122]. One of the most widely used and recommended systems is 4D-CT. The CTV-GTV is contoured in each respiratory phase, or directly in the maximum intensity projection reconstruction. If this is not possible, a slow acquisition CT, or CT on inspiration, expiration and free breathing can be acquired, contouring the CTV-GTV at each point (III, B).

Planning target volume: This is generated by expanding the ITV to account for geometric uncertainties. The planning target volume (PTV) will vary according to the RT centre since differences between centres (*e.g.*, the immobilization system, the method used to compensate for respiratory motion, the specific image-guided technique, *etc.*) can affect the PTV (III, A).

OARs in SBRT and 3D/4D-RT

In many cases, the radiation dose is limited by OARs in the chest cavity. Accurate contouring of these organs is essential, especially for extreme hypofractionated schemes. In 2003, Collier *et al*[123] described the intra- and inter-observer uncertainty in manual contouring of thoracic OARs, thus making it possible to determine the dosimetric impact of these uncertainties. In the last decade, several different contouring atlases have been published to assist in contouring tissues in this anatomic region[124,125].

Lung (lung window settings): Although each lung should be contoured separately, the dosimetric evaluation should be based on the sum of doses to both lungs, excluding the main bronchial tree, the trachea, areas of atelectasis, and the primary GTV (IV, A).

Esophagus (mediastinal window): All layers (mucosa, submucosa and muscular) from the cricoid cartilage to the gastroesophageal junction should be included (IV, A). Oral contrast can be used to ensure correct visualization. For SBRT, contouring of the esophagus should start ≥ 10 cm above the upper limit of the PTV to ≥ 10 cm below the lower limit.

Heart (mediastinal window): There are various approaches to contouring this organ, although the most common approach is to contour the entire heart, including the pericardium and cardiac base, from the lower limit of the pulmonary artery below the aortic arch to the cardiac apex at the level of the diaphragm (IV, A). The pulmonary artery, aorta, and superior vena cava should be excluded. In some

Table 7 Dose constraints in normofractionated radiotherapy

Organ	Volume	Endpoint	Dose (Gy), dose/volume	Rate, %	Ref.
Spinal cord	Partial	Myelopathy	Dmax 50, Dmax 60, Dmax 69	0.2%, 6%, 50%	
Lung	Whole organ, both lungs	Pneumonitis	V20 ≤ 30%, MD = 7, MD = 13, MD = 20, MD = 24, MD = 27	< 20%, 5%, 10%, 20%, 30%, 40%	Palma *et al*[133], 2013 Marks *et al*[130], 2010
Esophagus	Whole organ	≥ Grade 3 acute esophagitis, ≥ grade 2 acute esophagitis	MD < 34, V60 ≤ 17%, V35 < 50%, V50 < 40%, V70 < 20%	5%-20%, < 30%, < 30%, < 30%	Al-Halabi *et al*[135], 2015
Heart	Pericardium. Whole organ	Pericarditis. Cardiac mortality long term	MD < 26, V30 < 46%, V25 < 10%, V50 ≤ 25%	< 15%, < 15%, < 1%	Speirs *et al*[136], 2017
Brachial plexus	Whole organ	Brachial plexopathy	MD > 69 Gy. Dosis maximum 75 Gy to 2 cc of the brachial plexus		Amini *et al*[137], 2012

Dmax: Maximum dose; MD: Median dose.

cases, other subvolumes, such as the coronary arteries (IV, C), can be included[125].

Spinal cord (mediastinal window): Generally, for EBRT, the spinal canal is delineated on the planning CT, corresponding to the planning risk volume (PRV) for the spinal cord (IV, B). For SBRT, the GTV should be contoured if it is located close to the spinal cord; MRI images are useful in these cases. Next, a PRV of the area of interest should be created.

Brachial plexus[126]: Tumors located at the lung apex should be contoured to avoid neurotoxicity (IV, B). A contrast-enhanced CT (or fusion MRI/CT) should be performed to ensure contouring accuracy. The brachial plexus is located between the anterior and middle scalene muscles. There are 5 roots (C5-T1), as follows: (1) Upper limit: The exit point between C4-C5; (2) Lower limit: Subclavian artery and vein; (3) Internal limit: The neural foramina extending from the lateral aspect of the spinal canal to the small space between the two scalene muscles; and (4) Outer limit: The space between the two scalene muscles. For tumors located in the right lung base, the liver should also be contoured (IV, C).

SBRT OARs[127]: Chest wall[128] (mediastinal window): The involved hemithorax should be contoured from the sternal border to the vertebral body, including the ribs and intercostal muscles, excluding other muscles and skin (IV, B). In peripheral tumors, the ribs closest to the tumor should be contoured separately in a bone window setting (IV, C). Trachea (mediastinal window): Include the mucosa, submucosa, and tracheal rings from the lower edge of the cricoid to the upper limit of the proximal bronchial tree (2 cm above the carina). This can also be delineated starting 10 cm above the PTV extension or 5 cm above the carina (whichever is more superior). The lower border is the upper limit of the proximal bronchial tree (IV, B). Proximal bronchial tree (mediastinal window for the trachea and carina and lung window for the bronchi). This includes the area 2 cm distal from the trachea, right and left (R/L) main bronchi, upper lobe (R/L), intermediate bronchus, middle lobe bronchus, lingula, and lower lobe (R/L) (IV, B). Aorta and great vessels[129] (mediastinal window): The aorta and superior vena cava should be included. The vascular wall and all muscle layers must be included (IV, B), and contoured starting ≥ 10 cm above the upper limit of the PTV continuing to at least 10 cm below the lower limit. Skin (mediastinal window): This is a hollow organ. Automatically contour the body and subtract 5 mm (IV, B).

Constraints in normofractionated RT, hypofractionated RT, and SBRT

Normofractionated radiation therapy: The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study was published in 2010[130]. The aim of this study was to review the available data on the effects of radiation on normal tissue. QUANTEC updated and further refined the tolerance doses for normal tissues described by Emami *et al*[131] in 1991. QUANTEC provides normal tissue complication probability (NTCP) models, with summary tables of specific results for each organ. However, as the authors indicate, these limitations are not intended to replace comprehensive data provided by organ-specific reviews, and they apply primarily to adult patients. The NTCP according to organ and dose is summarised in Table 7.

The specific limits are as follows: (1) Lung: With conventional fractionation (2 Gy/fx), the recommended V20 limit for both lungs is ≤ 30%-35% and MD ≤ 20-23 Gy to minimize the risk of symptomatic pneumonitis to < 20%[132]. However, several different factors must be considered, included the patient's age and any concurrent systemic treatments. A meta-analysis of data from 836 patients treated with concurrent CRT (60 Gy; cisplatin-etoposide in 38%, carboplatin-paclitaxel in 26%, other schemes in 36%)[133] found that two variables - the lung volume receiving ≥ 20 Gy (V20) and carboplatin/paclitaxel ChT - were predictors of pneumonitis. The highest risk was observed in patients > 65 years receiving carboplatin/paclitaxel-based chemotherapy. The probability of fatal pneumonitis was greater if the daily dose was > 2 Gy and the tumor was located in the lower lobe. Although the latest results presented at ESMO 2020 have called into question the role of PORT in the absence of a

Table 8 Dose constraints for moderate hypofractionation

Organ	Concurrent RT/ChT (55 Gy/20 fx)	Sequential RT/ChT (55 Gy/20 fx)	RT (50-58 Gy/15 fx)	RT (50-60 Gy/15 fx) [138]
Spinal cord	MD 44 Gy (0.1 cc)	Dmax ≤ 36	MD 42 Gy (0.1 cc)	MD < 38 Gy
Esophagus[1]	MD < 55 Gy (1 cc)	V42 < 32%	MD < 52 Gy (1 cc)	MD < 50 Gy (1 cc), V45 < 10 cc
Lungs-GTV	V20 < 35%, MD < 18 Gy	V20 < 25%-30%, MD ≤ 15 Gy	V19 < 35%, MD < 16 Gy	V20 < 30%, V5 < 60%, MD < 20 Gy
Heart	V30 < 36%	V33 < 25%	D100% < 33 Gy, D67% < 40 Gy, D33% < 52 Gy	MD 63 Gy, V57 < 10 cc
Great vessels	NA	NA	MD 58 Gy	MD 63 Gy, V57 < 10 cc
Trachea, carina and main bronchus	NA	NA	MD 58 Gy	MD 63 Gy, V57 < 10cc
Rib	MD < 63 Gy	NA	V30 < 30 cc	MD 63 Gy; V30 < 30cc

[1]Esophagus within the planning target volume ≤ 12 cm.
MD: Median dose; Dmax: Maximum dose; Fx: Fraction; ChT: Chemotherapy; NA: Not available.

definitive analysis, in patients with involved margins PORT is still indicated. A recent study published by a group from the Memorial Sloan Kettering Cancer Center[134] compared dosimetric parameters in 285 patients with NSCLC treated with PORT between 2004 and 2017. The incidence of pneumonitis ≥ G2 was 12.6%. The following factors were associated with pneumonitis: Lung and heart dose, age, and carboplatin-based ChT. These data suggest that elderly patients may be more susceptible to lower lung doses. To limit the risk of pneumonitis ≥ G2 to less than 5% in patients receiving PORT, the authors recommended the following limits: (1) Lung V5 ≤ 65% in patients < 65 years of age and V5 ≤ 36% in patients ≥ age 65. After pneumonectomy, the recommended limits are lung V5 < 60%, V20 < 4%-10%, and median lung dose < 8 Gy[132]; (2) Esophagus: In a study published in 2015, Al-Halabi *et al*[135] evaluated 20 patients who underwent CRT for tumours located < 1 cm from the esophagus. The median radiation dose was 70.2 Gy (range: 63-72.15 Gy). Due to measures taken to protect the contralateral esophagus, there were no cases of esophagitis ≥ G3. The proposed dose contraints to the contralateral esophagus were: V45 < 2.5 cc and V55 < 0.5 cc. IMRT and VMAT allow for dose reduction to the esophagus, thus reducing the incidence of esophagitis; (3) Heart: A subanalysis of the RTOG 0617 dose escalation trial[136] evaluated the association between heart dosimetric parameters and OS. Heart V_{50} < 25% *vs* ≥ 25% was associated with a significant improvement in OS at both one and two years: 70.2% *vs* 46.8% and 45.9% *vs* 26.7% (P < 0.0001), respectively. The median heart V_{50} was significantly higher (20.8% *vs* 13.9%, P < 0.0001) in patients with ≥ G1 cardiac toxicity; and (4) Plexus: An analysis of 90 patients with apical lung cancer treated with CRT found an association between brachial plexopathy and the mean dose to the brachial plexus > 69 Gy (60% of doses > 69 Gy *vs* 13% ≤ 69 Gy) and maximum dose > 75 Gy at 2 cc of the brachial plexus (43% *vs* 13%)[137].

Hypofractionated radiation therapy: Several different total and fractional dose schedules have been used for moderate hypofractionation, including concurrent CRT with various ChT schemes and sequential RT after ChT, or EBRT alone. The dose constraints were not reported in all studies. Table 8 summarises the recommended dose constraints for the most common moderately hypofractionated schemes published by Faivre-Finn *et al*[87].

SBRT: Several reviews have described the constarints to OARs in SBRT base on the studies shown in Table 9[19,31,36,43,139-145].

RT TECHNIQUES (3D-RT, IMRT, VMAT, RESPIRATORY CONTROL, PROTONS, ADAPTIVE RT)

Technological advances in recent years have led to significant changes in the radiotherapeutic treatment of NSCLC, which has progressed from 3D-CRT to IMRT and VMAT, together with advances in image-guided RT (IGRT) and the introduction of proton RT.

Based on data from non-randomised studies, these more sophisticated techniques reduce toxicity to OARs and improve tumor control, thereby leader to better survival outcomes when compared to 3D-CRT[147,148]. The phase III RTOG 0617 trial comparing IMRT to 3D-CRT in advanced stage disease showed that IMRT reduced lung doses (V20), leading to lower rates of severe (≥ G3) pneumonitis and

Table 9 The constraints to organs at risk s in stereotactic body radiotherapy based on the studies

Organ	Single fraction (30-34 Gy)		Three fractions (54-60 Gy)		Four fractions (48 Gy)		Five fractions (50-60 Gy)		Eight fractions (60 Gy)		Ref.
	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Brachial plexus	14 Gy < 3 cc	17.5 Gy ≤ 0.035 cc	20.4 Gy < 3cc	24 Gy ≤ 0.035 cc			27 Gy < 3 cc	30.5 Gy ≤ 0.035 cc			Benedict *et al*[139], Grimm *et al*[140]
	14.4 Gy < 3cc	17.5 Gy Dmax	22.5 Gy < 3 cc	24 Gy			30 Gy < 3 cc	32 Gy			Bezjak *et al*[43]
					23.6 Gy < 3 cc, 30 Gy < 10 cc, 35 Gy < 1 cc	27.2 Gy Dmax, 40 Gy Dmax					Videtic *et al*[31], Chang *et al*[146]
			24 Gy ≤ 0.5 cc	26 Gy ≤ 0.5 cc			27 Gy ≤ 0.5 cc	29 Gy ≤ 0.5 cc	27 Gy ≤ 0.5 cc	38 Gy ≤ 0.5 cc	Hanna *et al*[141]
Spinal cord	10 Gy < 0.35 cc, 7 Gy < 1.2 cc	14 Gy ≤ 0.035 cc	14 Gy < 0.35 cc, 12.3 Gy < 1.2 cc	18 Gy ≤ 0.035 cc			23 Gy < 0.35 cc, 14.5 Gy < 1.2 cc	30 Gy ≤ 0.035 cc			Benedict *et al*[139]
	7 Gy < 1.2 cc	7 Gy < 1.2 cc	18 Gy < 0.25 cc, 11.1 Gy < 1.2 cc	18 Gy	20.8 Gy < 0.35 cc, 13.6 Gy < 1.2 cc	26 Gy Dmax	22.5 Gy < 0.25 cc, 13.5 Gy < 1.2 cc, 13.5 Gy < 0.5 cc				Bezjak *et al*[43], Videtic *et al*[31], Timmerman *et al*[36]
			18 Gy < 0.1 cc	21.9 Gy < 0.1 cc			23 Gy < 0.1 cc	30 Gy < 0.1 cc	25 Gy < 0.1 cc	32 Gy < 0.1 cc	Hanna *et al*[141]
Esophagus	11.9 Gy < 5 cc, 14.5 Gy < 5 cc	15.4 Gy Dmax	17.7 Gy < 5 cc	25.2 Gy			19.5 Gy < 5 cc	35 Gy			Videtic *et al*[31]
			21 Gy < 5 cc	27 Gy	18.8 Gy < 5 cc, 30 Gy < 10 cc, 35 Gy < 1 cc	30 Gy Dmax, 50 Gy Dmax	27.5 Gy < 5 cc	35 Gy, 52.5 Gy			Timmerman *et al*[36], Bezjak *et al*[43], Chang *et al*[146]
				25.2 Gy < 0.5 cc			32 Gy < 0.5 cc	34 Gy < 0.5 cc		40 Gy < 0.5 cc	Hanna *et al*[141]
Heart	16 Gy < 15 cc, 16 Gy < 15 cc	22 Gy Dmax, 22 Gy Dmax	24 Gy < 15 cc, 24 Gy < 15 cc	30 Gy Dmax, 30 Gy Dmax	28 Gy < 15 cc, 35 Gy < 10 cc, 40 Gy < 1 cc	34 Gy Dmax, 50 Gy Dmax	32 Gy < 15 cc, 32 Gy < 15 cc	38 Gy Dmax, 38 Gy Dmax, 52.5 Gy Dmax			Benedict *et al*[139], Timmerman *et al*[36], Bezjak *et al*[43], Chang *et al*[146]
			24 Gy < 0.5 cc	26 Gy < 0.5 cc			27 Gy < 0.5 cc	29 Gy < 0.5 cc	50 Gy < 0.5 cc	60 Gy	Hanna *et al*[141]
Great Vessels	31 Gy < 10 cc	37 Gy Dmax	39 Gy < 10 cc	45 Gy Dmax			47 Gy < 10 cc	53 Gy Dmax			Benedict *et al*[139]
	31 Gy < 10 cc	37 Gy < 0.035 cc	39 Gy < 10 cc	45 Gy Dmax	43 Gy < 10 cc, 35 Gy < 10 cc, 40 Gy < 1 cc	49 Gy Dmax	47 Gy < 10 cc	52.5 Gy Dmax			Bezjak *et al*[43], Videtic *et al*[31], Chang *et al*[146]
				45 Gy < 0.5 cc		53 Gy < 5 cc					Hanna *et al*[141]

Trachea and bronchus	10.5 Gy < 4 cc	20.2 Gy Dmax	15 Gy < 4 cc	30 Gy Dmax			16.5 Gy < 4 cc	40 Gy Dmax			Benedict *et al*[139]
	8.8 Gy < 4 cc, 10.5 Gy < 4 cc	22 Gy Dmax, 20.2 Gy < 0.035 cc	21 Gy < 5 cc	30 Gy Dmax	30 Gy < 10 cc, 35 Gy < 1 cc, 15.6 Gy < 4 cc	50 Gy Dmax, 34.8 Gy Dmax					Bezjak *et al*[43], Videtic *et al*[31], Timmerman *et al* [36], Chang *et al*[146]
			30 Gy < 0.5 cc	32 Gy < 0.5 cc			32 Gy < 0.5 cc	35 Gy < 0.5 cc	32 Gy < 0.5 cc	44 Gy < 0.5 cc	Hanna *et al*[141]
Skin	23 Gy < 10 cc, 14.4 Gy < 10 cc	26 Gy Dmax, 16 Gy Dmax	30 Gy < 10 cc, 22.5 Gy < 10 cc	33 Gy Dmax, 24 Gy Dmax	35 Gy < 10 cc, 40 Gy < 1 cc, 33.2 Gy < 10 cc	36 Gy Dmax	36.5 Gy < 10 cc, 30 Gy < 10 cc	39.5 Gy Dmax, 32 Gy Dmax			Benedict *et al*[139], Chang *et al*[146], Videtic *et al*[31]
Chest wall	22 Gy < 1 cc	30 Gy Dmax	28.8 Gy < 1 cc, 30 Gy < 30 cc	36.9 Gy Dmax			35 Gy < 1 cc	43 Gy Dmax			Benedict *et al*[139]
	22 Gy < 1 cc	30 Gy Dmax	30 Gy < 30 cc, 50 Gy < 2.3 cc		35 Gy < 10 cc, 32 Gy < 1 cc	40 Gy Dmax	30 Gy < 30 cc, 50 Gy < 2.3 cc, 60 Gy < 1.4 cc				Videtic *et al*[31], Kong *et al* [145], Liao *et al*[147]
			37 Gy < 0.5 cc, 30 Gy < 30 cc				39 Gy < 0.5 cc, 32 Gy < 30 cc		39 Gy < 0.5 cc, 35 Gy < 30 cc		Hanna *et al*[141], Dunlap *et al*[142], Ma *et al*[143]
			40 Gy < 5 cc, 60 Gy < 0.5 cc				V30 < 30 cc, V30 < 70 cc				Herth *et al*[19]
Normal lungs	Minimal critical volume under threshold. 1500 cc, 1000 cc	Threshold dose: 7 Gy, 7.4 Gy		Threshold dose: 11.6 Gy, 12.4 Gy			Threshold dose: 12.5 Gy, 13.5 Gy				Benedict *et al*[139]
	Minimal critical volume under threshold. 1500 cc, 1000 cc, 1500 cc, 1000 cc	7 Gy, 7.4 Gy	20 Gy < 10%, 20 Gy < 15%	10.5 Gy, 11.4 Gy	11.6 Gy, 12.4 Gy, 20 Gy < 20%, 30 Gy < 10%		12.5 Gy, 13.5 Gy, 20 Gy < 20%, 30 Gy < 10%				Bezjak *et al*[43], Videtic *et al*[31], Chang *et al*[146]
				V20 < 10%, V12.5 < 15%			V20 < 10%, V12.5 < 15%		V20 < 10%, V12.5 < 15%		Hanna *et al*[141]
	Treatment on lesion: V20 < 10%; treatment 2-3 lesions: V20 < 12.5% (optimal); V20 < 15% (acceptable); V20 < 20% (selected cases) 3-8 fractions on alternating days. If the lesions are not included in the treatment field, alternate the treatment days for the different lesions										Hanna *et al*[141]
	In 3-5 fraction Dmean ≤ 8 Gy and V20 ≤ 10%-15%										Kong *et al*[145]

lower heart doses, which is a predictor of survival[149,150]. VMAT offers many of the same advantages as IMRT, including a reduction in the number of treatment sessions, similar lung doses and PTV coverage, but with lower heart doses; as a result, VMAT is becoming more common in the treatment of NSCLC[151].

Intrathoracic motion of lung tumor and healthy tissues is a major challenge that can significantly influence treatment delivery. Breathing control techniques can help reduce PTV margins and allow for more precise treatment delivery based on the unique motion of a given tumor, thus providing better tumor control and lower doses to OARs. During planning, several techniques can be used to quantify

tumor motion, including "slow" CT, inspiration-expiration CT, or 4D-CT, as well as techniques to control movement, such as abdominal compression, deep-inspiration breath hold, and breath synchronization techniques such as "gating" in which CT acquisition and treatment are performed in specific phases of the respiratory cycle, and "real-time" tumor tracking-used mainly in SBRT[152]. A useful resource for the implementation of respiratory control is the AAPM Task Group 76 report, which can be used to develop institutional guidelines based on the technical resources available at each centre[153].

The incorporation of CBCT has improved IGRT. CBCT allows for more accurate positioning and reduces inter- and intrafraction errors, thus resulting in smaller PTV margins and lower OAR doses. In addition, CBCT can measure changes in location, morphology, and physiology, thus permitting changes in the initial treatment plan[154-156]. This capacity to adjust the treatment plan, known as adaptive RT, permits administration of higher radiation doses to the tumor with lower doses to the OARs[155,157,158]. Data from small studies suggest that adaptive RT improves LC[159]. This technique is currently being evaluated in the phase II RTOG 1106 trial (NCT01507428) comparing standard concomitant CRT (60 Gy) to adaptive RT based on PET-CT imaging.

Data from both retrospective and prospective studies suggest that proton radiation therapy (PRT) may be superior to photon RT in the treatment of NSCLC[160-162]. However, only one randomised study has compared SBRT to PRT in stage I disease and that trial was closed early[163]. In patients with stage III disease, prospective and retrospective studies have shown acceptable locoregional control with PRT combined with ChT[164]. PRT has the potential to reduce toxicity to OARs such as the lung, heart, and esophagus, especially in unresectable central tumors[165-167]. However, to date, only one randomised phase II trial has compared IMRT to PRT, finding no significant advantages for PRT, nor any significant differences between these modalities in terms of pneumonitis or LC[168]. Consequently, the theoretical advantages of PRT need to be validated in randomised trials, such as RTOG 1308, which is currently recruiting patients[169].

REIRRADIATION

Approximately 20%-40% of patients with early stage or locally-advanced NSCLC develop locoregional progression or metachronous disease at 2 years[170]. Most of these recurrences or second primaries are unresectable, which explains the growing interest in reirradiation. Due to technological advances in radiation therapy delivery - IMRT, SBRT, proton therapy, and IGRT - it is now possible to consider reirradiating certain tumors. However, there is no consensus on the optimal approach to RT for local recurrences in previously-irradiated patients[171].

Reirradiation with photons

The two most common techniques in the radical dose reirradiation setting are IMRT and SBRT. To select the technique that provides the best local disease control with acceptable toxicity, it is important to consider the following parameters: Type of prior RT, anatomic location of the recurrence, and whether the lesion is located in or outside of the original RT field. Several factors - good PS, lung function, small PTV, and a BED dose > 100 Gy - are predictive of better LC and survival. Consequently, these factors should be considered when determining suitability for reirradiation.

SBRT is the technique of choice for peripheral recurrences located far from the mediastinum[172] because SBRT-related toxicity can be severe when the tumor is located near the bronchial tree and/or esophagus. Vyfhuis *et al*[173] reported a 92% LC rate in patients treated with 50 Gy in four fractions (SBRT) while Kilburn *et al*[174] reported a 2-year LC rate of 67% for recurrences located within the prior treatment field, with an acceptable toxicity profile (G2 = 30%, only case of G3 toxicity). The findings of the MD Anderson studies[175] show that IMRT is the most appropriate technique for reirradiation in central tumors, as high doses are required to achieve better LC. IMRT also reduces the dose to healthy tissues, thus limiting toxicity.

Reirradiation with particle therapy (protons and carbon ions)

Particle therapy (protons/carbon ions) is another option to consider for re-irradiation, mainly to reduce toxicity to OARs, as the physical characteristics of these particles reduces the integral dose (low-dose bath of photons at the beam exit point). However, these patients have a high rate of metastases. Some studys reported a significant decrease in OAR toxicity in patients reirradiated with PRT[176,177].

Proton therapy is increasingly being used as a primary treatment for NSCLC and may also have an important role in the reirradiation setting, mainly due to the lack of exit doses. Although carbon ion radiation therapy (CIRT) appears to be superior to proton therapy, due to greater linear energy transfer and relative biological effectiveness, its use is currently very limited[178].

The ROCOCO dosimetric comparison study[179] showed that PRT reduced the integral dose and doses to OARs, even with dose escalation. Chao *et al*[180] found that patients treated with PRT had a high rate of toxicity, with 39% of patients developing ≥ G3 toxicity. In that study, the one-year OS and DFS rates were 59% and 58%, respectively. However, given the toxicity findings, the authors recommended careful selection of patients.

Several studies are currently evaluating reirradiation in NSCLC. Some of these trials have completed patient recruitment and results are pending. One trial (NCT01808677) is evaluating reirradiation with IMRT or PRT; the main endpoint is severe toxicity (≥ G3) and survival is a secondary endpoint.

Reirradiation with CIRT has shown moderate efficacy and acceptable toxicity, suggesting that this modality could be an effective treatment option in selected patients[181]; however, large multicentre trials are required to confirm these findings.

To conclude this section, the best candidates for reirradiation have the following characteristics: Good PS, small volume recurrences, non-central locations, and the capacity to tolerate high dose radiation (SBRT, IMRT, or particle therapy)[175,182].

MANAGEMENT OF TREATMENT INTERRUPTIONS

Management of the overall treatment time (OTT) is especially important in NSCLC. Depending on the fractionation scheme, the effects of prolonging the OTT may vary, and different strategies can be employed to minimize these deleterious effects. In normofractionated schemes, extending the OTT will negatively impact locoregional control and OS[183-186]. One report suggested that OS rates may decrease by up to 1.8% for each day of treatment prolongation[187]. In hyperfractionated regimens, interruptions that increased the OTT by ≥ 5 d in high dose schemes (≥ 69.6 Gy) negatively impact OS, especially in patients with good prognostic factors, such as Karnofsky Performance Status 90%-100%, weight loss < 5%, and ≤ N2[185].

Compensation for treatment interruption

In the year 2000, the Royal College of Radiologists in the United Kingdom published recommendations for the management of unscheduled treatment interruptions, which were updated in 2019[188]. These recommendations divide the treatment type into three categories: Radical (categories 1 and 2) and palliative (category 3) treatment, as follows: (1) Category 1: Patients whose tumors have a high repopulation rate (*e.g.*, squamous cell tumors) who are being treated with radical curative-intent RT. The United Kingdom recommendations include both NSCLC and SCLC in this group. Treatment prolongation in these patients should be no more than two days beyond the prescribed time in 95% of patients; (2) Category 2: Patients with slow growing cancers (mainly adenocarcinomas) receiving radical-intent RT. This group includes breast, transitional bladder carcinoma, and prostate cancer; and (3) Category 3: Patients undergoing palliative-intent RT. OTT prolongation is less critical in these cases. However, it is advisable to compensate for prolonged (> 7 d) interruptions.

Compensation methods

Some authors have suggested that modern RT techniques such as IMRT reduce the incidence of treatment interruptions[189]. Nevertheless, the general principle is to ensure that interruptions are kept as short as possible and to anticipate interruptions whenever possible.

In general, treatment delays can be classified into two main groups: Planned and unplanned interruptions. Two types of measures - universal and specific - can be applied to address these scenarios. Universal measures are useful in both groups, while specific measures will depend on whether the interruption is programmed or not.

There are two main types of universal compensation measures, as follows: (1) Compensation on weekends and holidays; and (2) The use of compatible linear accelerators, which allow for treatment delivery on either machine. Although this is a "planned" measure, it also allows for compensation in the event of unexpected equipment malfunction.

Specific measures can be classified according to whether the interruption was planned or unplanned, as follows: (1) Unplanned: Option 1: Administer two sessions on the same day, 6 h apart, to compensate for the delay. Option 2: Compensate for the dose in the remaining fraction based on the BED, taking into account the a/b for healthy tissue or tumor according to the following formula[190].

$$N.d\left[1+\frac{d}{\alpha/\beta}\right]$$

Where N is the number of fractions, d is the dose per fraction, and α/β is the repair coefficient between lethal and sub-lethal damage. If we take into account the accelerated repopulation time, assuming a tumor α/β ratio of 10, the formula would be as follows.

$$N.d\left[1+\frac{d}{\alpha/\beta}\right]-K\,(T-T\kappa)=\;30.2\left[1+\frac{2}{10}\right]-0.45\,(39-28)=\;67.05\ \text{Gy}$$

Where: + K (esti-mated loss of biological efficacy in Gy per day of delay that would need to be added to compensate)[183]: (1) Stages T1-3, N0-1: 0.27 Gy/d; stages T1-3 N2-3 or T4: 0.75 Gy/d; all stages: Mean 0.45 Gy/d. + T: Total treatment time. In the example, the T is 39 d and treatments assumed to start on a Monday. + Tκ (time from the start of RT at which accelerated repopulation begins) reported: 3-4 wk [187]: 28 d. Therefore, to calculate the dose per remaining fraction, we need to consider the remaining BED needed to reach 67.05 Gy, and the remaining fractions not to exceed two days of treatment

Table 10 Summary of recommendations

Diagnosis	Level of evidence, grade of recommendation
If lung cancer is suspected, refer patient to a rapid diagnostic service for evaluation by a multidisciplinary team	II, C
PET-CT is recommended for initial staging in patients with stage I-III disease who are candidates for radical treatment	I, A
EBUS/EUS is recommended for clinical staging in patients with enlarged lymph nodes without distant metastases, with or without PET uptake	I, C
EBUS/EUS is recommended for stating in patients with positive PET-CT scans and normal-sized lymph nodes without distant metastases	I, A
Histological confirmation of the mediastinum by EBUS/EUS is recommended in central tumours, tumours > 3 cm, and N1 cases	I, C
Histological confirmation is required in cases with a single metastatic lesion and positive PET-CT	II, A
Brain MRI is recommended in candidates for curative-intent treatment	II, A
VAMS should be performed when EBUS/EUS findings are not evaluable	I, B
Differentiation between adenocarcinomas and squamous cell carcinomas is recommended even for small biopsies or cytology	I, B
EGFR mutations and ALK rearrangements should be assessed in patients with stage IV, non-squamous cell carcinomas. This determination should be performed in all cases (regardless of smoking status) and in all non-smokers independently of tumour histology	I, B
Early stage NSCLC - SBRT	
Inoperable	II, A
Operable	III, C
High surgical risk	III, A
Locally-advanced disease	
Concomitant radiotherapy: This is the treatment of choice for unresectable stage IIIA/IIIB with ECOG 0-1 and weight loss < 5% in 3 mo	I, A
60-66 Gy in 30-33 daily fractions of 2 Gy/fx and 2-4 ChT cycles	I, A
Platinum-based ChT	I, A
Treatment should be completed in < 7 wk	III, B
Sequential radiotherapy	
If concomitant treatment is not possible, the alternative is sequential CRT	I, A
Treatment should be completed in a short period of time	I, A
Neoadjuvant radiotherapy	
Assessment by a multidisciplinary team is recommended	IV, C
In potentially-resectable upper sulcus tumours, the recommended approach is neoadjuvant CRT followed by surgery	III, A
This approach can be considered in potentially-resectable T3/T4 tumours, but only in well-selected cases at experienced centres	III, B
Surgery must be performed within 4 wk after completion of RT	III, B
Adjuvant radiotherapy	
Not recommended in early stage disease with complete resection (R0)	I, A
It should be considered if resection is incomplete or margins are involved (R1)	IV, B
Not recommended as standard in R0 cases with N2 involvement	I, A
In N2 disease, adjuvant RT could be considered based on risk factors for local recurrence	IV, C
If adjuvant ChT and RT are both administered, the recommended sequence is ChT followed by RT	V, C
Altered fractionation schemes	
Accelerated hyperfractionation schemes provide better disease control than conventional RT	I, A

Recommended fractionation schemes for RT administered alone or sequentially after ChT: 55 Gy (20 fx, 2.75 Gy), 60 Gy (20 fx, 3 Gy), 60 Gy (15 fx, 4 Gy), 45-50 Gy (15 fx, 3-3.33 Gy)	II, A
If RT administered concurrently with ChT in patients with good performance status: 55 Gy (20 fx 2.75 Gy)	II, B
General considerations: There is no evidence to support prophylactic WBRT in stage III disease	II, A

PET-CT: Positron emission tomography-computed tomography; fx: Fractions; MRI: Magnetic resonance imaging; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; NSCLC: Non-small cell lung cancer; ECOG: Eastern Cooperative Oncology Group; ChT: Chemotherapy; CRT: Conformal radiotherapy; RT: Radiotherapy; WBRT: Whole-brain radiotherapy.

extension. Using this equation, we calculate the *d* (dose per fraction); and (2) Planned: Option 1: Compensate on a holiday. Option 2: Perform the dose calculation per fraction to compensate for the missed treatment days using the formulas described above, provided that the dose is ≤ 3.5 Gy/fx and the OAR dose tolerance is within the stipulated limits, after adjusting for the relevant biological calculation.

Recommendations: Prioritise patients with squamous cell tumors. Use IMRT whenever possible, especially in locoregionally-advanced cases**.** Conventional fractionation: Keep delays to a minimum. Compensate if the OTT is > 45-50 d and/or the interruption is ≥ 4-5 d. Adjuvant RT: Although there are no published data in this scenario, as a precautionary measure, avoid delays ≥ 5-10 d, especially in patients without signs of poor prognosis or squamous cell tumors. In hyperfractionated schemes, compensation strategies are more complex, which is why treatment on holidays is preferred. However, if the treatment delay is ≥ 10 d, full compensation is not recommended due to the risk of excess toxicity [188]. The number of indications for moderately hypofractionated RT and SBRT has increased substantially during the COVID-19 pandemic. Specific guidelines for these cases have been published[191].

FOLLOW-UP (AFTER SBRT, EARLY STAGE AND LOCALLY ADVANCED)

Approximately 40% of patients with lung cancer will develop a distant recurrence from 3 to 5 years after treatment completion. At 3-years, approximately 30% of patients will develop a locoregional recurrence (potentially-curable)[55]. After SBRT, approximately 12% of patients develop locoregional recurrence at 4 years[36].

The risk for development of a second primary lung cancer after treatment ranges from 1% to 6% per patient per year and this risk does not decrease over time. The mean interval from the first to the second primary tumor ranges from 59 to 62 mo[192]. Early management of these relapses, whether curative or palliative intent, is associated with better survival and QoL, which underscores the importance of close follow-up[193,194]. For the assessment of treatment-related toxicity and recurrence, we recommend the following follow-up measures.

Patients treated with SBRT

Most recurrences occur more than 6 mo after treatment. Based on recommendations from the ESTRO [47], the United Kingdom SBRT consensus statement[195], and updates on high-risk CT features[196] , the following follow-up procedures are recommended.

First year post-treatment: The first clinical follow-up visit (complete medical history and physical examination) should take place within 4-6 wk of treatment completion. The first CT scan should be performed at least 3 mo after treatment. Clinical evaluation, including contrast-enhanced CT, should be performed every 3 mo for at least one year.

Second to third year after treatment: After the first year, follow-up should be performed every 3-6 mo for three years. CT images performed every 3 mo should be compared to previous CTs.

Third to fifth year after treatment: CT imaging should be performed every 6 mo from year three to year five. Low-dose CT should be performed annually from that time if risk factors are present. If the CT scan reveals risk factors[197,198], then a PET scan (III, B) should be ordered. If salvage therapy is feasible, then a biopsy should be performed to confirm the PET findings (III, B). Lung function testing should be performed annually.

CONVENTIONAL FRACTIONATION AND LOCALLY-ADVANCED DISEASE

Based on recommendations from ESMO[59], the Italian Association of Medical Oncology[199], and SEPAR[15], we recommend the following: (1) Unsalvageable patients. Perform clinical evaluations

(complete medical history, physical examination, and blood tests) every 6 mo for two years. A chest CT should be performed at months 12 and 24, with annual follow-up thereafter (III, B); and (2) Salvageable patients. First three years: CT IV contrast every 3-6 mo (III, B). Years four and five: Follow-up every 6 mo; thereafter, annual low-dose CT without contrast. If pathologic findings are detected on CT, perform PET-CT and brain MRI. Obtain histopathologic confirmation of PET findings in accordance with the therapeutic option (III, B). Maintain follow-up for at least 5 years.

General recommendations: The treating physician should actively participate in follow-up (I, C). In patients unlikely to benefit from salvage therapy, the frequency of follow-up should be adapted to the patient's individual needs (V, B). Follow-up with PET-CT or abdominal ultrasound is not recommended (I, C). Smoking cessation[200] (III, A). Behavioral therapy combined with pharmacological intervention (I, A). Influenza and pneumococcal vaccination should be offered if not contraindicated.

RECOMMENDATIONS

Summary of recommendations is provided in Table 10.

CONCLUSION

Radiotherapy is a critical component of multi-modality treatment of NSCLC. This GOECP/SEOR guidelines, can help physicians to improve medical knowledge and find better ways to treat their NSCLC patients. Following the level of evidence this guidelines are summarized in Table 10.

FOOTNOTES

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MINIREVIEWS

Tsunami of immunotherapy reaches mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) is the most common type of malignant mesothelioma. It is a rare tumor linked to asbestos exposure and is associated with a poor prognosis. Until very recently, patients with advanced or unresectable disease had limited treatment options, primarily based on doublet chemotherapy with cisplatin and pemetrexed. In 2020 and 2021, after more than a decade with no major advances or new drugs, two phase III clinical trials published results positioning immunotherapy as a promising option for the first- and second-line treatment of MPM. Immunotherapy has revolutionized the treatment of many cancers and is also showing encouraging results in malignant mesothelioma. Both immune checkpoint inhibition and dual cytotoxic T-lymphocyte–associated antigen 4 and programmed death-ligand 1 pathway blockade resulted in

significantly improved overall survival in randomized phase III trials. In the CheckMate 743 trial, first-line therapy with nivolumab plus ipilimumab outperformed standard chemotherapy, while in the CONFIRM trial, nivolumab outperformed placebo in patients previously treated with chemotherapy. These two trials represent a major milestone in the treatment of MPM and are set to position immunotherapy as a viable alternative for treatment-naïve patients and patients with progressive disease after chemotherapy.

Key Words: Mesothelioma; Malignant pleural mesothelioma; Immunotherapy; Immune checkpoint inhibitors; Cytotoxic T-lymphocyte–associated antigen 4; Programmed cell death protein 1; Nivolumab; Ipilimumab; Immunotherapy combo; CheckMate 743; CONFIRM

Core Tip: Malignant pleural mesothelioma (MPM) is the most common type of malignant mesothelioma and is associated with a poor prognosis. The treatment options for advanced MPM were limited until very recently, when the results from two phase III trials showed improved survival in patients treated with immunotherapy. In the first trial, CheckMate 743, nivolumab plus ipilimumab as first-line therapy achieved better overall survival than standard chemotherapy, while in the second trial, CONFIRM, nivolumab *vs* placebo significantly improved overall survival in patients previously treated with chemotherapy. In this article, we discuss recent advances and highlights in the treatment of MPM.

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INTRODUCTION

Malignant mesothelioma (MM) is a rare tumor, with just 30870 cases diagnosed in 2020. The annual incidence is 0.3 cases per 100000 inhabitants worldwide, but rates vary depending on the region. In more developed areas, such as Europe, the annual incidence of MM is > 1 case per 100000 population [1]. MM arises from the mesothelial cells of serous membranes such as the pleura, peritoneum, pericardium, and tunica vaginalis of the testes. Malignant pleural mesothelioma (MPM) accounts for approximately 80% of all cases and carries a poor prognosis, with an overall 5-year survival rate of just 10%. There is a clear causal link between MM and a history of asbestos exposure, although the latency period between exposure and tumor development is between 20 years and 50 years. MPM mainly affects men (male to female ratio, 3:1) and is considered an occupational disease. The mean age at presentation is 74 years[2]. MPM has three subtypes with distinct histologic, biologic, and prognostic features: The epithelioid subtype, which accounts for 50%-70% of cases; the sarcomatoid subtype, which accounts for 7%-20% of cases and carries the worst prognosis; and the biphasic subtype, which carries a moderate prognosis[3].

The standard treatment for MM up to 2020 was doublet chemotherapy with cisplatin and pemetrexed, and no relevant advances had been made in this area for over a decade. As has occurred in many cancers, the advent of immunotherapy is changing the landscape of MM treatment and has already shown promising results[4].

In this article, we review the history of treatment options for MPM, including attempts to add immunotherapy-based strategies to the existing armamentarium. We then analyze the recent results from two phase III clinical trials set to position immune checkpoint inhibitors as effective first- and second-line treatments for MPM.

HISTORICAL HIGHLIGHTS IN THE TREATMENT OF MESOTHELIOMA IN THE PRE-IMMUNOTHERAPY ERA

Polychemotherapy, with or without antiangiogenic therapy, was the only option for treating MPM until the recent approval of nivolumab plus ipilimumab. The standard first-line treatment, based on the results of a phase III trial of 456 patients published in 2003, is pemetrexed 500 mg/m^2 plus cisplatin 75

mg/m^2 every 21 d. In the trial, this combination significantly outperformed cisplatin alone in terms of overall survival (OS) [12.1 mo *vs* 9.3 mo; hazard ratio (HR) = 0.77; P = 0.02], progression-free survival (PFS) (5.7 mo *vs* 3.9 mo; HR = 0.68; P = 0.001), and response rates (41.3% *vs* 16.7%; P < 0.001). The most common adverse effect was hematologic toxicity (grade 3/4 neutropenia, 27.9%; grade 3/4 leukopenia, 17.7%)[5].

Contrasting with the situation for non-small cell lung cancer, it has not been confirmed that maintenance treatment with antifolates improves survival in patients with MM after four to six cycles of chemotherapy with cisplatin plus pemetrexed[6]. In 2019, the results of a phase II trial of patients who had achieved at least stable disease with cisplatin plus pemetrexed showed no significant differences for PFS [3.4 mo *vs* 3.0 mo; HR = 0.99; 95% confidence interval (CI): 0.51-1.9; P = 0.9733] or OS (11.8 mo *vs* 16.3 mo; HR = 0.86; 95%CI: 0.44-1.71; P = 0.6737) between patients randomized to maintenance treatment with pemetrexed and those randomized to placebo[7]. In the same year, however, another phase II trial showed a survival benefit for maintenance gemcitabine *vs* palliative treatment only (median DFS, 6.2 mo *vs* 3.2 mo; HR = 0.42; 95%CI: 0.28-0.63)[8], but the improvement was not considered important enough for this option to be included in clinical guidelines.

Carboplatin plus pemetrexed can be used in patients unfit for cisplatin, as several phase II trials have shown that it has comparable efficacy to the cisplatin-pemetrexed doublet[9-11].

Attempts to improve survival outcomes in patients treated with standard chemotherapy include the addition of antiangiogenic therapy (bevacizumab or nintedanib). The rationale is that vascular endothelial growth factor (VEGF) is a key mitogen for MM cells[8]. The open-label phase III MAPS trial showed that adding bevacizumab 15 mg/kg to first-line cisplatin plus pemetrexed chemotherapy improved median OS (18.8 mo *vs* 16.1 mo; HR = 0.77; 95%CI: 0.62-0.95; P = 0.0167). It also allowed the use of bevacizumab as maintenance therapy. Patients treated with bevacizumab plus chemotherapy, however, showed higher rates of hypertension (26% *vs* 0%, grade 3/4) and thrombotic events (6% *vs* 1%, grade 3/4)[12]. The addition of bevacizumab to cisplatin and pemetrexed chemotherapy is recommended in clinical guidelines but has not yet received regulatory approval. The phase III LUME-Meso trial found no significant improvements in PFS following the addition of nintedanib, a tyrosine kinase inhibitor, to the combination of cisplatin and pemetrexed. Other studies of second-line vascular endothelial growth factor receptor tyrosine kinase inhibitors used as second-line treatments have also reported no significant benefits, but their findings may have been influenced by the profile of patients studied[13].

Chemotherapy combining cisplatin and gemcitabine showed promising activity against MM in two phase II multicenter trials conducted before the approval of pemetrexed in this setting[14,15]. This combination thus would be the treatment of choice for previously treated patients, unless, of course, they had not received first-line treatment with pemetrexed[16]. Poor results have been reported for other second- and third-line treatments investigated. The only drugs that have shown a slight survival benefit to date are weekly vinorelbine (median PFS, 2.3 mo and median OS, 6.2 mo)[17] and weekly gemcitabine[18]. The use of these drugs is supported by data from small phase II trials, subgroup analyses from first-line studies, and retrospective analyses. Nonetheless, the phase II trial, RAMES, whose results were published in 2020, showed a significant OS benefit for gemcitabine plus ramucirumab *vs* gemcitabine only in previously treated patients (13.8 mo *vs* 7.5 mo; HR = 0.71; 95%CI: 0.59-0.85; P = 0.057), positioning this combination as a promising second-line option[19].

IMMUNOTHERAPY-BASED TREATMENT STRATEGIES FOR MESOTHELIOMA

MM is considered to be an inflamed tumor. High programmed death-ligand 1 (PD-L1) expression is associated with a worse prognosis and increased immune infiltration[20,21]. Immunotherapy is thus an attractive option for this tumor and has attracted increasing attention from researchers in recent years. Numerous types of immunomodulatory treatments have been investigated, including interferon, interleukin 2, tumor necrosis factor-α, granulocyte/macrophage colony-stimulating factor, oncolytic viruses, dendritic cell immunotherapy, and, currently at the forefront of efforts, immune checkpoint inhibitors[4,22]. Currently, most developed ICIs in the treatment of solid tumors are anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1)/PD-L1 monoclonal antibodies (mabs), each of which acts at a different level of activation of immune response. Anti-CTLA-4 mabs promote T cell proliferation and trigger antitumor response acting in the priming of immune response in peripheral lymphoid organs. On the other hand, anti-PD-1/PD-L1 mabs make their action in the tumor restoring the antitumor function of T cells, avoiding to become exhausted T lymphocytes. Attempts to find an effective immunotherapy-based treatment, however, were largely unsuccessful, until the phase III CheckMate 743 and CONFIRM trials, whose results were released in 2020 and 2021.

Tremelimumab, a CTLA-4 inhibitor, was investigated as an option for progressive disease after chemotherapy in two open-label single-arm trials - MESOT-TREM-2008[23] and MESOT-TREM-2012[24] - and a randomized, placebo-controlled, phase IIb trial - DETERMINE[25]. The two single-arm trials evaluated different dosages of tremelimumab, but only MESOT-TREM-2012 met the primary endpoint,

with an objective response rate (ORR) of 52%. The results for the secondary endpoints, OS and PFS, were promising and the drug also showed a favorable safety profile. The larger DETERMINE trial, which compared tremelimumab and placebo in patients who progressed after chemotherapy, did not demonstrate any significant differences in OS, PFS, or ORR.

Anti-PD-1/PD-L1 monotherapy as both a first- and second-line option has also been studied but mostly in phase Ib and II trials. The multicenter phase II DREAM trial evaluated the combination of durvalumab and standard first-line chemotherapy[26]. Its results were encouraging, with a median OS of 6.9 mo, a median PFS of 18.4 mo, an ORR of 48%, and an acceptable safety profile. They have not, however, been validated in comparative study or phase III trial. In a phase Ib trial, avelumab, an anti-PD-L1 drug, showed a good ORR in previously treated patients, with a complete response rate of 2% and a partial response rate of 8%[27]. Nonetheless, although the adverse events reported were to be expected, 8% of patients had an event that resulted in death[27].

The ETOP-PROMISE-Meso-Trial is the only phase III trial conducted in the setting of previously treated MM. It compared pembrolizumab and chemotherapy (gemcitabine or vinorelbine) in patients with MM that had progressed after at least one treatment but found no significant differences for PFS (primary endpoint) or OS[28]. While ORR was significantly higher in the pembrolizumab group (22% *vs* 6%; $P = 0.004$), responses were mostly short lived. Nivolumab, another anti-PD-1 drug, was studied in patients with pretreated MM in two single-arm phase II trials. The results for ORR, disease control rate, and OS were promising and were further investigated in the phase III placebo-controlled CONFIRM trial, whose results were recently published. The results for the two primary endpoints - OS and PFS - were positive, with an OS of 9.2 mo (*vs* 6.6 mo in the placebo group) (HR = 0.72; 95%CI: 0.55-0.94; $P = 0.02$) and a PFS of 3 mo (*vs* 1.8 mo) (HR = 0.6; 95%CI, 0.48-0.77; $P < 0.001$). These results undoubtedly represent a milestone in the management of previously treated mesothelioma, but as the comparator was placebo, it remains unclear whether nivolumab is truly a better option than chemotherapy or gemcitabine plus ramucirumab in this setting[29-31].

Combination immunotherapy with the immune checkpoint inhibitors CTLA-4 (ipilimumab) and PD-1 (nivolumab) showed promising results in two phase II trials - MAPS2[32] and INITIATE[33], leading to further investigation in the phase III CheckMate 743 trial. Combined tremelimumab and durvalumab therapy also showed activity against mesothelioma and an acceptable safety profile in the phase II NIBIT-MESO-1 trial[34] (Table 1).

NIVOLUMAB AS NEW SALVAGE THERAPY OPTION

Stand-Up-To-Cancer Cancer Research United Kingdom CONFIRM trial is a double blind phase 3 randomized study evaluating nivolumab (3 mg/kg/q2w) *vs* placebo with 2:1 ratio in patients with previously treated unresectable MM (pleural or peritoneal) until disease progression or a maximum of 12 mo. Co-primary objectives were investigator-assessed PFS and OS. 221 patients were randomized to nivolumab and 111 to placebo. Preliminary data were presented in World Conference of Lung Cancer 2020, and although OS was not mature, longer survival was achieved with nivolumab (9.2 mo *vs* 6.6 mo; HR = 0.72; 95%CI: 0.55-0.94; $P = 0002$), and PFS was also better for nivolumab arm (3.0 mo *vs* 1.8 mo; HR = 0.62; 95%CI: 0.49-0.78; $P < 0.001$). In the subgroup analysis of OS by histologic subtype, significant benefit was found in the epithelioid subtype but not significant benefit in non-epithelioid one. Grade 3-4 treatment-related adverse effects were reported in 19% on nivolumab *vs* 6.3% on placebo arm[29] (Table 2).

NIVOLUMAB AND IPILIMUMAB AS NEW FRONTLINE OPTION

The pivotal open-label, multicenter CheckMate 743 trial represented a major step forward in the treatment of mesothelioma, as it was the first phase III trial to publish results on the use of immunotherapy as first-line therapy. It compared nivolumab plus ipilimumab against standard chemotherapy in previously untreated patients with unresectable MPM[35]. In total, 605 patients were randomly assigned (1:1) to receive nivolumab 3 mg/kg every 2 wk plus ipilimumab 1 mg/kg every 6 wk for 2 years or standard chemotherapy with six cycles of cisplatin 75 mg/m^2 or carboplatin with an area under the curve value of 5 plus pemetrexed 500 mg/m^2. Patients in both arms continued to receive treatment until disease progression or unacceptable toxicity; the maximum time established for the experimental arm was 24 mo. The characteristics of the two groups were comparable; 77% of the participants were men and 75% had an epithelioid subtype. The results of the first prespecified interim analysis, at 29.7 mo, showed higher median OS (the primary endpoint) in the immunotherapy group (18.1 mo *vs* 14.1 mo; HR: 0.74; $P = 0.002$). OS in the immunotherapy *vs* chemotherapy group was 68% *vs* 58% at 1 year and 41% *vs* 27% at 2 years. Median duration of response was 11.0 *vs* 6.7 mo. All the subgroup analyses showed trends that favored nivolumab plus ipilimumab over chemotherapy. On stratifying the results by MPM subtype and PD-L1 expression, the survival benefit was higher for patients in the immunotherapy group, with a median OS of 18.1 mo *vs* 8.8 mo for patients with non-epithelioid MPM and 18

Table 1 Main pre-phase III clinical trials of immunotherapy-based strategies for the treatment of mesothelioma

Clinical trial (Phase): Drug analyzed	Setting	Primary endpoint
MESOT-TREM 2008 (Phase II): Tremelimumab 15 mg/kg every 90 d[23]	Salvage setting	ORR: 6.9%
MESOT-TREM 2012 (Phase II): Tremelimumab 10 mg/kg every 4 wk[24]	Salvage setting	ORR: 13.7%
DETERMINE (Phase IIb): Tremelimumab 10 mg/kg every 4 wk *vs* Placebo[25]	Salvage setting	OS: 7.7 mo *vs* 7.3 mo (HR = 0.92; P = 0.41)
DREAM (Phase II): Durvalumab 1125 mg + Cisplatin 75 mg/m^2 or Carboplatin AUC 5 + Pemexetrad 500 mg/m^2 every 3 wk[26]	Front-line setting	6-mo PFS: 57%
JAVELIN Solid (Phase Ib): Avelumab 10 mg/kg every 2 wk[27]	Salvage setting	ORR: 9%

AEs: Adverse events; AUC 5: Area under the curve value of 5; HR: Hazard ratio; ORR: Overall response rate; OS: Overall survival; PFS: Progression free survival.

Table 2 Recently published practice changing phase 3 studies in Malignant Pleural Mesothelioma

Clinical trial (Phase)	Population	Treatment arms	mOS		mPFS		AEs G3
CheckMate 743 (Phase III)[35]	Untreated MPM	Nivolumab 3 mg/kg every 2 wk + ipilimumab 1 mg/kg every 6 wk	18.1 mo	HR: 0.74, P = 0.002	6.8 mo	HR: 1.00	30%
		Cisplatin + pemetrexed	14.1 mo		7.6 mo		32%
CONFIRM (Phase III)[29]	Relapsed MPM	Nivolumab 3 mg/kg every 2 wk	9.2 mo	HR: 0.72, P = 0.002	3 mo	HR: 0.61; P < 0.001	19%
		Placebo	6.6 mo		1.8 mo		6.3%

MPM: Malignant pleural mesothelioma; MM: Malignant mesothelioma (pleural or peritoneal); AEs: Adverse events; mOS: Median overall survival; mPFS: Median progression free survival; G: Grade; HR: Hazard ratio.

mo *vs* 13.3 mo for those with PD-L1 expression > 1%. In the nivolumab plus ipilimumab group, the survival outcomes were similar across the different subtypes and were independent of PD-L1 expression. The incidence of grade 3-4 adverse events was similar in both groups: 30.3% in the immunotherapy group and 32% in the chemotherapy group. Adverse events led to treatment discontinuation in 15% of the patients treated with immunotherapy and 7.4% of those treated with chemotherapy. The most common adverse effect of any grade in immunotherapy arm was diarrhea (21%), and nausea in the chemotherapy group (37%). Most commonly reported any-grade immunotherapy-related adverse effects were skin (36%), gastrointestinal (22%), endocrine (17.3%), hepatic (12%), hypersensitivity/infusion reaction (12%), pulmonary (6.7%), and renal (5%).

The safety profile observed for the combined use of nivolumab and ipilimumab was comparable to that reported elsewhere[36]. Based on these results, the United States Food and Drug Administration approved nivolumab plus ipilimumab as a first-line treatment for MPM in October 2020 (Table 3).

IMMUNOTHERAPY BIOMARKERS IN MESOTHELIOMA

Numerous biomarkers of response to immunotherapy have been investigated in recent years, but the results have varied widely, precluding any definitive conclusions. In this section, we review the most promising results reported to date.

Approximately 38%-75% of MMs express PD-1/PD-L1, and this variability is partly due to the immune microenvironment that characterizes this tumor. PD-1/PD-L1 expression has been linked to significantly worse OS, suggesting that it might be a marker of poor prognosis, especially at values > 30%[22,37]. PD-1/PD-L1 Levels are higher in sarcomatoid tumors, which have a worse prognosis than epithelioid subtypes. Nonetheless, contradictory findings have been reported for the relationship between PD-1/PD-L1 expression and response to different forms of immunotherapy. The CONFIRM trial performed subgroup analyses according to PD-L1 expression but found no significant differences supporting the predictive value of this marker. In the PD-L1 ≥ 1% subgroup, patients treated with nivolumab had a median OS of 8 mo *vs* 8.7 mo for those treated with placebo (HR = 0.95; 95%CI: 0.51-1.76; P = 0.864), while in the < 1% PD-LI group, they had a median OS of 9 mo *vs* 6.4 mo for those in the placebo group (HR = 0.74; 95%CI: 0.51-1.08; P = 0.115)[29]. The predictive value of PD-L1 expression was a secondary endpoint in the CheckMate 743 trial, and the data showed a significant OS benefit for immunotherapy *vs* chemotherapy in patients with PD-L1 ≥ 1% (HR = 0.69; 95% CI 0.55-0.87). By

Table 3 Comparison of safety and efficacy of frontline Nivolumab + Ipilimumab *vs* chemotherapy in malignant pleural mesothelioma

Clinical trial	Phase	Treatment arm	mOS		mPFS		ORR	AEs G3
CheckMate-743 [35]	III (open-label)	Nivolumab 3 mg/kg every 2 wk + Ipilimumab 1 mg/kg every 6 wk	18.1 mo	HR: 0.74, P = 0.002	6.8 mo	HR: 1.00	32%	30%
		Cisplatin + Pemetrexed	14.1 mo		7.6 mo		8%	32%
EMPHACIS[5]	III (single blind)	Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2	12.1 mo	HR: 0.77, P = 0.002	5.7 mo	HR: 0.68, P = 0.001	41.3% *vs* 16.7% (P < 0.001)	
		Cisplatin 75 mg/m^2	9.3 mo		3.9 mo		16.7%	
MAPS[12]	III (open-label)	Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2 with 15 mg/kg Bevacizumab in	18.8 mo	HR: 0.77, P = 0.0167	9.2 mo	HR: 0.61, P < 0.0001	NR	71%
		Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2	16.1 mo		7.3 mo			62%

AEs: Adverse events; mOS: Median overall survival; mPFS: Median progression free survival; ORR: Overall response rate; G: Grade; HR: Hazard ratio.

contrast, OS rates were similar in the two groups with < 1% PD-L1 expression (HR = 0.94; 95%CI: 0.62-1.40)[35].

The V-domain Ig-containing suppressor of T-cell activation (*VISTA*) gene has also shown promise as an immunotherapy biomarker in MM. It has been detected in > 85% of patients with MPM, and in two-thirds of cases, it was present in > 50% of cells. Unlike PD-1/PD-L1, it was primarily detected in epithelioid tumors and was associated with significantly improved OS, especially at an expression level > 40%[38]. The *VISTA* gene is thus a promising immunotherapy target and is currently being analyzed in prospective studies.

Tumor mutational burden (TMB) is another potential target, but expression levels vary considerably according to tumor type and are low in mesothelioma. Nonetheless, a recent study of pembrolizumab in the treatment of advanced solid tumors, including MM, showed that high tumor mutational burden expression (> 10 mutations) could identify patients with a better response to pembrolizumab monotherapy[39].

FUTURE PERSPECTIVES IN MESOTHELIOMA

Further advances in immunotherapy for MM in the near future will probably involve combinations of strategies with proven efficacy drugs and continued investigation of new targets and approaches, such as immune checkpoint inhibition combined with chemotherapy and/or antiangiogenic drugs (BEAT-Meso, PrE0506/DREAM3R, PEMBIB)[40]; targeted therapy with AXL inhibitors[41]; other checkpoint inhibitors such as VISTA (NCT02812875), BH73, lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin and mucin-domain containing-3 (TIM-3); radiotherapy; vaccine-based strategies (MESOVAX); and mesothelin-targeted and metabolism-based therapies.

Other immunomodulatory strategies under investigation are vaccination, T-cell transduction pathway therapies, dendritic cell immunotherapy, adoptive cell therapy (chimeric antigen receptor T-cell) (MesoCancerVa, DENIM)[42], and oncolytic viruses.

Vaccination with Wilms Tumor antigen (WT1) combined with chemotherapy (MESODEC, NCT02649829) and autologous tumor-infiltrating lymphocytes plus interleukin-2 is also being investigated.

Apart from exploring different treatment combinations in advanced MM, researchers should also analyze the benefits of immunotherapy in earlier-stage disease and its perioperative use with multimodal treatment approaches.

CONCLUSION

The treatment options for patients with MPM were very limited until recently and had remained largely unchanged for more than a decade. Recent years, however, have witnessed dramatic improvements in our understanding of this disease and a surge in new research and treatments. From a practical perspective, the main breakthrough has been made in the field of immunotherapy, with two phase III trials set to mark a paradigm shift positioning immune checkpoint inhibitors as first- and second-line

treatment options for MPM. CheckMate 743 is the first phase III trial in over a decade to show a survival benefit for a new treatment—combined CTLA-4 and PD-L1 inhibition–over standard chemotherapy in MPM. The data showed that nivolumab plus ipilimumab significantly improved OS and, as was to be expected based on data from other settings, had an acceptable safety profile. This new strategy is set to become a priority alternative for the frontline treatment of unresectable MPM. The results of the CONFIRM trial signaled another major milestone. In this double-blind randomized phase III trial, intravenous nivolumab 240 mg every 2 wk achieved a significant improvement in OS compared with placebo in patients with previously treated MPM, positioning it as a very likely alternative for the second-line treatment of patients with progressive disease after chemotherapy. Efforts to identify reliable biomarkers to help select the best candidates for immunotherapy must be intensified in the coming years. The evolving landscape will also drive further research into treatment combinations that will hopefully continue to improve OS in this population.

FOOTNOTES

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MINIREVIEWS

New horizons for uncommon mutations in non-small cell lung cancer: *BRAF*, *KRAS*, *RET*, *MET*, *NTRK*, *HER2*

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Abstract

The 2004 discovery of *EGFR* mutations, followed by *ALK* rearrangements, ushered in a targeted therapy era for advanced non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors targeting gene alterations have substantially improved survival and quality of life for patients with NSCLC. In the last decade, rearrangements of the ROS1 oncogene have been incorporated into healthcare

practice that are applicable to another small subgroup of patients who benefit from similar targeted strategies. Recent genome studies of lung adenocarcinoma have identified other possible therapeutic targets, including *RET*, *NTRK* fusions, *c-MET* alterations, and activating mutations in *KRAS*, *BRAF*, and *HER2,* all with frequencies greater than 1%. Lung cancers harbouring these genome changes can potentially be treated with agents approved for other indications or under clinical development. This review updates the therapeutic arsenal that especially targets those genes.

Key Words: *BRAF*; *NTRK*; *KRAS*; *MET*; *RET*; *HER2*; Non-small cell lung cancer; Targeted therapy; Uncommon mutations

Core Tip: Compared to other types of cancer, non-small cell lung cancer (NSCLC) is highly genetically altered. Outside of *EGFR, ALK,* and *ROS1*, reflecting 15%-20% of clinical practice, other molecular alterations with important recent advances in their therapeutic arsenal and already in phase II/III trials are *BRAF, KRAS, RET, MET, NTRK,* and *HER2*. The goal is to achieve, compared to conventional treatments such as chemotherapy, better symptom control, better response rates, and improved progression-free survival and overall survival in patients with NSCLC.

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INTRODUCTION

Approximately 60% of lung adenocarcinomas harbour molecular alterations in driver oncogenes, with incidence, which varies according to ethnic origin and alteration, as follows: epidermal growth factor receptor (EGFR) mutation, 15%-20%[1]; anaplastic lymphoma kinase (*ALK*) rearrangement, 5%-7%[2]; and c-ros 1 (*ROS1*) rearrangement, approximately 1%[3]. There has been an impressive improvement in survival in response to tyrosine kinase inhibitors (TKIs), which also have a better toxicity profile compared to standard chemotherapy.

The consequent improvement in molecular understanding of non-small cell lung carcinoma (NSCLC) has allowed increasingly exhaustive molecular classification as well as identification of a subset of patients susceptible to specifically targeted therapy. The outcome of massive gene-sequencing platforms with higher throughput than gene-to-gene determinations is that patients can be offered more treatments that more specifically impact on their quality of life and survival. The current recommendation is to carry out a comprehensive molecular analysis using multiplex platforms – next-generation sequencing (NGS) – if available, considering advantages in terms of coverage, time, and a favorable economic profile[4]. NGS is capable of detecting less common or difficult-to-identify oncogenes, such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations (30%-35%), V-raf murine sarcoma viral oncogene homolog B (*BRAF*) mutations (4%-5%), mesenchymal-epithelial transition factor (*c-MET*) alterations, exon 14 insertions and/or amplifications (5%-9%), rearrangements during transfection (*RET*) (1%-2%), human epidermal growth factor receptor 2 (*HER2*) mutations (2%), and neurotrophic receptor tyrosine kinase (*NTRK*) fusions (< 1%)[5]. Identifying these alterations is increasingly important, as new specific drugs in clinical development show promise in terms of modifying the natural history of NSCLC. We focus on direct inhibitors of pathways and their practice-changing results.

BRAF

Present in 2%-3% of NSCLC cases, the *BRAF* mutation is mostly encountered in patients diagnosed with adenocarcinoma[6]. The most common variant is *V600E*, found in 50%-60% of patients with *BRAF*-mutated (*BRAF*m) NSCLC. Not clear is the prognostic value of *BRAF-V600E* compared with non-*V600E* or with the rest of patients with NSCLC[7].

The drugs used to date for this molecular alteration are the same TKIs that have proven to be effective in treating melanoma, a tumour with high *BRAF*m frequency.

Table 1 summarizes the efficacy of the main drugs used to date. The best results have been reported for dabrafenib combined with trametinib, which attempt to block the MAPK pathway at two different sites (*BRAF* and *MEK*), thus overcoming possible tumour resistance to TKIs. The BRF113928 study in patients who received 2-4 Lines of therapy reported an objective response rate (ORR) of 63.2%, and a first-line ORR of 64%[8-12].

However, the absence of comparative data for first and subsequent lines of therapy as currently used for this group of patients means that it is not possible to confirm significant clinical benefit and efficacy over alternative therapies. Dabrafenib and trametinib may therefore be of use for patients for whom standard therapies are not possible or have failed.

Phase II studies are also currently recruiting for the encorafenib + binimetinib (NCT04526782) and cobimetinib + vemurafenib (NCT03178552) combinations.

KRAS

KRAS is the most common mutation in NSCLC, present in up to 30% of adenocarcinomas[13]. In 80% of cases it is located at codon 12, and the most frequent mutation is *KRAS-G12C*, reflected in 13% of all lung adenocarcinomas. It is considered practically exclusive in relation to any other clinical practice drivers, although co-occurrences have been found with alterations in *TP53*, cyclin dependent kinase inhibitor 2A/B (*CDKN2A/B*), *STK11*, and *KEAP1 (*Kelch Like ECH Associated Protein 1)[14].

While *KRAS* has been a therapeutic target for decades, no direct therapeutic option has been established. In recent years, new direct inhibitors of *KRAS-G12C* have emerged. Phase II trial results for sotorasib, an irreversible and highly selective *KRAS-G12C* inhibitor, have positioned it as a major lung cancer milestone for the *KRAS* mutation[15,16]; for 126 included patients, the ORR was 37.1%, there were three complete responses (CRs) and 43 partial responses (PRs), and the disease control rate was 80.6%, for a median progression-free survival (PFS) of 6.8 mo and a good tolerability profile. Based on those data, an application for marketing authorization has been submitted to the FDA and EMA.

In two presentations at the 32nd Symposium on Cancer Therapeutics and Molecular Targets EORTC-NCI-AACR[17,18], investigators from the KRYSTAL-1 phase I and II clinical trial reported that adagrasib clinical activity has been demonstrated in previously treated patients with NSCLC and the *KRAS-G12C* mutation. Promising preliminary data for this drug are to be further evaluated in trials, along with combinations, including with pembrolizumab in the KRYSTAL-7 phase 2 trial (NCT04613596) of untreated patients[19].

RET

RET gene fusions and activating point mutations are primary oncogenic drivers that are usually mutually exclusive with other oncogenic driver alterations[20]. Among the various oncogene drivers in NSCLC, the *RET* gene is involved in various chromosomal rearrangements, found in 1%-2% of all NSCLC patients[21].

Most of the drugs active against *RET* are TKIs. Multikinase inhibitors initially studied in phase II clinical trials include cabozantinib, nintedanib, lenvatinib, vandetanib, and sorafenib, each with a different ORR (Table 2)[22-25].

Selpercatinib (LOXO-292) is a highly selective, potent, central nervous system (CNS)-active, small-molecule *RET* kinase inhibitor. Selpercatinib has nanomolar potency against wild-type *RET* and other *RET* alterations, including the *KIF5B-RET* fusion and *V804M* gatekeeper mutation, in both enzyme and cellular assays, with minimal activity against other kinase and non-kinase targets[26].

In the LIBRETTO-001 phase I/II trial, selpercatinib treatment demonstrated clinically meaningful responses and sustained antitumour activity, for a manageable toxicity profile, in both heavily pre-treated and treatment-naive patients, and including patients with brain metastases and with *RET* fusion-positive NSCLC (intracranial CNS (n = 10/11): ORR 91%). In May 2020, selpercatinib was approved by the FDA under the Accelerated Approval programme for the treatment of *RET*-altered cancers (NSCLC and thyroid cancer)[27].

Pralsetinib (BLU-667) is a novel small-molecule *RET* inhibitor, designed for high potency and selectivity against oncogenic *RET* alterations, including the most frequent *RET* rearrangements (*e.g.*, *KIF5B–RET* and *CCDC6–RET*). The global phase I/II ARROW study has demonstrated broad and durable antitumour activity for pralsetinib in a variety of advanced *RET*-altered solid tumours, including *RET* fusion+ NSCLC. For 354 patients with advanced solid tumours who received pralsetinib as first-line treatment, the ORR was 73%, for a 12% CR rate (n = 26). Treatment-related adverse events were most frequently grade 1-2[28]. Table 2 summarizes the activity of the different TKIs against *RET*.

Table 1 Phase II trials with BRAF inhibitors

Drug	*n*	ORR (%)	PFS (mo)	OS (mo)
Vemurafenib BRAF V600E[8]	62	37.1	6.51	15.38
Vemurafenib V600E[9]	101	0	5.2	10
Vemurafenib non-V600E[9]	17	44.9	NR	NR
Dabrafenib in 2nd line or beyond[10]	78	33.3	5.5	12.7
Dabrafenib + trametinib in 2nd line or beyond[11]	57	63.2	10.2	18.2
Dabrafenib + trametinib en 1st line[12]	36	64	10.9	24.6

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

Table 2 Phase II trials with multikinase RET inhibitors

Drug	*n*	ORR	PFS	OS
Cabozantinib[22]	25	28%	5.5 mo	9.9 mo
Vandetanib[23]	18	18%	4.5 mo	11.6 mo
Lenvatinib[24]	25	16%	7.3 mo	NR
Sorafenib[25]	3	0	NR	NR
Selpercatinib[26]	105	64% in platinum chemotherapy pretreated 85% in platinum chemotherapy naïve	90% in response at 6 mo	NR
Pralsetinib[27]	106	61% in platinum chemotherapy pretreated 73% in platinum chemotherapy naïve	NR	NR

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

RXDX-105 differs from the other multi-targeted TKIs because it has *RET* activity but limited activity against the vascular endothelial growth factor (*VEGF*) receptors. In *RET* TKI-naive patients, the drug showed modest activity. Subset analysis revealed that the ORR varied by fusion partner. ORRs were 0% (0/20) in the *RET-KIF5B* rearrangement subset (the most common rearrangement) and 67% (6/9) in the *RET*-non-*KIF5B* rearrangement subset[29].

MET

c-MET is an oncogene that encodes a tyrosine kinase receptor whose ligand is hepatocyte growth factor (*HGF*). Alterations in *c-MET* (mutation, amplification, or overexpression) cause abnormal receptor activity that is associated with rapid tumour growth, greater tumour aggressiveness, and resistance to cancer treatments[30].

c-MET amplification is present in 1%-6% of patients with NSCLC. Skipping mutation of exon 14 occurs in 3%-4% of cases, most frequently for non-squamous and sarcomatoid histologies (20%-30%). This alteration occurs most frequently in older patients and in smokers.

Selective and non-selective *c-MET* inhibitors (Tables 3 and 4) are currently available that can impact on survival in patients with NSCLC. The first drug to demonstrate efficacy with this tumour subtype was crizotinib: In the PROFILE 1001 study, the ORR was 32% and PFS was 7.3 mo[31].

Capmatinib is another drug that has been shown to be active: in the GEOMETRY MONO-1 study, the ORR was 41% and PFS was 5.4 mo in previously treated patients; in first-line patients, the ORR was 68% and PFS was 12.4 mo, while ORR was 54% for intracranial activity[32]. In the VISION study, tepotinib achieved an ORR greater than 40%, irrespective of the therapy line, PFS of 8.5 mo, and an ORR of 55% for intracranial activity[33]. Regarding *MET* amplification, TKIs have only significantly benefited tumours with a high level of amplification (*MET/CEP7* > 5), for an ORR of 40% with crizotinib and of 47% with capmatinib.

Amplification, which may appear de novo or as a mechanism of resistance to the targeted treatment of *EGFR* tumours, is present in 4% of cases of progression to first/second generation inhibitors, and in 15% of cases of progression to osimertinib. Being explored, therefore, is the combination of *EGFR*

Table 3 Mesenchymal-epithelial transition factor inhibitors

Drug	MET-specific	Type	Other targets	IC50 (nmol/L)
Crizotinib	No	Ia	ALK, ROS1	22.5
Capmatinib	Yes	Ib	--	0.6
Tepotinib	Yes	Ib	--	3
Salovitinib	Yes	Ib	--	2.1
Bozitinib	Yes	I	--	0.51
Cabozantinib	No	II	RET, ROS1, VEGFR2, KIT	7.8
Merestinib	No	II	TIE-1, AXL, ROS1, DDR1/2, FLT3, MERTK, RON	8.1
Glesatinib	No	II	MET, VEGFR, RON, TIE-2	21.1

IC50: Half maximal inhibitory concentration; MET: Mesenchymal-epithelial transition factor.

Table 4 Clinical trials of mesenchymal-epithelial transition factor inhibitors

Drug	Clinical trial	Phase	Treatment	Objective	Status
Glesatinib	NCT02954991	2	Glesatinib + Nivolumab	ORR	Active, not recruiting
Multi-TKI					
Glesatinib	NCT02544633	2	Glesatinib	ORR	Completed
Multi-TKI					
Merestinib	NCT02920996	2	Merestinib	ORR	Active, not recruiting
Multi-TKI					
Savolitinib	NCT02897479	2	Savolitinib	ORR	Active, not recruiting
Selective-TKI					
Telisotuzumab (ABBV 399)	NCT03574753	2	ABBV-399	ORR	Completed
MET-mab					
JNJ-61186372	NCT02609776	1	JNJ-61186372	ORR, security	Recruiting
EGFR and MET mab					

TKI: Tyrosine kinase inhibitor; mab: Monoclonal antibody; ORR: Overall response rate; MET: Mesenchymal-epithelial transition factor; EGFR: Epidermal growth factor receptor.

inhibitors and *MET* inhibitors.

The TATTON study explored osimertinib combined with savolitinib in patients with NSCLC and mutated *EGFR*. In the group that received initial treatment with a first/second generation inhibitor, the ORR was 52%, while in the group that received osimertinib, the ORR was 25%, for an acceptable toxicity profile[34].

As for immunotherapy, despite the fact that the tumours may present with elevated *PD-L1* expression, the benefit reported for retrospective studies by a French group was limited, at an ORR of 16% and PFS of 3.4 mo[35].

NTRK

The tropomyosin receptor kinase (*TRK*) family consists of three tyrosine kinase receptors – *TRKA, TRKB,* and *TRKC* isoforms, encoded by the *NTRK1, NTRK2,* and *NTRK3* genes, respectively – that are mainly expressed in the nervous system. Their fusions involve some 80 associated genes and they are known oncogenic drivers[35-38]. The incidence of *NTRK* fusions in NSCLC is estimated to be 0.1%-0.2%, affecting a population that is unselected in terms of sex, age, or smoking[37].

Currently, two first-generation TKIs targeting *NTRK* fusions have been approved by the FDA and the EMA: entrectinib (multikinase *ALK, ROS1,* and pan-*TRK* inhibitor) and larotrectinib (selective pan-*TRK* inhibitor). Both have demonstrated great efficacy (irrespective of histology or fusion gene) and intracranial activity, as well as good toxicity profiles[38-41].

Larotrectinib efficacy and safety in patients with solid tumours and *NTRK* fusions have been evaluated in two registrational phase I/II studies (NCT02122913 and NCT02576431). By July 2020, 20 patients with TRK fusion-positive lung cancer had been treated. Joint analysis of those studies, yielded an ORR of 73% and a CR rate of 7% for patients with lung cancer. The median PFS and OS in lung cancer patients was 35.4 and 40.7 mo. Among patients with baseline central nervous system metastases, the ORR was 63%. Reported adverse events were mostly grade 1-2[38].

Entrectinib was evaluated in the phase I ALKA-372-001 trial, phase I STARTRK-1 trial and phase II STARTRK-2 basket trial. For the 10 patients with NSCLC, the ORR was 70%, the CR rate was 10%, and PFS was 14.9 mo. Entrectinib showed a good toxicity profile; most adverse events were grade 1 or 2 and reversible, *e.g.*, dysgeusia, constipation, fatigue, diarrhoea, oedema, and dizziness[39].

Selitrectinib (LOXO 195), repotrectinib (TPX-0005), and taletrectinib (DS-6051b/AB-106) are second-generation drugs capable of inhibiting on-target resistance of *NTRK*[37,40]. They are currently being evaluated in phase I/II clinical trials in patients with *NTRK*-positive tumours who have progressed to first-generation inhibitors (NCT03215511, EudraCT 2017-004246-20, NCT04094610, TRIDENT-1: NCT03093116, NCT02279433).

HER2

HER2 is a cell growth promoting protein, a member of the *ERBB* family of tyrosine kinase receptors expressed on the surface of many types of tumours.

Overexpression, which occurs in 2%-20% of cases depending on the immunohistochemistry (IHC) level (IHC2+/3+), is associated with a poor prognosis. *HER2* amplification occurs, especially in adenocarcinomas, in around 3% of cases without prior treatment and in approximately 10% of cases of *EGFR* resistance to TKIs[42].

HER2 mutations *(HER2*m) – usually consisting of insertions in exon 20, especially in codon 776 – appear mainly in women, in adenocarcinoma cases, and in the Asian population, and never in smokers. The insertions cause constitutive activation of the receptor, making it sensitive to dual TKI action against *EGFR* and *HER2*, but not exclusively to *EGFR* inhibition[43].

The therapies commonly used to target *HER2* in breast cancer have not had the same results for NSCLC. The emergence of new TKIs and conjugated antibodies have given a new boost to therapies for this molecular alteration in NSCLC (Table 5). Reported for the largest retrospective EUHER2 study, which included patients with *HER2* exon 20 insertions, was an ORR of 7.4% for treatment with the TKIs afatinib, lapatinib, and neratinib; for the trastuzumab antibody and the trastuzumab emtansine (T-DM1) antibody-drug conjugate, the ORR was a more effective 50.9%, but that treatment was in most cases combined with chemotherapy[44,45].

Two phase II studies, of neratinib combined with trastuzumab in *HER2*m patients in first or successive therapy lines (NCT01953926) and of neratinib with temsirolimus (NCT01827267), have reported ORRs of 17% and 19%, respectively[46]. Zhou *et al*[47] explored the efficacy of pyrotinib in monotherapy, reporting an ORR of 30%, median PFS of 6.9 mo, and overall survival (OS) of 14.4 mo; the main toxicity, as with other *HER2*-targeting TKIs such as neratinib and lapatinib, was diarrhoea. In the phase II ZENITH20 trial of poziotinib, another pan-*HER* TKI, for the *HER2*m treatment the ORR was 28%, PFS was 5.5 mo, and the toxicity profile was similar to that for pyrotinib[48].

In addition to the *HER2* TKIs, also being evaluated in this setting are antibody-drug conjugates such as T-DM1 and trastuzumab deruxtecan (DS-8201, T-Dxd). Peters *et al*[49]. explored responses to TDM-1 in 49 patients with IHC2+/3+ overexpression, reporting no response for the IHC2+ cohort and 4 PRs for the IHC3+ cohort (20%). Better data is available for trastuzumab deruxtecan. For 42 patients with *HER2* m in the DESTINY-Lung01 cohort, the ORR was 62%, PFS was 14 mo; median OS was not achieved, while OS was 24.5% in the IHC2+/3+ overexpression cohorts[50].

To confirm the PFS benefit, a phase III trial of pyrotinib *vs* docetaxel called PYRAMID-1 (NCT04447118) is ongoing.

CONCLUSION

Compared to traditional chemotherapy, the improved TKI targeting of *EGFR* mutations and *ALK/ROS1* translocations has led to significant efficacy and quality of life improvements in the management of patients with NSCLC. While this subgroup of patients inevitably develops resistance to TKIs, this can be overcome by developing new next-generation TKIs or drugs aimed at overcoming resistance from the outset or from the time of discovery[51,52].

Table 5 Phase II trials with HER2 inhibitors

Drug	Molecular alteration	*n*	ORR%	PFS (mo)	OS (mo)
Dacomitinib[44]	HER2 mutant	26	12	NR	NR
	HER2-amplified	4	0	NR	NR
Neratinib + Trastuzumab[46]	HER2 mutant	52	17	4	10.2
Neratinib + Temsirolimus[46]	HER2 mutant	43	19	4	15.1
Pyrotinib[47]	HER2 mutant	60	30	6.9	14.4
Poziotinib[48]	HER2 mutant	90	28	5.5	NR
Trastuzumab emtansine[49]	IHC 2+	29	0	2.6	12.2
	IHC 3+	20	20	2.7	15.3
Trastuzumab deruxtecan[49]	HER-2 mutant	42	61.9	NR	NR
Trastuzumab deruxtecan[49]	IHC 2+	39	25.6	5.4	11.3
	IHC 3+	10	20		

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

These developments may also be transferable to the treatment of patients with other molecular alterations of *BRAF, KRAS, RET, MET, NTRK* and *HER2*. As can be seen above, a growing number of drugs and combinations are becoming available that target these alterations, often producing a significant improvement in response and survival rates.

Given the many common and rare molecular alterations in NSCLC, full-panel multigene NGS is recommended rather than gene-by-gene sequencing, as not only is it more cost-effective, it allows patients with a target to be easily identified and treated, whether with an approved drug or in a clinical trial of a promising drug[53-55].

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Is there utility for fluorine-18-fluorodeoxyglucose positron-emission tomography scan before surgery in breast cancer? A 15-year overall survival analysis

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Abstract

BACKGROUND

The prognostic value of preoperative fluorine-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) scan for determining overall survival (OS) in breast cancer (BC) patients is controversial.

AIM

To evaluate the OS predictive value of preoperative PET positivity after 15 years.

METHODS

We performed a retrospective search of the Universitair Ziekenhuis Brussel patient database for nonmetastatic patients who underwent preoperative PET between 2002-2008. PET positivity was determined by anatomical region of interest (AROI) findings for breast and axillary, sternal, and distant sites. The prognostic role of PET was examined as a qualitative binary factor (positive *vs* negative status) and as a continuous variable [maximum standard uptake value (SUVmax)] in multivariate survival analyses using Cox proportional hazards models. Among the 104 identified patients who received PET, 36 were further analyzed for the SUVmax in the AROI.

RESULTS

Poor OS within the 15-year study period was predicted by PET-positive status for axillary (P = 0.033), sternal (P = 0.033), and combined PET-axillary/sternal (P = 0.008) nodes. Poor disease-free survival was associated with PET-positive axillary status (P = 0.040) and combined axillary/sternal status (P = 0.023). Cox models confirmed the long-term prognostic value of combined PET-axillary/sternal status [hazard ratio (HR): 3.08, 95% confidence interval: 1.42-6.69]. SUVmax of ipsilateral breast and axilla as continuous covariates were significant predictors of long-term OS with HRs of 1.25 (P = 0.048) and 1.54 (P = 0.029), corresponding to relative increase in the risk of death of 25% and 54% per SUVmax unit, respectively. In addition, the ratio of the ipsilateral axillary SUVmax over the contralateral axillary SUVmax was the most significant OS predictor (P = 0.027), with 1.94 HR, indicating a two-fold relative increase of mortality risk.

CONCLUSION

Preoperative PET is valuable for prediction of long-term survival. Ipsilateral axillary SUVmax ratio over the uninvolved side represents a new prognostic finding that warrants further investigation.

Key Words: Restricted mean survival time; Long-term prognosis; Overall survival; Preoperative workup; Breast surgery; Positron-emission tomography scan

Core Tip: In our study population of nonmetastatic breast cancer patients, preoperative fluorine-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) scan provided valuable overall survival prognostic information. This retrospective study included the longest (15-year) follow-up observation period to date in a series of these patients. Data from anatomical regions of interest and statistical analyses determined that the ipsilateral axillary maximum standard uptake value (SUVmax) with reference to the contralateral uninvolved axilla was the strongest predictor of survival.

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INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer in the female population worldwide, as well as the most common cause of cancer deaths among women[1]. For staging and disease assessment, current guidelines acknowledge the use of fluorine-18-fluorodeoxyglucose (National Library of Medicine Medical Subject Headings [MeSH] entry term: ^{18}F-FDG) positron-emission tomography [MeSH entry term: positron-emission tomography (PET) scan] before surgery for patients with a IIB or higher stage of BC, and reservedly for patients in stage IIA[2,3]. The potential staging advantage of PET combined with computed tomography (PET/CT) over CT scan alone or even bone scintigraphy is that PET/CT can more efficiently detect lymph node invasion and distant metastases[4].

Unfortunately, the published evidence to support the use of PET/CT to predict disease prognosis has been contradictory or of insufficient quality. Some studies have indicated that the specific survival rate is significantly shorter when metastases have been detected on PET[5]. One study determined PET-positive status for axillary nodes to be the foremost preoperative prognostic factor for disease-free survival (DFS) at 5 years[6]. Additionally, a few studies have suggested that the maximum standard uptake value (SUVmax) of the primary tumor could be predictive of survival; however, the threshold values have differed among studies[7,8].

The lack of consensus on the prognostic value of PET may be due to short follow-up times in the previous studies. Additionally, in a study that compared PET with various prognostic markers, the value of PET was overshadowed by assessment of lymph nodes obtained *via* axillary lymph node dissection (authors' reference cited in Data Sharing Statement). However, sentinel node biopsy has taken precedence over axillary dissection, and analyzing the data without axillary dissection would be more relevant to current practice. Furthermore, the potential role for SUVmax in prognosis has not yet been fully considered, and no consideration has been given to the restricted mean survival time (RMST), although it enjoys a growing acceptance rate among clinical practitioners as a preferred survival measurement[9]. Based on all these factors, renewed analyses into the prognostic role of preoperative PET positivity on the long-term outcome of BC needs to be addressed.

MATERIALS AND METHODS

Study design, patients and data

Patients with primary BC who underwent a PET scan prior to their originally recommended surgery as part of the multidisciplinary team management at the Universitair Ziekenhuis Brussel (UZ Brussel; https://www.uzbrussel.be/) between 2002-2008 were identified retrospectively. Patients who met any one or more of the following criteria were excluded: noncarcinoma histology; palliative surgery; or clinically-detected metastatic disease. Follow-up data was collected for each included patient, with the last update having occurred on January 31, 2020.

This study was approved by the institution's ethics committee. All diagnostic and therapeutic procedures had been performed in accordance with the local national guidelines and the Declaration of Helsinki 1964. All patients had received appropriate information and provided informed consent to undergo the procedures. All clinical data were described previously[6], and the steps used in data acquisition are detailed at https://dx.doi.org/10.17504/protocols.io.bf7jjrkn. The study's collective data are available at https://doi.org/10.17632/sfvtmrd8z9.2.

^{18}F-FDG PET scan image acquisition

Patients had fasted for + 6 h, and the PET scan had been rescheduled if hyperglycemia was detected. For all, the tracer activity was in the range of 370-536 MBq (mean: 464 ± 56 MBq). Sixty minutes after tracer perfusion, each patient had been placed in a supine position with arms extended above the head. Whole-body images had then been acquired using attenuation correction and an interleaved protocol with an LSO PET camera (ECAT Accel; Siemens, Hoffman Estates, IL, United States). The parameters of emission data, 2-dimensional mode, and reconstruction-segmentation used were identical to the procedure described elsewhere[6]. Synchronous computed tomography had not been available at the time.

Image analyses

We abstracted the PET image data according to the anatomical regions of interest (AROIs) and according to the source of the available image media storage.

The AROI selected for this study conformed to anatomical regions considered in the radiotherapy of the breast[10], including the whole ipsilateral breast, whole contralateral breast, ipsilateral axillary-supraclavicular lymph node region (shortened to "axillary" in the remainder of the present report), contralateral axillary-supraclavicular lymph node region, sternal-mediastinal area (internal mammary chain), and the remaining body volume (*i.e.* distant, outside the breasts, axillary and sternal areas).

The image media storage comprised two forms: a medical FDG-PET diagnostic report with a screen image printout (for all patients) and image files archived on the PET server (for some patients). First, using the medical diagnostic report, the image in each AROI was assigned a binary score of positive or negative according to visibly increased activity or lack thereof in the AROI. Next, using the PET server workstation and accompanying free-hand volumetric drawing tool, the 3-dimensional AROIs were delineated on all available patient PET scan datasets. Ultimately, the SUVmax was abstracted for each patient from their AROIs (Figure 1).

Repeated PET scans were excluded. For bilaterally involved breasts, only the scan from the first side involved was retained, or from the side with more extensive axillary surgery if there was doubt about the diagnostic precedence.

Statistical analysis

Missing data were imputed using multivariate imputation by chained equations[11] for first histopathology finding (1 missing), HER2-neu score (1 missing), estrogen receptor (ER) and progesterone receptor (PR) status (1 missing), grade (4 missing), tumor size (1 missing), and number of examined and positive nodes (5 missing). Lymphovascular invasion was dichotomized as present *vs* no invasion or unknown (20 missing). HER2 fluorescence *in situ* hybridization (FISH) status was considered as nonimputable and was therefore excluded from the analysis (51 missing).

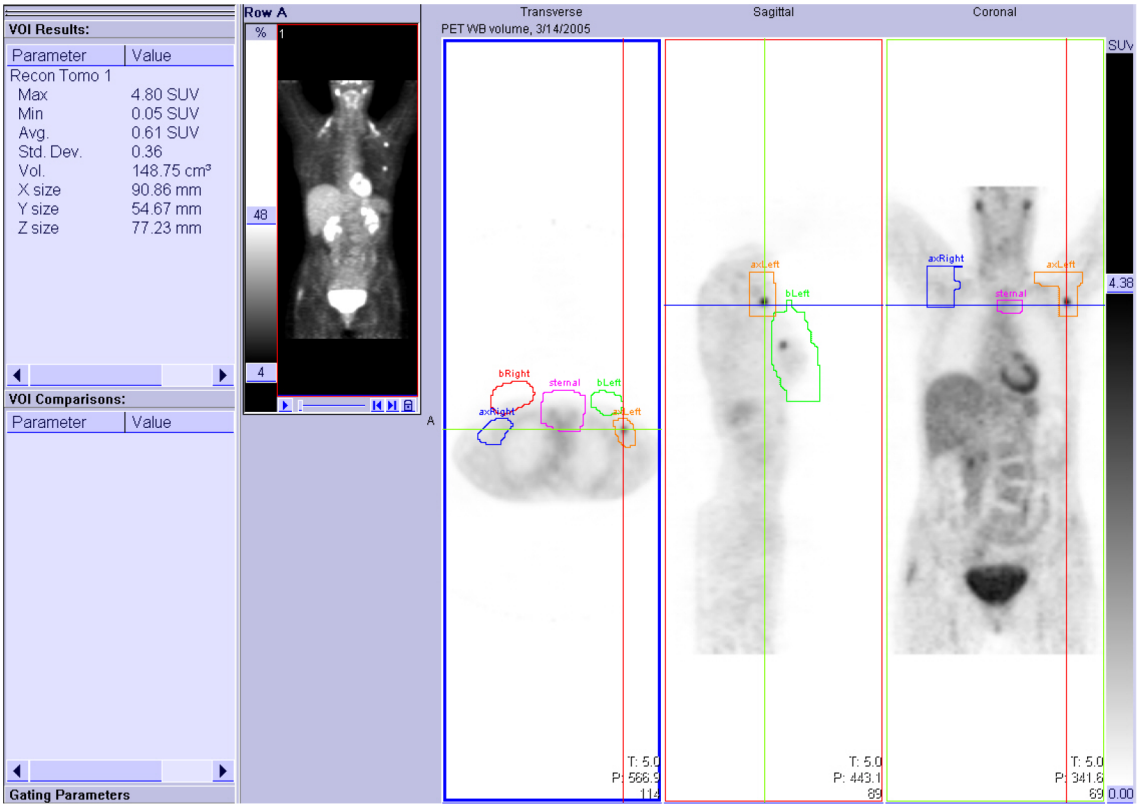

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Figure 1 Anatomical regions of interest. Free-hand three-dimensional non-overlapping anatomical regions of interest (AROI) volumes drawn on the PET scan workstation for the right breast (red), right axilla-supraclavicular nodal area (blue), left breast (green), left axilla-supraclavicular (orange), and sternal-mediastinal area (purple). Viewing planes are indicated by crosshairs.

Survival analyses used times from the date of first pathological diagnosis to the date of last known status. The outcome event for overall survival (OS) was death from any cause. The outcome events for DFS were any local-regional or distant recurrence, secondary tumor, or death from any cause. Survival rates were computed using the Kaplan-Meier method[12]. The expectation of remaining years of life, or the RMST, up to a time horizon of 15 years was used to summarize the patients' survival[9]. This value was calculated as the area below the survival curve. The area between survival curves measures the difference between RMSTs (Δ), but the precision and statistical significance are affected by the amount of censoring. As in other tests comparing survival curves, the difference and the area between the two curves can appear large and still might be nonsignificant when there are few events. Δ is expressed in years, in the same unit of time as the survival time, and indicates the impact of prognostic factors in terms of difference in life expectancy according to the prognostic levels.

The prognostic role of PET was examined as a qualitative binary factor (positive *vs* negative status) and as a continuous variable (SUVmax) in multivariate survival analyses using Cox proportional hazards models[13]. The models excluded pathological lymph node involvement, which is a strong predictor of survival that would otherwise confound and mask the significance of other factors (authors' reference cited in Data Sharing Statement). Long-term follow-up with OS and DFS at 15 years was used to validate models previously reported elsewhere[6]. The Nagelkerke index of explained variation (*R2N*) and the Royston-Sauerbrei index of prognostic separation (*R2D*) were computed to evaluate the Cox models[14].

All computations was carried out with the R statistical software, version 3.6.3[15], with the *mice* package for missing data imputation, and the *survRM2* package for the RMSTs.

RESULTS

A total of 157 consecutive records were identified, out of which 53 cases were excluded for postsurgical PET performance (n = 17), breast surgery not specified in the original multidisciplinary team's recommended management of the case (n = 12), history of previous cancer (n = 8), nonunique records (n = 5), no diagnosis of cancer (n = 2), axillary surgery not performed (n = 2), no histology data (n = 2), noncarcinoma (n = 2 sarcoma, n = 1 noninvasive tumor), and no information on the primary therapy (n = 2). Among the remaining 104 patients representing the study population, surgery had been performed

at a median of 6 d after the PET imaging for the 85 (81.7%) patients who did not receive neoadjuvant therapy and at a median of 83 d after the PET imaging (range: 5-201 d, n = 1 date unknown) for the 19 (18.3%) patients who received neoadjuvant therapy. The type of breast surgery performed was lumpectomy in 26 (25.0%) patients, mastectomy in 77 (74.0%), and exclusive radiotherapy assimilated to mastectomy in 1 (1.0%). All lymph node surgeries were limited to the axilla, without exploration of the internal mammary chain. Table 1 summarizes the main characteristics of the study's patient population.

The patterns of PET observed among the total 104 patients were abstracted as binary score, and the SUV measurements of 36 patients for whom imaging could be retrieved are listed in Table 2 and Table 3, respectively. PET status of axillary, combined PET axillary/sternal, and combined PET all-sites were significantly related to tumor size (Table 2). SUVs were measured on the AROIs regardless of visual enhancement, making them available in all breast, axillary, and sternal sites. Ipsilateral local-regional uptake also correlated with tumor size (Table 3). For distant sites, the SUV measurements were carried out on visually hypermetabolic areas only, and therefore, the information was limited to 8 non-analyzable cases.

Surviving patients (no OS event) had a median follow-up of 15.1 years. The OS was significantly worse for those who had a PET-positive axillary nodal status (Δ = 2.2 years, P = 0.033); thus, at a time horizon of 15 years, patients with a PET-positive axillary status had a life expectancy that was 2.2 years shorter than patients with a PET-negative axillary status. Patients with a PET-positive sternal nodal status also had a shorter life expectancy, with Δ of 5.1 years (P = 0.033) (Figure 2). When patients were considered as a group defined by PET-positive axillary status and/or sternal status but without distant positivity (*i.e.*, regional positivity without distant positivity, regardless of breast local status), life expectancy was decreased, with Δ of 2.6 years (P = 0.008). When patients were considered as a group defined by any PET-positive status for axillary, sternal or distant (*i.e.* any regional or distant positivity, regardless of breast local status), life expectancy was also decreased, with Δ of 2.1 years (P = 0.025). Survival differences were not evident when comparing the PET-positive groups for breast or distant separately (Figure 2). Survival differences were also not evident on subgroup analyses for PET-positive axillary status for tumors ≤ 20 mm (TNM T1 classification[16]). For tumors > 20 mm, survival differences were evident when axillary and/or sternal status were PET-positive (*i.e.*, regional positivity), with Δ of 3.0 years (P = 0.015).

DFS was also worse for patients with a PET-positive axillary nodal status (Δ = 2.5 years, P = 0.040) and with a PET-positive status in any of the axillary and sternal regions (Δ = 2.6 years, P = 0.023) (Figure 3). DFS was not statistically different for patients with tumors ≤ 20 mm; however, in patients with tumors > 20 mm, DFS was significantly worse for those with PET-positive axillary status (Δ = 3.4 years, P = 0.017), sternal status (Δ = 5.9 years, P = 0.048), and combined axillary and sternal status (Δ = 3.9 years, P = 0.005). The pattern of the DFS survival curves according to tumor size ≤ 20 mm or > 20 mm (data not shown) were comparable to the global DFS's shown in Figure 3.

Multivariate OS and DFS analyses used PET axillary | sternal status, age at diagnosis, and adjuvant hormone therapy covariates, which were the same parameters used previously in our short-term follow-up study[6]. In the earlier study, OS was inconclusive and was not reported, and DFS at 5 years of follow-up indicated significance for PET-positive axillary status only[6]. Table 4 shows a comparison of the previous short-term follow-up DFS hazard ratios (HRs) with the current OS and DFS HRs for the longer follow-up period. The DFS HRs for age and adjuvant hormone therapy at 15 years of follow-up were 1.03 and 0.51, respectively, comparable to the previous DFS HRs of 1.05 and 0.43, respectively, at 5 years of follow-up. That is, despite patients becoming older, from diagnosis at 58.9-years-old (Table 1) to near 75-years-old in the present study, age and adjuvant hormone therapy retained their prognostic value. Of note, however, the DFS HR for PET was 1.74 at 15 years of follow-up, as compared with 2.81 at 5 years of follow-up, suggesting some loss of prognostic value regarding DFS. In contrast, regarding the OS, the *R2N* of 0.077 and *R2D* of 0.159 for PET positivity at 15 years of follow-up (Table 4) indicate that the PET covariate provided prognostic information almost half that of the *R2N* of 0.189 and *R2D* of 0.396 from a full model that was computed by taking into account all three covariates together.

The impact of SUVmax on OS is shown in Table 5. The regions of interest were the tumor and ipsilateral breast, the ipsilateral axillary lymph node region, and the internal mammary chain (sternal). In addition to the absolute SUVmax, the ratios of ipsilateral breast SUVmax relative to the contralateral breast and ipsilateral axillary relative to the contralateral axillary SUVmax were computed.

The absolute SUVmax of the uninvolved contralateral breast and contralateral axilla did not correlate with OS (P = 0.528). Likewise, SUVmax of the contralateral axillary site also did not correlate with OS (P = 0.969). In contrast, the SUVmax of the involved breast and the ipsilateral axillary were significantly associated with OS (P = 0.048 and P = 0.029, respectively). The SUVmax on all combined local-regional sites was also significant (P = 0.032). However, the ratio of SUVmax ipsilateral axilla over SUVmax contralateral was the most significant of all factors examined (P = 0.027), with HR of 1.94, indicating a two-fold relative increased risk of death (Table 5).

Table 1 Patient characteristics

Characteristic	*n*	%
Sex		
Male	2	2.0
Female	102	98.0
Age at diagnosis (yr)		
Median (range)	58.9	(32.5–83.0)
< 40	8	7.7
40-59	51	49.0
≥ 60	45	43.3
Histology		
Invasive ductal carcinoma	84	80.8
Lobular carcinoma	14	13.4
Other	6	5.8
Tumor laterality		
Bilateral	5	4.8
Left	45	43.3
Right	54	51.9
Tumor quadrant		
Inner	16	15.4
Central	14	13.5
Outer	64	61.5
Other	10	9.6
Clinical T4 stage	8	7.7
Tumor size		
0-20 mm (TNM T1 classification[16])	37	35.6
> 20 mm (one imputed as 30 mm)	67	63.5
Stage		
I	18	17.6
IIA	28	27.5
IIB	18	17.6
III	34	33.3
IV	4	3.9
Unknown	2	–
Grade		
1	29	29.0
2	42	42.0
3	29	29.0
Unknown	4	–
Hormone receptor status		
ER+/PR+	67	64.4
ER–/PR–	20	19.2
Other	17	16.3

Events		
Loco-regional recurrence	4 of 104	3.8
Distant metastases	31 of 104	29.8
Death from any cause	28 of 104	26.9

ER+: Estrogen receptor-positive; ER-: Estrogen receptor-negative; PR+: Progesterone receptor-positive; PR-: Progesterone receptor-negative.

Table 2 Positron-emission tomography negative or positive status according to anatomical region of interest and according to tumor size, *n* (%)

Anatomical region of interest	Tumor ≤ 20 mm	Tumor > 20 mm	*P*
	n = 37	*n* = 67	
Breast ipsilateral			< 0.001
PET negative	12 (32.4)	5 (7.5)	
PET positive	25 (67.6)	62 (92.5)	
Axillary ipsilateral			0.006
PET negative	29 (78.4)	34 (50.7)	
PET positive	8 (21.6)	33 (49.3)	
Sternal			0.906
PET negative	35 (94.6)	63 (94.0)	
PET positive	2 (5.4)	4 (6.0)	
Distant			0.447
PET negative	32 (86.5)	54 (80.6)	
PET positive	5 (13.5)	13 (19.4)	
Any of axillary or sternal			0.019
PET negative	27 (73.0)	33 (49.3)	
PET positive	10 (27.0)	34 (50.7)	
Any of axillary, sternal, or distant			0.005
PET negative	26 (70.3)	28 (41.8)	
PET positive	11 (29.7)	39 (58.2)	

PET: Positron-emission tomography.

DISCUSSION

PET-positive axillary nodal and sternal status were found to be the predominant preoperative prognostic factor for OS, providing a stronger prognostic perspective than previously found[6]. Although the present study is limited by its retrospective design, it represents the longest observation period published for the prognostic role of PET scan status in OS of BC patients[7].

To place the present study in context, it started 20 years ago with the first patient diagnosed and receiving preoperative PET in 2002, while the principal investigator was working at his alma mater the UZ Brussel, a university hospital in Belgium. The first case series was presented at the San Antonio Breast Cancer Symposium in 2004 (Poster 2010, *Breast Cancer Res Treat* 2004; 88: S90, reference omitted). Among the patients who had received adjuvant radiotherapy, 32 had previously undergone a PET scan and we found an association between the PET nodal positivity and more extensive nodal involvement. We hypothesized that the larger number of nodes retrieved in PET-positive cases suggested lymphangiogenesis factors associated with an increased tumor metabolic activity. Obviously, preoperative PET would have served as an important tool to tailor radiation treatment fields in BC, as reported by Bral *et al*, who showed how ignorance of PET imaging could lead to failed targeting of radiation for hypermetabolic lymph nodes (*Strahlenther Onkol* 2008; 184(2): 100-4, reference omitted). It was, however, impossible to implement preoperative PET scan in our daily practice at the time of treatment of our

Table 3 Maximum standardized uptake value according to anatomical region of interest and according to tumor size

Anatomical region of interest	Tumor ≤ 20 mm	Tumor > 20 mm	*P*
	n = 18	*n* = 18	
Breast ipsilateral			
SUVmax, mean (SD)	2.3 (1.4)	4.4 (3.1)	0.012
Breast contralateral			
SUVmax, mean (SD)	1.7 (1.3)	1.7 (0.6)	0.918
Axillary ipsilateral			
SUVmax, mean (SD)	1.8 (0.9)	2.8 (1.8)	0.063
Axillary contralateral			
SUVmax, mean (SD)	1.5 (0.5)	1.8 (0.5)	0.140
Sternal			
SUVmax, mean (SD)	1.8 (0.5)	2.1 (0.6)	0.061
All breast, axillary and sternal regions combined			
SUVmax, mean (SD)	2.7 (1.5)	4.8 (3.0)	0.014

SUVmax: Maximum standardized uptake value; SD: Standard deviation.

Table 4 Multivariate models, original model with 5 years follow-up, *vs* current models with 15 yr follow-up

	Disease-free survival 5 yr of follow-up[6]		Disease-free survival 15 yr of follow-up, present study			Overall survival 15 yr of follow-up, present study		
Variable	HR (95%CI)	R2N	HR (95%CI)	R2N	R2D	HR (95%CI)	R2N	R2D
PET axillary/sternal (positive *vs* negative)	**2.81** (1.17, 6.74)	0.059	**1.74** (0.96, 3.14)	0.030	0.053	**3.08** (1.42, 6.69)	0.077	0.159
Age at diagnosis (yr)	**1.05** (1.01, 1.09)	0.046	**1.03** (1.00, 1.06)	0.047	0.075	**1.06** (1.02, 1.10)	0.109	0.227
Adjuvant hormone therapy (yes *vs* no)	**0.43** (0.16, 1.13)	0.030	**0.51** (0.24, 1.08)	0.025	0.049	**0.46** (0.18, 1.18)	0.020	0.083
Full model		NA		0.091	0.142		0.189	0.396

R2N and R2D values shown are the differences between the full model (computed with all three PET, age, adjuvant hormone therapy variables together) and the same full model without the variable. Higher values indicate higher importance of the variable in the model. Hazard ratios > 1 indicate increased risk of mortality. CI: Confidence interval; NA: Not available; HR: Hazard ratio; R2D: Royston-Sauerbrei index of prognostic separation; R2N: Nagelkerke proportion of explained variation.

study's cases because of a Belgium healthcare restriction on PET scan. Only 13 facilities nationwide were allowed to implement PET and our cases fell beyond the defined population restrictions; moreover, BC was not a recognized indication for PET scan[17].

Despite these precluding logistical healthcare restrictions, the need for PET did not abate and we continued to observe a trickle of patients who had received PET. The 2004 study reported only on nodal pathology but had no follow-up. By simple logic, if PET correlates with lymph node involvement, then it would also correlate with survival. The study was reconducted in 2010 without funding, by investigators devoting volunteer time, accruing the present cohort of 104 patients. That study confirmed the nodal correlation and, indeed, provided evidence for the expected impact on early DFS. The analysis was published 2 years later, in 2012[6]. Meanwhile, guidelines did not change and still considered PET inappropriate for the early assessment of BC. To address that issue, we established a quasi-prospective protocol in 2015, with the intent to increase the number of observations with a second cohort of patients. The protocol is available at https://www.isrctn.com/ISRCTN17962845 through the linked file https://www.isrctn.com/editorial/retrieveFile/b3691bca-5277-4025-bd3e-ebea2701d143/38272.

As detailed in the protocol, the number of patients needed was 162. We expected 210 cases to be retrieved in 2015 to allow for comparison of patterns of practice between the cohorts from 2002-2008 (PET without CT) and 2009-2015 (PET with CT). The analysis was intended to be completed in 2020, with the intent to give precedence to explore the innovative concept of SUV ratios (protocol, link in

Table 5 Mortality hazard ratio of the maximum standard uptake value according to the anatomical region of interest, single or combined, where the maximum standard uptake value was measured

Region of interest	HR	*P*
Sternal	3.50	0.080
Breast ipsilateral	1.25	0.048
Breast contralateral	0.72	0.528
Axillary ipsilateral	1.54	0.029
Axillary contralateral	1.03	0.969
Combined breast/axillary/sternal	1.27	0.032
Ratio SUVmax breast ipsilateral/ SUVmax breast contralateral	1.34	0.101
Ratio SUVmax axillary ipsilateral/ SUVmax axillary contralateral	1.94	0.027
Ratio SUVmax in any of breast/axillary/sternal/lowest of SUVmax breast or axillary contralateral	1.50	0.036

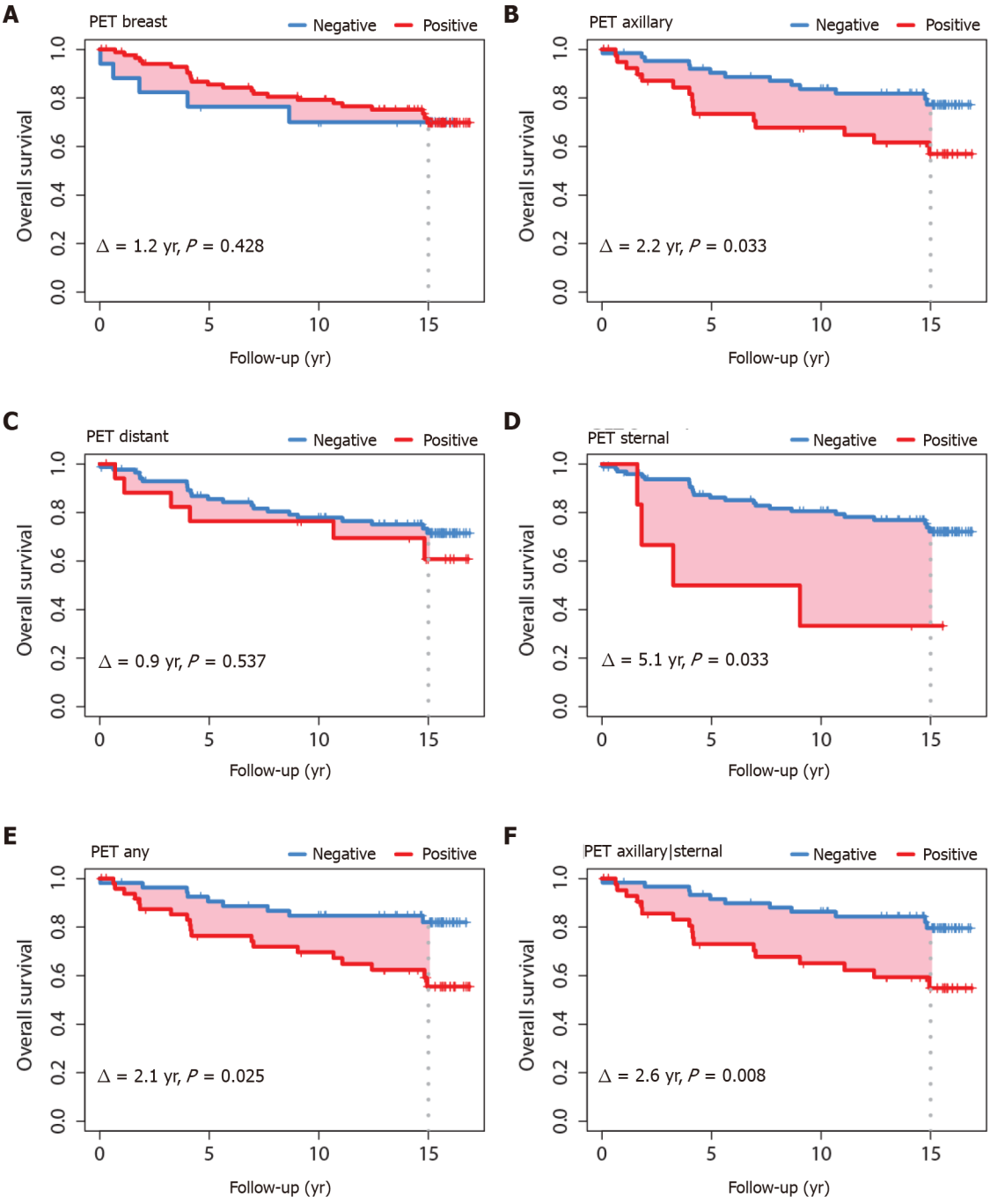
HR: Hazard ratio; SUVmax: Maximum standard uptake value.

ISRCTN17962845). As planned and reported herein, we updated the follow-up of the present cohort on January 31, 2020. Unexpectedly, however, when we returned to the PET server workstation, the 3-dimensional irregular free-hand volumetric measurement tool (Figure 1) had been wiped out by an upgrade to the system. As such, we could not verify the consistency of our earlier AROI delineations and SUVmax measurements. Repeated delineation measurement and extending the present study to a larger cohort have had to be deferred.

The focus of this study was on prognosis, rather than diagnostic accuracy. Nevertheless, a note on the latter is warranted. Out of the 63 patients who had PET-negative axillary status (Table 2, axillary ipsilateral), 29 (imputed) had histopathologically identified involved lymph nodes, and out of the 41 PET-positive axillary patients, 5 had no histopathologically identified node involvement. These data yield a sensitivity of 55% [95% confidence interval (CI): 43%-68%] and a specificity of 87% (95%CI: 73%-96%) which indicate that PET, like other imaging modalities, cannot replace pathology to determine microscopic involvement. This is concordant with findings from a United States' multicentric prospective study for the detection of axillary nodal metastasis; the sensitivity and the specificity of PET were 61% (95%CI: 54%-67%) and 80% (95%CI: 79%-81%) respectively[18]. A meta-analysis of 19 studies including 1729 patients evaluated the performances of PET (with or without CT) for axillary detection and found that the sensitivity was 66% (95%CI: 50%-79%) and the specificity was 96% (95%CI: 90%-99%) [19]. Several tumor characteristics are known to correlate with higher rates of false negatives, such as low tumor grade or proliferation index, lobular histology, estrogen receptor- or progesterone receptor-positive status[20,21], in contrast to higher FDG uptake being less likely to cause false negativity in tumors exhibiting high proliferation rate and enhanced microvasculature[22].

In a previous study that focused on metastatic disease, the OS for 47 out of 189 patients with stage IIB and higher classified M1 by PET in a 3-year follow-up was significatively shorter (57% *vs* 88%, $P < 0.0001$)[23]. Other authors also noted that at stage IIB and higher, survival of patients was shorter when a distant metastasis was detected on PET-CT regardless of tumor phenotype[5]. However, several studies found that positive PET status is predictive of recurrence and survival, irrespective of metastatic status, most likely because of the correlation with poor clinicopathologic factors[24]. Our study was not designed to correlate between distant metastasis and survival. Metastatic patients were excluded from the selection, hence, there were few remaining cases detected afterwards with additional distant localizations (8 in this series).

PET-positive status was found to not be significantly predictive of OS and DFS for patients with tumors ≤ 20 mm, which can be explained by the small number of patients and the lower mortality in this subgroup. This could also be explained by the spatial resolution of PET for small tumors and small axillary node, especially data obtained in 2002 during which PET performance was lower than that of sentinel lymph node biopsy[19,25]. In the subgroup of tumors ≤ 20 mm, corresponding to stage I, a multicentric study concluded that out of the 325 women with a BC, only 13 had a PET-positive status, and of those, only 3 were confirmed and 10 were deemed false positives[25]. Considering the whole series, PET status in the breast was not prognostic. The contribution of primary breast tumor size, which affects PET detection, is a long-standing debate[26] (see also Claire Verschraegen, on the effect of tumor size in breast cancer, *Ann Surg* 2005; 241: 309-318, reference omitted). The issue, however, is beyond the scope of this report. We can only remark that most patients in our study (74%) received mastectomy.



DOI: 10.5306/wjco.v13.i4.287

Figure 2 Overall survival according to fluorine-18-fluorodeoxyglucose positron-emission tomography status in anatomical regions of interest. A: Breast; B: Axillary; C: Distant; D: Sternal; E: Any axillary, sternal or distant; F: Any axillary or sternal.

Compared to the previous study involving 5 years of follow-up, PET-positive axillary and combined axillary and sternal status remained significant predictors of DFS at the extended follow-up of 15 years, although to a lesser extent (Figure 3 and Table 4). A diagnostic check of the DFS model revealed a violation of the proportional hazards assumption of the Cox model. The assumption requires that the HRs between two treatment groups be independent of time[27]. The assumption fails if the survival curves cross over or overlap for a long time, or when the treatment has an early effect but the initial separation gets smaller over time[27]. This latter pattern of violation is evidenced in Figure 3, where the differences between the pairs of DFS curves show a tendency to narrow with longer follow-up, in contrast to Figure 2 where the OS curves remain proportionally distinct. OS is the gold standard; several studies have shown that DFS is not always predictive of OS[28]. Also, OS has the advantage of being unambiguously defined, in contrast to DFS, which has multiple definitions depending on the type of study and cancer involved. DFS is frequently used because it requires less observation time and fewer patients. However, with longer survival, patients advance in age. They present with increasing

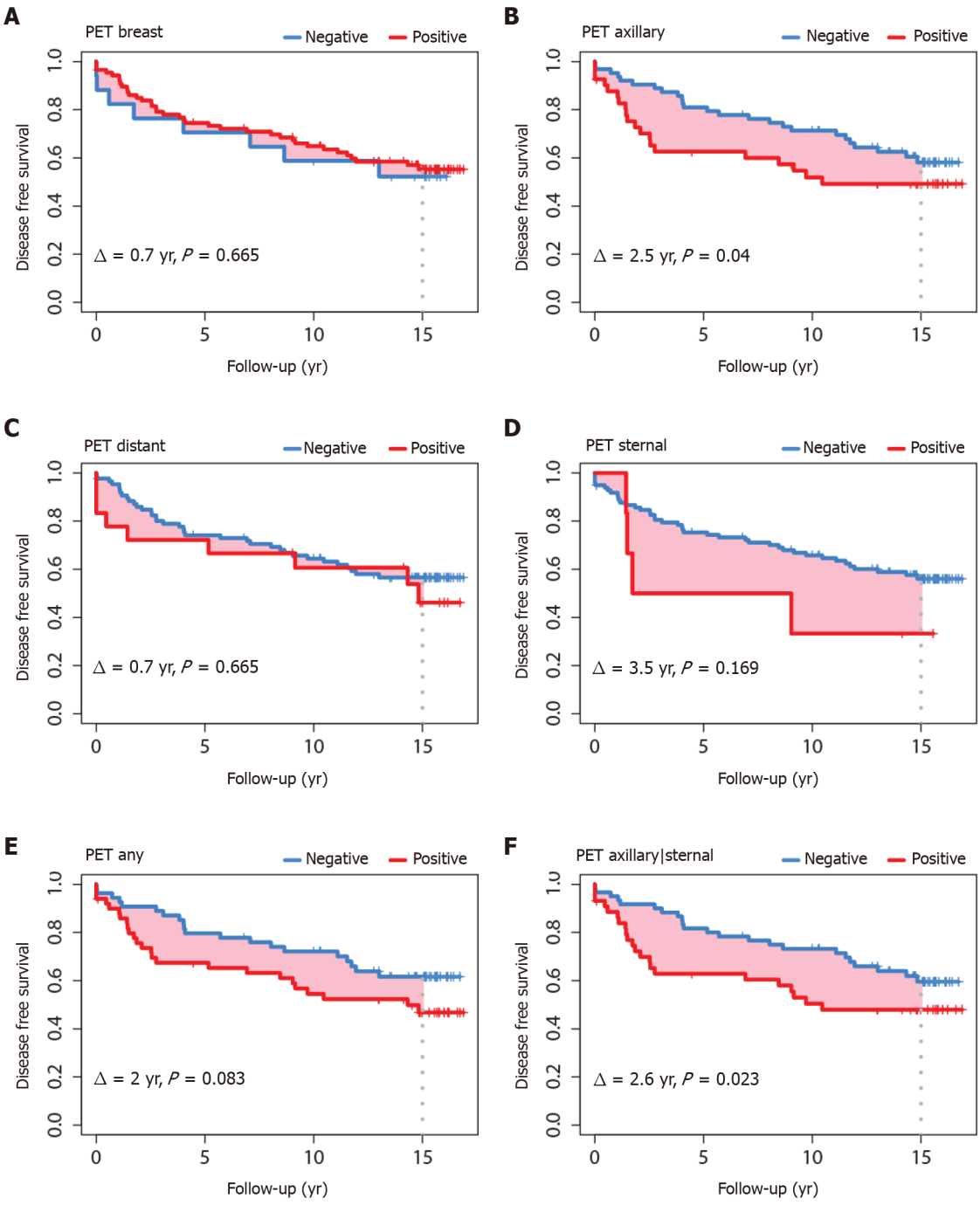


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Figure 3 Disease-free survival according to fluorine-18-fluorodeoxyglucose positron-emission tomography status in anatomical regions of interest. A: Breast; B: Axillary; C: Distant; D: Sternal; E: Any axillary, sternal or distant; F: Any axillary or sternal.

comorbidities or with physical function deterioration and they are no longer willing or are unable to attend oncology consultations (typically when we call to enquire, patients would report a neurological, cardiac, respiratory, or joint and mobility problem) or in case they remain fit, the follow-up consultation is often discontinued after 10 years. Severe comorbidities can mask recurrence, and over time cancer surveillance loses priority for attending physicians. Consequently, less information on recurrence is available over time, whereas information on living or dead status can be obtained through national registries and is more reliable than disease status. These reasons likely explain why prognostication is better with DFS outcome in the short-term and better with OS outcome in the long-term.

Limitations of the study include bias inherent to its retrospective design. Beyond that, the investigators were not blinded to patients' outcomes, which could have affected the scoring of the PET images; moreover, the scoring itself depended upon the visual appreciation of screen printouts and predefined rules to abstract images were not established. There was also no assessment of inter-observer agreement on the scores. The patients had been treated 15 years prior, which represented both a

strength and a weakness, with the latter being related to medical management and treatment changes over that time. Most of the patients had presented with advanced tumors, for which a high prevalence of lymph node involvement and increased likelihood of PET positivity could be expected. Few patients presented with T1 tumors (Table 2); no conclusion could be drawn for these smaller tumors.

Molecular subtypes are known to affect PET positivity, as already mentioned[20-22]. However, the small study size (with only 28 events for OS; Table 1) precluded extensive analyses. By the one-in-ten rule of thumb (*i.e.* one variable for ten events[29]), it was decided to retain only the three-variables parsimonious model of Table 4 in the multivariate analysis, as built onto the precursor study[6]. Interestingly, despite the small study size, these three variables illustrate distinct facets relevant to BC management, specifically: PET as an indicator of disease aggressivity; age as a potential surrogate of increased risk of co-morbidity; and adjuvant hormone therapy as a surrogate of tumor subtype reflecting that hormone therapy is normally given only when the breast tumor expresses hormone receptors.

The present study innovates measurement of SUVmax based on a full-anatomical region of interest. The AROI's were defined regardless of SUV pattern, avoiding the potential arbitrary selection of small presumably pathological areas; although, without dual acquisition of CT, delineation of the anatomical boundaries was uncertain.

Surprisingly, few studies have implemented PET image analysis using AROIs. Yoo *et al*[30] delineated the nipple-areolar complex on the ipsilateral index breast and the contralateral normal breast. The ratio of the ipsilateral over contralateral SUVmax in the delayed image phase PET was then found to be an independent predictor of nipple-areolar involvement. Other than study of PET for nononcological cognitive symptoms and dementia, where the interest was in the whole brain and subregions [31], we are not aware of any other BC study implementing full-AROI-based PET measurements. Reflecting on PET studies in the peer-reviewed literature, the European Association of Nuclear Medicine Guidelines define volumes of interest only as relative to tumor areas, without allowance to full organs or anatomic regions[32].

The prognostic value of FDG-PET in particular has been demonstrated in numerous disease conditions[33-38]. The present study shows that the prognostic role in BC is no different than that with other cancers, serving as an indicator of increased metabolism and therefore adverse survival outcome. The SUVmax in different anatomical regions was related to the overall risk of death. There is a growing recognition that quantitative continuous SUVmax and other SUV metrics have an important prognostic role[39]. Our study adds to the evidence that SUVmax as a continuous variable improves the power of the analysis to optimize research yield, which can be particularly important when the resources and number of patients are restricted. The study also contributes a new intuitive finding, in that using the uninvolved side as a reference for SUV measurements can improve PET prognostication; the observation, however, deserves further study.

CONCLUSION

This study confirms that PET-positive axillary status in preoperative BC is a significant predictor of OS after 15 years of follow-up, and more so with breast tumors > 20 mm. In view of the long-term survival impact, the finding argues that preoperative PET should be considered as a standard in all BC cases whenever the primary tumor size exceeds 20 mm. The role of preoperative PET in tumors ≤ 20 mm is less clear and warrants further investigation.

ARTICLE HIGHLIGHTS

Research background

The role of preoperative fluorine-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) scan (referred to hereafter as FDG-PET) in early operable breast cancer (BC) is considered controversial and is even discouraged by clinical guidelines.

Research motivation

In dissension with guidelines, the evidence indicates that FDG-PET is a metabolic indicator of aggressive disease, warranting reconsideration of its role in the preoperative evaluation of BC.

Research objectives

Long-term follow-up is needed to address the importance of any marker. The study evaluates the very long-term (15-year) prognostic role of preoperative FDG-PET.

Research methods

The medical records of clinically nonmetastatic BC patients receiving preoperative FDG-PET were retrieved. Survivals were compared according to FDG-PET positive/negative status using the restricted mean survival time at a time horizon of 15 years. Multivariate analyses was performed with Cox proportional hazard models. In addition, the survival impact of absolute maximum standard uptake value (SUVmax) and ratios of SUVmax relative to the contralateral uninvolved side were evaluated.

Research results

Among 104 patients, regional FDG-PET positivity in the axillary or the sternal region was found to be a strong predictor of 15-year overall survival (P = 0.008). Patients with a positive regional PET status had an expected survival that was 2.6 years shorter than patients with negative regional PET status. Statistical significance was maintained for tumors > 20 mm, though not for tumors ≤ 20 mm. Cox models demonstrated the independent prognostic role. In addition, in a subgroup of 36 patients for whom quantitative SUV was available, representing 36 × 15 years = 540 patient-years follow-up and hence no lesser importance than a study of 189 patients but with only 3 years of follow-up, the ratio of ipsilateral axillary SUVmax *vs* uninvolved contralateral axillary SUVmax was the most significant among other SUV measures (P = 0.027).

Research conclusions

This study involved the longest known follow-up of preoperative FDG-PET in early operable BC. It provides survival information heretofore unavailable. Predicting an expected survival difference of 2.6 years out of a time horizon of 15 years can be a major consideration in the initial management of BC. In addition, the SUVmax ratio of ipsilateral over uninvolved side might represent a new finding that warrants investigation.

Research perspectives

FDG-PET might have a predominant role in the workup of BC. The present research did not have sufficient power to address the role of preoperative FDG-PET in tumors ≤ 20 mm. Future studies should consider accruing patients presenting with small tumors.

FOOTNOTES

Author contributions: Vinh-Hung V and Everaert H were responsible for conception and design of the study; Vinh-Hung V, Everaert H and Van Parijs H were responsible for acquisition of the data; Vinh-Hung V, Hendrik Everaert, Gorobets O, Perrin J and De Ridder M were responsible for drafting of the manuscript; Perrin J, Vinh-Hung V, Nguyen NP and Djassemi N were responsible for reviewing the literature; Vinh-Hung V was responsible for analysis of the data; Perrin J, Farid K, Djassemi N, De Ridder M, Nguyen NP and Everaert H were responsible for further writing of the manuscript; Vinh-Hung V, Gorobets O and Perrin J were responsible for generating the tables and figures; all authors performed critical review and gave final approval of the version to be published.

Institutional review board statement: The study was reviewed and approved by the UZ Brussel Ethics Committee. All diagnostic and therapeutic procedures were performed in accordance with the local national guidelines and the Declaration of Helsinki 1964. The study registration occurred on 12 May 2020, No. ISRCTN17962845 (https://www.isrctn.com/ISRCTN17962845).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to the diagnosis and treatment procedures by written consent.

Conflict-of-interest statement: The authors declare that they have no financial relationships to disclose.

Data sharing statement: Data can be openly accessed at: https://doi.org/10.17632/sfvtmrd8z9.2. The protocol is deposited at: https://www.isrctn.com/ISRCTN17962845. Step-by-step data for the procedure is deposited at: https://dx.doi.org/10.17504/protocols.io.bf7jjrkn.

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CASE REPORT

Mesentery solitary fibrous tumor with postoperative recurrence and sarcomatosis: A case report and review of literature

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Abstract

BACKGROUND

Solitary fibrous tumors are rare neoplasms of mesenchymal origin. They are often of low malignant potential and rarely metastasize. They frequently arise from the pleura and can occur at any soft tissue site in the body. However, these tumors rarely develop in the mesentery, peritoneal cavity or peritoneum.

CASE SUMMARY

We report on a scarce case of solitary fibrous tumor of the rectal mesentery showing sarcomatosis about 4 years after previous tumor resection. This 69-year-old male had no clinical symptoms but was transferred to our hospital because of a suspected tumor recurrence from follow-up abdominal computed tomography.

Tumor markers (CEA, CA 19-9 and CA 125) were within the normal range. Open laparotomy showed sarcomatosis, and pathology confirmed its mesenchymal origin and diagnosis as the solitary fibrous tumor. Our case may be the second recurrent mesentery solitary fibrous tumor reported to date, and the only one with progression to sarcomatosis. There has been no evidence of recurrence in follow-up at the 28th mo after extensive intra-operative peritoneal lavage and cytoreductive surgery.

CONCLUSION
Although there are few risk factors of cancer recurrence in this patient, careful long-term follow-up after cytoreductive surgery is necessary.

Key Words: Solitary fibrous tumor of rectum mesentery; Recurrence; Sarcomatosis; Extensive intra-operative peritoneal lavage; Cytoreductive surgery; Case report

Core Tip: Solitary fibrous tumors (SFTs) are mostly benign and they rarely develop in the mesentery and cause sarcomatosis. The favored treatment strategy is whole-tumor excision with continued follow-up. According to a literature review, our patient is the first case report of mesentery SFT with the presentation of postoperative intraperitoneal recurrence and sarcomatosis.

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INTRODUCTION

Solitary fibrous tumors (SFTs) are mostly of mesenchymal origin and were first documented by Klemperer and Rabin[1]. SFTs growing from the mesentery are very rare[2]. In this paper, we report a patient with SFT of mesentery origin with postoperative recurrence and sarcomatosis, and subsequently we provide a review of the literature.

CASE PRESENTATION

Chief complaints

According to regular computed tomography (CT) follow-up, a 69-year-old Japanese man was noted to have a suspected SFT recurrence.

History of present illness

This patient received surgical resection of a rectal mesenteric tumor on 13 January 2016. Pathology confirmed a pedunculated rectal mesenteric tumor of mesenchymal origin to be SFT with malignant potential in terms of mildly positive p53 immunoreactivity. In addition to the primary tumor, a white nodule found on the peritoneal cavity was simultaneously resected and was noted with the same pathologic characteristics. He underwent regular follow-up without any symptoms at the hospital, but according to CT images on 1 March 2020, SFT recurrence was suspected. For further management he was referred to Kishiwada Tokushukai Hospital in Osaka Prefecture, Japan.

History of past illness

He had no medical history except for the surgical resection of a rectal mesenteric SFT with malignant potential on 13 January 2016.

Personal and family history

The patient had no family history.

Physical examination

Physical examination revealed no evident abnormalities on admission except for the previous abdominal operation scar.

Laboratory examinations

Routine blood results were normal, including the levels of the tumor marker cancer antigen 19-9 (CA 19-9; < 2.0 U/mL; normal level < 37.0 U/mL), carcinoembryonic antigen (CEA; 1.1 ng/mL; normal level < 5.0 ng/mL), and cancer antigen 125 (CA 125; 9.1 U/mL; normal level < 35.0 U/mL).

Imaging examinations

Contrast-enhanced CT images of the abdomen and pelvis revealed large and small nodules in the peritoneal cavity around the pelvic floor as well as suspected disseminated lesions. No prominent abnormal findings were noted in the liver, biliary system, pancreas, spleen or adrenal glands with no evident ascites (Figure 1).

FINAL DIAGNOSIS

Pathological findings

This patient received cytoreductive surgery and the specimen was examined. Macroscopic examination revealed more than 100 whitish tumor nodules (each measuring 1-3 mm) seeded over the parietal peritoneum and visceral peritoneum of the partial ileum and colon as well as the urinary bladder. The specimens were noted to have relatively clear boundaries, and some were noted to have fat infiltration (Figures 2 and 3).

Histopathologically, this tumor had a heterogeneous cell population comprising mainly spindle cells with proliferated fibrous collagen and diverse groups of cells exhibiting patternless or storiform growth. No tumor necrosis, nuclear polymorphism or cellular atypia was noted. The nuclear mitotic index was 4 mitoses/50 high-power fields (Figure 4A and B).

Immunohistochemically, the tumor showed diffuse strong immunoreactivity against CD34 (Figure 5A), CD99 (Figure 5B) and Bcl-2 (Figure 5C). The patient was diagnosed with SFT. Immunoreactivity for p53 was mildly positive (Figure 5D). The mitotic proliferative index for Ki-67 immunostaining was fewer than 4 mitoses/HP, representing a Ki-67 mitotic proliferative index of approximately 5% (Figure 5E). However, the tumor stained negatively for S100, HMB45, actin, desmin, CD10, cytokeratin, cytokeratin 7, CD31, EMA and CD68.

Grossly, pathology examination indicated that our patient's tumor fitted both the histopathological and immunohistochemical characteristics of SFT. Moreover, the washing cytology of the pelvis did not reveal any suspicious malignant cells.

TREATMENT

Operative intervention

A midline laparotomy was performed from the xiphoid to the pubis. The old abdominal incision was also excised. Nearly 100 whitish tumor nodules (each measuring 1–3 mm) were seeded over the parietal peritoneum and visceral peritoneum of the partial ileum and colon as well as the urinary bladder, with no ascites in the pelvis (Figure 6). The intraoperative peritoneal carcinomatosis index was 19 (2-0-0-0-2-2-2-2-2-1-2-2-2).

The laparotomy procedure was initiated after extensive intraoperative peritoneal lavage (EIPL) with 10 L of saline in the abdominopelvic cavity. Cytoreductive surgery (CRS) with electroevaporation was performed, which included adhesiolysis, umbilical and falciform ligament resection, total anterior parietal peritonectomy, bilateral subphrenic peritonectomy, complete pelvic peritonectomy (Figure 7), greater and lesser omentectomy, cholecystectomy, stripping of the tumor from Glisson's capsule and hepatoduodenal ligament, stripping of the floor of the omental bursa, circumferential resection of hepatogastric ligaments and extended radical right hemicolectomy. Subsequently, EIPL was performed with 10 L of saline in the abdominopelvic cavity. At the end of the surgery, primary ileo-transverse colon anastomosis was performed without stoma establishment. The overall cancer resection score was 0 and the operative duration was 285 minutes. Total blood loss was 1180 mL, and blood component transfusion (total packed red blood cells = 4 units, fresh frozen plasma = 8 units) was required.

OUTCOME AND FOLLOW-UP

The patient experienced an uneventful recovery with no postoperative complications and was

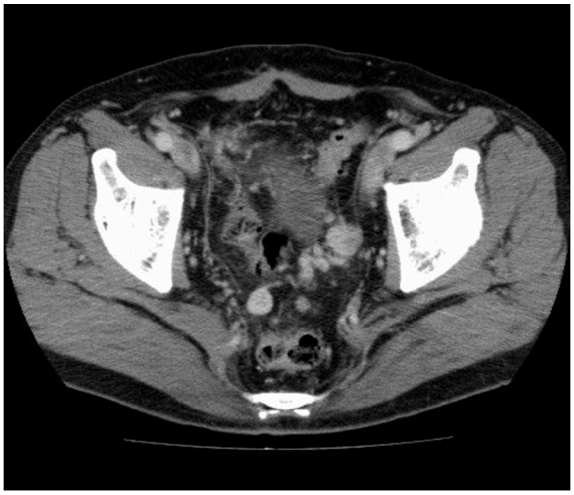

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Figure 1 Image of abdominal computed tomography. Suspected carcinomatosis or sarcomatosis was noted in the pelvis with no evident ascites.

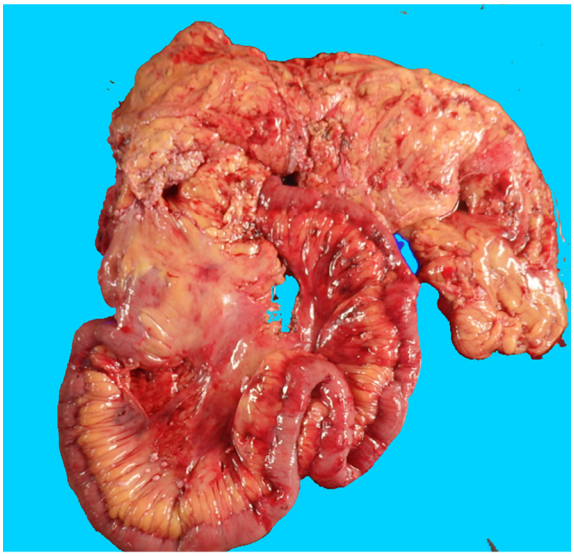

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Figure 2 Intestine specimen after extended radical right hemicolectomy. Multiple whitish tumor nodules seeding over the visceral peritoneum of the partial ileum and colon.

discharged 13 d after surgery. Neither chemotherapy nor radiation therapy was administered. Repeat CT imaging was performed for every 4 mo during the first 2 years of follow-up. He has been in good general condition without evidence of recurrence or metastasis 28 mo after our surgical management. Subsequent CT imaging every 6 mo through the subsequent 5 years is planned.

DISCUSSION

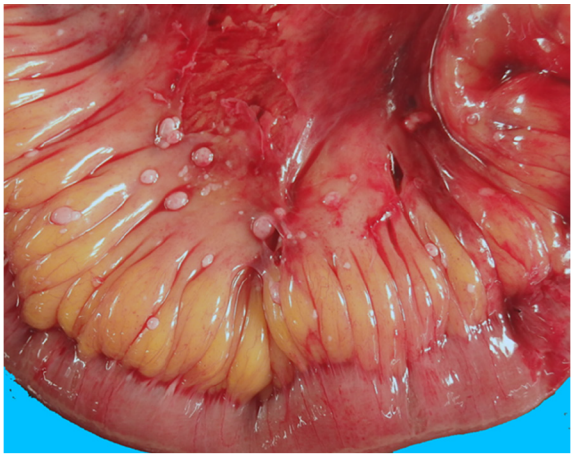
SFT was first described by Klemperer and Rabin in 1931[1] and was originally an exclusive diagnosis of pleural neoplasms[3]. Later, some SFTs were recognized as originating in various extra-thoracic sites[4]. They are predominantly localized in the pleura, followed by the head and neck, and are seldom present in the abdomen or pelvis[1,5-7]. To date, fewer than 1,000 cases of SFT in the pleura[8], as well as fewer than 100 cases of SFT in the abdomen or pelvis[9] have been reported. SFT of mesentery origin is extremely rare. We searched the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) and reviewed the relevant papers published. Of these reports of SFTs originating from the mesentery retrieved from the literature, we only found 13 cases (Table 1)[2,10-20].

SFT is predominant in the sixth and seventh decades of life with no difference in sex distribution[5, 21]. To date, no definite causative/contributing etiology or genetic predilection exists for this tumor[8].

Table 1 Patients with mesentery solitary fibrous tumors

Patient	Age	Sex	Symptom	Tumor location	Tumor size in cm	Management	Follow-up (F/U) in mo	Recurrence during F/U	Ref.
1	33	M	NM	Mesentery	NM	Operation	NM	NM	[10]
2	68	M	Abdominal pain	Sigmoid mesentery	18	Operation	NM	NM	[11]
3	53	M	Abdominal pain	Ileum mesentery	22	Operation	1	NM	[12]
4	73	M	Abdominal pain	Mesentery	25	Operation	NM	NM	[13]
5	71	M	Abdominal mass	Mesentery	16	Operation	12	No	[14]
6	41	M	Abdominal pain	Mesentery	23	Operation	7	No	[15]
7	26	M	Abdominal distension	Ileum mesentery	12	Operation	18	No	[16]
8	36	M	Abdominal pain	Rectum mesentery	16	Pre-op radiotherapy → operation	NM	NM	[17]
9	59	F	Abdominal pain	Mesentery	21	Operation	9	Yes	[18]
10	61	M	No symptom	Jejunum mesentery	3	Operation	2	NM	[19]
11	32	M	Abdominal mass	Sigmoid mesentery	13	Operation	252	No	[19]
12	41	M	Abdominal mass	Ileum mesentery	10	Operation	NM	NM	[20]
13	65	M	Abdominal pain	Ileum mesentery	26	Operation	12	No	[2]
14	69	M	No symptom	Sarcomatosis (rectum mesentery recurrence related)	Multiple	Operation (cytoreductive)	28	No	Our patient

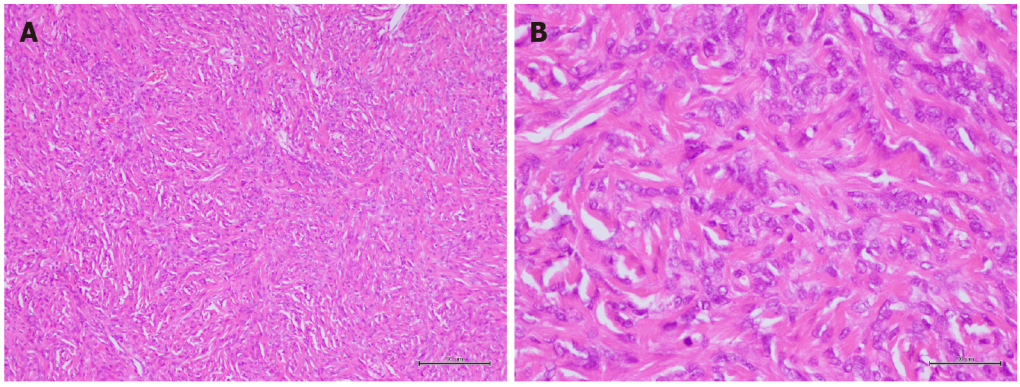
F: Female; NM: Not mentioned; M: Male.



DOI: 10.5306/wjco.v13.i4.303

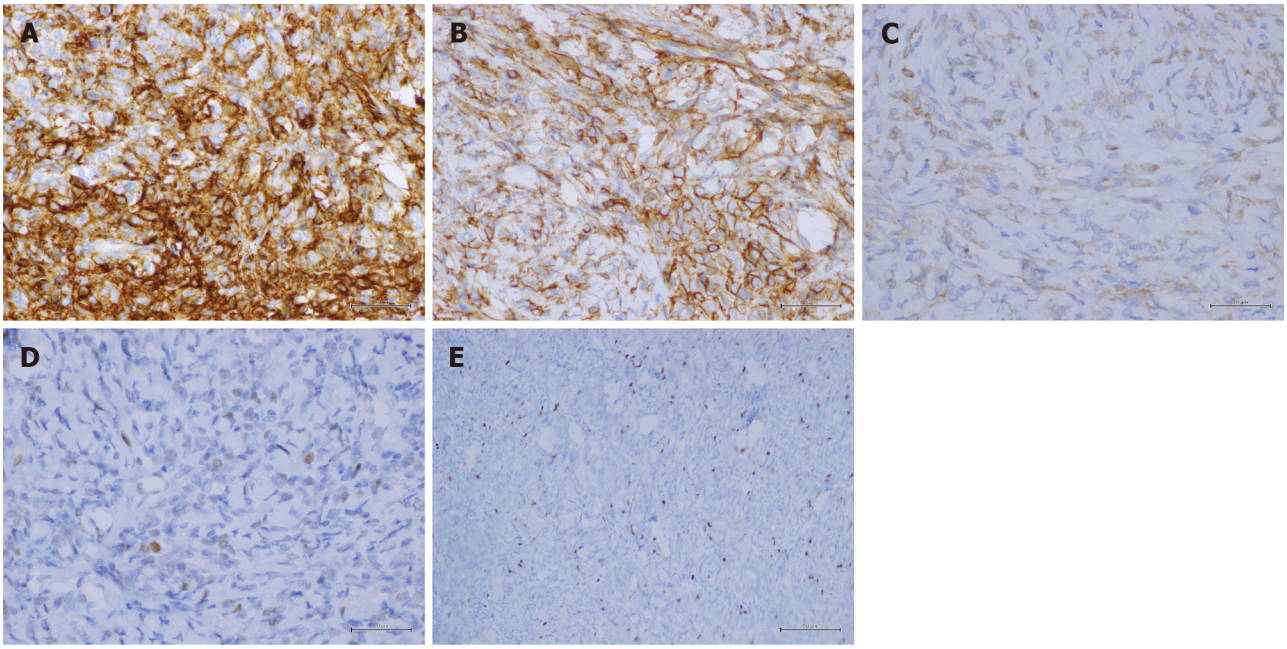
Figure 3 Image of an ileum specimen. Multiple whitish tumor nodules seeding over the visceral peritoneum of the distal ileum.

Patients with SFT may be asymptomatic at presentation[8]. However, extra-pleural lesions may cause clinically related symptoms to the tumor site. Systemic symptoms such as hypoglycemia (caused by insulin-like growth factor II secretion from the tumor[22]), arthralgia, osteoarthritis and clubbing have been documented[21]. These symptoms usually resolve upon tumor removal. In the present case, recurrent SFT was incidentally detected during regular follow-up and the patient did not exhibit any



DOI: 10.5306/wjco.v13.i4.303

Figure 4 Microscopic features. The heterogeneous cell population comprised of mostly spindle cells with fibrous collagen proliferation as well as various other cell populations exhibiting patternless or storiform growth. No tumor necrosis, nuclear polymorphism, or cellular atypia was noted. The nuclear mitotic index was 4 mitoses/50 high-power fields (A: × 100 original magnification; B: × 400 original magnification).



DOI: 10.5306/wjco.v13.i4.303

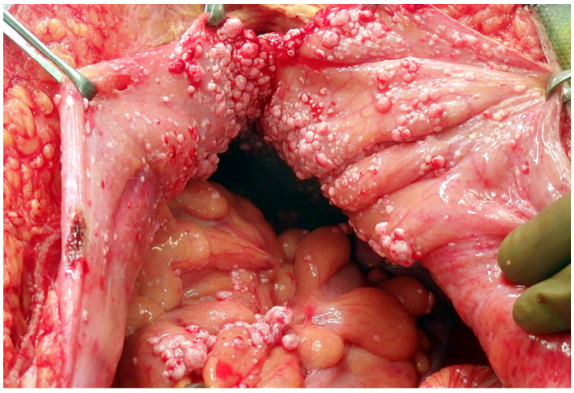
Figure 5 Immunohistochemical staining. A-E: The lesion showed diffuse strong staining for CD34 (× 400 original magnification) (A); CD99 (× 400 original magnification) (B); Bcl-2 (× 400 original magnification) (C); mildly positive immunoreactivity for p53 (× 400 original magnification) (D); and a Ki-67 mitotic proliferative index of approximately 5% (× 100 original magnification) (E).

symptoms.

SFTs do not display any tumor markers. Fluorodeoxyglucose positron emission tomography (FDG-PET) manifestations of SFT have been sparsely reported in the literature and clinical use of FDG-PET imaging for SFT detection remains unclear[23,24]. Cardillo *et al*[24] showed a weak association between malignancy and FDG-PET uptake in their eight-case study. However, we could acquire important information about the lesions or detect postoperative recurrence according to the radiological examinations, such as type-B ultrasonic, CT and magnetic resonance imaging scans[25,26].

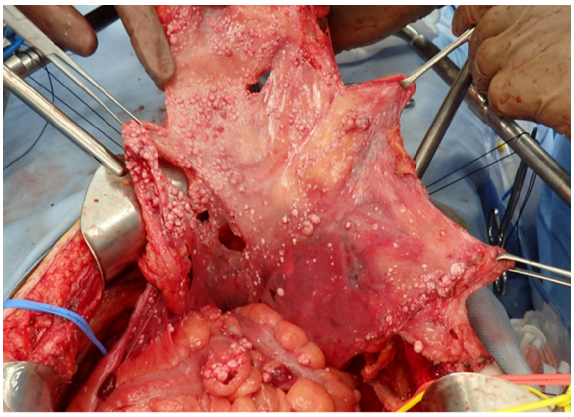
Type-B ultrasonic examination could show intraperitoneal SFT as a hypoechoic but sometimes as a heterogeneous lesion. Besides, this lesion might exhibit flow during Doppler imaging due to its characteristic of high vascularity[23].

On CT imaging, we could note that some well-circumscribed SFT lesions compress adjacent tissues and organs and even cause colon obstruction, urinary retention or bilateral hydronephrosis[27,28]. After contrast use, larger lesions would present with scattered intratumoral foci of hypoenhancement or non-enhancement in the necrosis, hemorrhage or cystic change regions. On the contrary, the homogeneous enhancement would be typically demonstrated in the smaller lesions[29]. Besides, it could provide information on the local extent of disease and the presence of distant metastases. However, the malignancy potential could not be decided according to this radiological distinction.



DOI: 10.5306/wjco.v13.i4.303

Figure 6 Image of the pelvis during operation. Multiple whitish nodules were noted to be seeded over the parietal peritoneum and visceral peritoneum of the partial ileum and colon as well as the urinary bladder, with no ascites in the pelvis.



DOI: 10.5306/wjco.v13.i4.303

Figure 7 Peritonectomy during cytoreductive surgery. Total anterior parietal peritonectomy, bilateral subphrenic peritonectomy, and complete pelvic peritonectomy (including the visceral peritoneum covering the urinary bladder) were performed.

T1 weighted signal enhancement of MRI imaging could identify subacute hemorrhage of the lesion with the characteristic of intermediate heterogeneous signal intensity. On T2 weighted images, flow voids could also be noticed as areas of heterogeneous low-signal intensity[30]. Besides, intense heterogeneous enhancement of the lesion is noticed in the arterial phase of Gadolinium-enhanced, fat-suppressed T1 weighted images and progressive enhancement in the venous phase[29].

Definite diagnosis of SFT is confirmed through histopathology and immunohistochemical staining. Histopathologically, most SFTs have a patternless or storiform architecture characterized by the coexistence of hypo- and hypercellular areas separated by fibrous stroma, with hemangiopericytoma-like branching blood vessels[31]. Studies of immunohistochemical and electron microscopic aspects have proven that SFTs grow from fibroblastic or myofibroblastic cells of the mesothelium[32,33]. Although differential diagnosis includes other spindle cell tumors, SFT has a unique staining pattern (positive for STAT6, CD34, CD99 and Bcl-2). Among these immunohistochemical markers, STAT6 is probably the most sensitive and specific marker of SFT, because most SFTs have an NAB2-STAT6 fusion gene, which is specific to this tumor type[34]. By contrast, SFTs generally exhibit negative reactivity to cytokeratin, alpha-SMA, S-100, CD31 and c-kit[35]. In our patient, intense diffuse strong staining for CD34, CD99 and Bcl-2 was detected, and SFT was confirmed, although the STAT6 marker was not examined.

SFTs have historically been considered indolent tumors that rarely metastasize in the literature. However, their behavior is unpredictable, with a broad spectrum of biologic behavior. Most SFTs behave benignly after complete surgical resection; however, some have been reported to behave aggressively either through local recurrence or distant metastasis[35]. The 2013 World Health Organization classification of SFT defines malignant forms as having a large tumor size (longer than 5 or 10 cm), sessile lesions, hypercellularity, and increased mitotic index (> 4 mitoses/10 high-power fields) [36,37], with cytological atypia, nuclear pleomorphism, tumor necrosis, infiltrative margins or hemorrhage[38]. However, discrepancies of morphological malignancy and clinical malignancy have been observed for SFT[3]. Some experts have advocated that malignant transformation with dedifferen-

tiation of tumor cells might contribute to such discrepancies[39]. Malignant transformation is of two types: malignant or high-grade SFT and the *de novo* occurrence of malignancy[21]. In our case, malignancy may be the recurrence of the previous tumor.

Immunohistochemistry for some proteins may clinically provide hints of SFT malignancy[3]. Takizawa *et al*[40] noted no tumor recurrence in cases with positive immunostaining for both CD34 and Bcl-2. Deprivation of CD34 and Bcl-2 immunoreactivity was observed in the component with malignant transformation[39,41]. In benign SFTs, p53 immunoreactivity was not detected. However, p53 immunoreactivity has been confirmed in morphologically and clinically malignant SFT[3,41]. According to these criteria, our present case had borderline benign (diffuse strong immunostaining for CD34, CD99 and Bcl-2) and malignant (mildly positive p53 immunoreactivity) pathologic characteristics. However, due to the clinical presentation of intraperitoneal sarcomatosis, recurrence remains a concern despite the complete removal of the seeding tumors achieved for our patient.

No consensus has been reached for the treatment guidelines for SFTs in this particular location (rectal mesentery) because of their scarcity and the confusion regarding their pathological confirmation[14]. However, complete surgical resection is the standard and mainstay treatment for most SFTs, including abdominopelvic SFTs and those that arise in other organs, regardless of histologic subtype[38]. The most essential prognostic factor is surgical resectability because complete resection of the tumor is curative in more than 90% of cases[1,42]. Poor prognosis is observed in patients with incomplete resection[43]. However, SFTs are hypervascular, complicating surgical resection[9] regardless of the tumor location.

Local recurrence or metastasis develops in 12%-22% of cases[44]. Patients with extra-thoracic SFTs are statistically more likely to develop the metastatic disease than those with thoracic SFTs[45]. Adjuvant chemoradiotherapy is not widely practiced or accepted as the standard of care[46]. Some experts have suggested radiotherapy or adjuvant chemotherapy, although poor outcomes have been reported for these treatments[43]. Some experts have used antiangiogenic agents as a therapeutic strategy in recent years. However, similar to the finding of the low response rate in standard chemotherapy, progression-free survival appeared similar between cytotoxic chemotherapy and antiangiogenic agents[47]. Thus, improved systemic therapies are required for metastatic or unresectable diseases.

To date, no standard therapy has been established for inoperable SFTs[4]. SFTs are generally regarded as chemoresistant tumors[48]. Our patient's Ki-67 mitotic proliferative index was only approximately 5%, suggesting that it was a type of low-grade sarcoma; we proposed that chemotherapy would have little effect. Although radiotherapy was another option, radiotherapy was not conducted for our patient because of the side effect of radiation injury on the small bowel related to the proposed large area of radiation and adhesion after two episodes of laparotomy. Instead, we sincerely believed that EIPL could effectively lower the amount of intra-abdominal free cancer cells, and it is a preventative strategy for further peritoneal recurrence. Moreover, we performed complete *en bloc* surgical resection with negative margins through CRS for this "inoperable" patient, which is of paramount importance.

Predicting the aggressive clinical behavior of SFTs is difficult[21,35]. Late recurrence or metastasis may develop even when the SFT has been identified as benign[49]. While surgical resection continues to be the initial modality for treating malignant SFTs, the utility of adjuvant chemotherapy or radiation is still unknown given that most data is based on small case series. Thus, no guidelines exist for determining the modality and frequency of post-treatment surveillance[31]. Long-term and regular surveillance is mandatory[50]. Some experts have suggested that long follow-up periods (≥ 15 years) should be maintained with closer follow-ups during the first 2 years[49], particularly for patients with high-risk features.

CONCLUSION

In conclusion, this article reported the first case of rectal mesentery SFT with postoperative recurrence and sarcomatosis. Instead of adjuvant chemotherapy or radiotherapy, we performed EIPL and CRS, and no evidence of recurrence was found during the 28-mo follow-up period.

FOOTNOTES

Author contributions: Chiu CC collected clinical records, wrote, revised and submitted the draft; Ishibashi H, Wakama S and Liu Y assisted with the operation and cared for the patient; Hao Y and Liu Y assisted with photo management; Hung CM provided critical opinion; Lee PH revised the manuscript; Rau KM and Lee HM searched the related references during the preparation process; Yonemura Y performed the operation, provided critical feedback, supervision, and opinion of this study.

Informed consent statement: Written informed consent for the publication of this case report was obtained from the patient.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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