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Editorial Board Member of *World Journal of Clinical Oncology*, Jin Wang, Ph.D. Professor, Shanghai Public Health Clinical Center, Fudan University, No. 2901 Caolang Road, Jinshan District, Shanghai 201508, China. jinwang@shaphc.org

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REVIEW

Systems biology and OMIC data integration to understand gastrointestinal cancers

Iasmin Moreira Costa Bispo, Henry Paul Granger, Palloma Porto Almeida, Patricia Belini Nishiyama, Leandro Martins de Freitas

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Iasmin Moreira Costa Bispo, Henry Paul Granger, Patricia Belini Nishiyama, Leandro Martins de Freitas, Núcleo de Biointegração, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45.029-094, Bahia, Brazil

Palloma Porto Almeida, Division of Experimental and Translational Research, Brazilian National Cancer Institute, Rio de Janeiro 20231-050, Brazil

Corresponding author: Leandro Martins de Freitas, BSc, MSc, PhD, Professor, Núcleo de Biointegração, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Rua Rio de Contas, 58, Bairro Candeias, Vitória da Conquista 45.029-094, Bahia, Brazil.
leandromartins@ufba.br

Abstract

Gastrointestinal (GI) cancers are a set of diverse diseases affecting many parts/organs. The five most frequent GI cancer types are esophageal, gastric cancer (GC), liver cancer, pancreatic cancer, and colorectal cancer (CRC); together, they give rise to 5 million new cases and cause the death of 3.5 million people annually. We provide information about molecular changes crucial to tumorigenesis and the behavior and prognosis. During the formation of cancer cells, the genomic changes are microsatellite instability with multiple chromosomal arrangements in GC and CRC. The genomically stable subtype is observed in GC and pancreatic cancer. Besides these genomic subtypes, CRC has epigenetic modification (hypermethylation) associated with a poor prognosis. The pathway information highlights the functions shared by GI cancers such as apoptosis; focal adhesion; and the p21-activated kinase, phosphoinositide 3-kinase/Akt, transforming growth factor beta, and Toll-like receptor signaling pathways. These pathways show survival, cell proliferation, and cell motility. In addition, the immune response and inflammation are also essential elements in the shared functions. We also retrieved information on protein-protein interaction from the STRING database, and found that proteins Akt1, catenin beta 1 (CTNNB1), E1A binding protein P300, tumor protein p53 (TP53), and TP53 binding protein 1 (TP53BP1) are central nodes in the network. The protein expression of these genes is associated with overall survival in some GI cancers. The low TP53BP1 expression in CRC, high EP300 expression in esophageal cancer, and increased expression of Akt1/TP53 or low CTNNB1 expression in GC are associated with a poor prognosis. The Kaplan Meier plotter database also confirmed the association between expression of the five central genes and GC survival rates. In conclusion,

GI cancers are very diverse at the molecular level. However, the shared mutations and protein pathways might be used to understand better and reveal diagnostic/prognostic or drug targets.

Key Words: Gastrointestinal cancers; Genome; Cellular pathways; Protein-protein interaction; Prognosis; OMIC data

Core Tip: We highlight the genomic mutations and cellular pathways in gastrointestinal (GI) cancers. These are responsible for the cell's behavior, allowing unlimited cell replication and invasion of other tissues. Using the STRING database, we found that Akt1, catenin beta 1, E1A binding protein p300, tumor protein p53 (TP53), and TP53 binding protein 1 are central nodes in the GI cancer protein network. Their expression is associated with poor survival in some GI cancers, which was confirmed by the Kaplan Meier plotter database. This information points to crucial and shared aspects of the most frequent GI cancers.

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INTRODUCTION

In 2020, the number of cancer cases in the digestive system was 5 million and 3.5 million deaths worldwide[1,2]; the physiologic system with the highest number of cases and among the highest percentage of deaths[3] (Table 1). The cancer types in this system can be classified as organ origin and cell type. The most frequent are esophageal cancer (EC), gastric cancer (GC), liver cancer, pancreatic cancer, and colorectal cancer (CRC)[2,3]. GC, liver cancer, and CRC are among the most common causes of cancer deaths annually[2]. Gastrointestinal (GI) cancers also have specific molecular changes in genetic/genome, epigenetics, gene expression, and cellular pathways contributing to tumor behavior. This information might be helpful in diagnosis, prognosis, and new drug development.

EC

EC has two subtypes: esophageal squamous cell cancer (ESCC) and esophageal adenocarcinoma (EAC)[4]. The incidence of ESCC increases globally and predominantly in Eastern Asia and Eastern/Southern Africa[4-7]. However, the ESCC decreases while EAC increases in the United States and a few European countries[5]. The ESSC and EAC incidence differences are geographically observed in sex and ethnic patterns[4,5].

There is also a well-established genetic factor associated with sex, and although it is still not well understood, it is known that the ratio between men to women is 2.5-4.4:1[4,6]. Studies indicate a protective effect of female sex hormones, including a lower risk of cancer for women previously breastfed. Nevertheless, environmental factors also influence this prevalence as, for example, men tend to abuse alcohol and tobacco, which are primary risk factors for the manifestation of EC[4,8].

The risk factors for ESCC are smoking, a low vegetables/fruit diet, and alcohol consumption[9], whereas for EAC, the risk factors are obesity and gastroesophageal reflux disease[9,10]. When alcohol and tobacco are used together, there is an increased risk. This combination is believed to be responsible for 70%-90% of cases, mainly because they cause chronic irritation and inflammation of the esophageal mucosa. In the case of obesity, the greater the abdominal circumference, the greater the intra-abdominal pressure increases the probability of developing gastroesophageal reflux[4,6,11-14].

Early diagnosis is fundamental to improving prognosis. However, dysplasia usually is asymptomatic[4,11,12,15] and manifests at an average age of 67 years, when there is a high incidence of metastasis, mainly in lymph nodes, liver, lungs, and bones[11,12]. These features make the EC an aggressive malignancy with a 15%-23% 5-year survival rate[9,10].

GC

GC has the fourth highest incidence and mortality worldwide[1,2]. The primary risk factors for GC are genetics, diet (high amount of salt and low consumption of fruits and vegetables), *Helicobacter pylori* or Epstein–Barr virus infection, smoking, alcohol intake, and sedentary life[16-19]. The principal risk factor for GC is *H. pylori* infection, accounting for 80% of the cases. Although the incidence of *H. pylori* infection is decreasing, GC deaths are still high. While the primary risk factor is *H. pylori* infection, many

Table 1 Gastrointestinal cancer data

Tissue	Incidence[1]	Mortality[1]	ASR incidence[1]	ASR mortality[1]	5-yr survival rate
Colorectum	1931590	935173	2.3	0.94	60%-70.9%[1]
Esophagus	604100	544076	0.78	0.68	14.6%-23.2%[1]
Liver	905677	830180	1.1	1.0	18%[3]
Pancreas	495773	466003	0.55	0.51	7.9%-14.3%[1]
Gastric	1089103	768793	1.3	0.90	20.8%-32.8%[1]

Age-standardized rate in 100000 people. ASR: Age-standardized rate.

genes are associated with GC[16,18,20], and some genetic variations that can interact with *H. pylori* increase the GC risk[21,22]. The incidence of GC is higher in males (1.32-2.2) and in Eastern/Central Asia and Latin America[16,18].

Obesity can induce inflammation of the stomach lining through tumor necrosis factor (TNF), interleukin 6 (IL-6), and C-C motif chemokine ligand 2. By contrast, a diet rich in fruits and vegetables has proven to be an ally in cancer prevention because it contains numerous antioxidants that prevent metabolic damage, especially vitamin C[18].

A relevant factor in the decline of GC has been the successful prevention and treatment of infections by *H. pylori*[18]. According to the International Agency for Research on Cancer, this is a carcinogen from group 1, meaning there is sufficient evidence of human carcinogenicity[23,24]. *H. pylori* infection affects more than half of the world's population, and its eradication may considerably decrease the chances of stomach cancer. However, it would increase the chances of esophageal adenocarcinoma. However, it is unknown how this esophageal protection mechanism occurs[18,24,25].

Hepatocellular carcinoma

There are about 1 million new cases of liver cancer each year, with hepatocellular carcinoma (HCC) responsible for most patients (90%) and the second most common cause of cancer death worldwide[26,27].

HCC presents a poor prognosis due to a late diagnosis. Multiple different tumors may occur in a single patient, leading to intra-tumor and intra-patient heterogeneity, which makes it difficult to establish a treatment line for HCC[27,28]. This heterogeneity can be caused by environmental factors and genomic and biological changes caused by the tumor lesion[27].

Cirrhosis and non-alcoholic fatty liver disease are risk factors associated with alcohol abuse and obesity that can lead to the onset of HCC. Genetic factors such as diabetes, exposure to carcinogens (aflatoxins), and biological factors, especially hepatitis virus infection, can be highlighted[28].

The HCC development is a multistep process. It starts as a chronic liver disease that leads to inflammation, fibrosis, or aberrant hepatocyte regeneration. This set of conditions can progress to cirrhosis and later malignancy. The causes of this inflammation can be hepatitis B virus/hepatitis C virus infection, fatty liver disease, excessive alcohol intake, and aflatoxin consumption[26,29]. The outcome of this inflammation can be influenced by epigenetics and the immunological response in the tumor microenvironment to create a preneoplastic lesion until producing cells with highly proliferative, invasive, and survival skills[26].

The geographic regions most affected by HCC are Southeast Asia and sub-Saharan Africa, where there is endemic infection by the hepatitis virus and high exposure to aflatoxin, which are responsible for 70%-90% of cases in these places[28]. Currently, there is no line of therapy based on biomarkers suitable for HCC, although some candidate genes already exist[30].

Pancreatic cancer

Pancreatic cancer, characterized by pancreatic ductal adenocarcinoma (PDAC), is the seventh leading cause of cancer-related deaths worldwide[31]. Its incidence is higher in Europe, followed by North America and Oceania, mainly in people over 70-years-old. Incidence and mortality increase with aging and are more common in men than women[32].

It is highly fatal because it presents aggressive growth and a lack of symptoms in the disease's initial stage. As the tumor progresses, a picture of nonspecific symptoms begins, including jaundice, weight loss, abdominal pain, and fatigue[32]. About 80% of diagnoses are made in the advanced clinical stages, leading to a low 5-year prognosis of survival after surgery[33]. Surgical resection is the single strategy capable of curing pancreatic cancer. Besides, using chemotherapy concomitantly improves survival rates [34].

The main risk factors for the onset of pancreatic adenocarcinoma are smoking, alcohol, obesity, *H. pylori*, and type 2 diabetes[34]. Other factors, such as fat infiltration into the pancreas, have been associated with developing intraepithelial neoplasms. Pancreatic cancer can also arise from genetic

factors that can cause familial syndromes, such as Peutz-Jeghers syndrome[31]. A history of pancreatic cancer in first-degree relatives leads to a 2- to 3-fold increase in incidence risk due to inherited genetic predispositions[35].

CRC

CRC is the second most deadly cancer worldwide (1.3 million) and is the third leading cause of cancer-related deaths (540000) annually[2]. CRC is responsible for about 10% of cancer-related deaths worldwide, and in the last 45 years, there has been an increase in this mortality rate[36]. Its incidence is higher in developed countries such as Australia and New Zealand, followed by countries in Europe, East Asia, and North America. The frequency increases as individuals age, usually appearing in people over 50 years[37].

The tumor can originate in both the colon and the rectum. However, usually fuse because they have similar clinical and biological characteristics, with adenocarcinoma as the primary cell type of the tumor [37]. Many factors are associated with this increase in the diagnosis/mortality rate, such as an increase in life expectancy, poor dietary habits, and risk factors: smoking, red meat consumption, sedentary lifestyle, obesity, alcohol intake, and genetics[36,38-40]. These factors change the genetic/molecular in colon epithelial cells deactivating suppressor tumor genes and activating oncogenes to create aggressive and malignant behavior[40].

In the early stages, the disease has no clinical manifestation. The patient may be asymptomatic for years, but as the disease progresses, it advances to a more severe condition, with symptoms such as changes in intestinal motility, hidden or evident colorectal bleeding, cramps, loss of weight, weakness, and fatigue are manifesting[37].

GENOME DATA IN GI CANCERS

EC

There are several generalized genomic changes when esophageal carcinoma cells are analyzed. The most evident is a somatic mutation in tumor protein p53 (TP53) that appears in about 83% of cells. The p53 protein is a tumor suppressor and one of the most important transcription factors for regulating proliferation, apoptosis, autophagy, and cell cycle. However, this gene has a high mutation percentage in cancer cases, reaching 75% in tumor cells[12,41].

There are also changes in genes that control cell cycle and differentiation, including cyclin-dependent kinase inhibitor 2A (CDKN2A), nuclear factor erythroid derived 2-like 2, checkpoint kinase 1/2, and Notch1/3. Others may appear overexpressed such as cyclin D1 (CCND1) and CDK4/6[12,42-44]. The B cell translocation gene 3 protein can regulate the cell cycle's progression; its low expression is related to the appearance of esophageal adenocarcinoma, and its expression level is directly correlated with lymph node metastasis[12,45].

The presence of mutations in the growth factors in cancer cells is well documented in the literature. Overexpression of epidermal growth factor receptor (EGFR) in carcinoma cells is associated with lymph node metastasis, and its expression level also influences the patient's clinical stage. Another growth factor correlated with esophageal carcinoma is vascular endothelial growth factor C (VEGFC), encoded by the Fms related receptor tyrosine kinase 1 gene, and its levels in the tissues correlate with tumor stages and metastasis state[12,41].

Using next-generation sequencing, frequent mutations in carcinoma cells have been observed in the lysine methyltransferase 2D (KMT2D), SET domain containing 2 histone lysine methyltransferase, Notch1, retinoblastoma 1, CDKN2A, BRCA1-associated protein-1, forkhead box O3, and MutS homolog 6 (MSH6) genes compared to adenocarcinoma. It was also observed that some copy number variations in fibroblast growth factor 3 (FGF3), FGF4, FGF19, and CCND1 are more expressed in carcinoma compared to adenocarcinoma[46].

GC

Besides the infectious causes, the genetic data have helped to classify the GC into three additional subtypes: microsatellite instability (21.7%), genome stability (19.6%), and chromosome instability tumors (49.1%)[47].

Although infection is environmental, GC caused by infection is associated with genetic modifications such as phosphoinositide 3-kinase catalytic subunit (PIK3CA) mutations or gene amplification of Janus kinase (JAK), programmed death-ligand 1/2, or ERBB2. The infectious pathogen can also induce epigenetic modifications in this type of GC as DNA methylation in the phosphatase and tensin homolog (PTEN) gene promoter[48] and tumor-suppressor gene adenomatous polyposis coli (APC)[49]. Microsatellite instability is more associated with many truncating or missense mutations. The genes with the highest number of mutations in microsatellite instability GC are EGFR, ERBB3, KRAS/NRAS, and PIK3CA[50].

Genomically stable tumors present many mutations, especially genes well associated with cancer. The gene Ras homolog family member A works as signal transduction inducing cell proliferation, actin cytoskeleton structure, and cell movement associated with metastasis[51,52]. The genes claudin 18 and Rho-GTPase-activating proteins are frequently translocated in genomically stable GC tumors. The gene cadherin 1 (CDH1) encodes a cell-cell adhesion protein, which is also currently mutated in this type of cancer[53]. Furthermore, CDH1 has a role in cell proliferation, invasive behavior, and migration[54-56]. In the CDH1 gene, autosomal dominant mutations increase stomach cancer risk, especially when one of its copies is lost, generating a scenario of diffuse hereditary GC[18].

The chromosomal alterations involve gene amplification of EGFR, ERBB2/3, KRAS/NRAS, and RASA1; gene deletion of PTEN. These genetic modifications probably would result in gene activation or deactivation, which would result in tumor cell phenotypes. EGFR, ERBB2/3, JAK2, FGFR2, MET, KRAS/NRAS, and PIK3CA are predicted to be active, while RASA1, PTEN, and PIK3R1 would be inactive.

HCC

Numerous genetic changes in HCC cells, including mutations, changes in the number of copies, and chromosomal rearrangements, lead to a very complex genomic picture. Its complexity is further aggravated when etiological factors that precede the tumor development for years are considered[57].

Some genes play a fundamental role in cancer development, which is why they appear more frequently as TP53, MYC, WNT, and CTNNB1. Also highlighted are genes related to the cell cycle, such as CCND1 and CDKN2A[57].

A study integrating RNA sequencing, DNA sequencing, T cell receptor sequencing, and single nucleotide polymorphism array was carried out to investigate the space-time interactions between cancer and immune cells. A difference in the interaction of the adaptive immune system was detected in different regions of the same tumor. The TP53 and CTNNB1 genes expressed clonal mutations. High-level amplifications have been reported for CCND1, FGF19, and VEGFA. Mutations related to environmental risk factors such as smoking and alcohol were found in telomerase reverse transcriptase (TERT), CTNNB1, TP53, axin 1, and AT-rich interactive domain-containing protein 1A (ARID1A). There were also mutations without an apparent etiological factor in TERT, KMT2B, CCNA2, and CCNE1[58].

HCC results from of a multistep process involving genetic, epigenetic, and transcriptomic interactions. Among these interactions, epigenetics is among the most affected, leading to profound gene expression changes that can facilitate tumor formation The most common form of epigenetic silencing of tumor suppressor genes is hypermethylation of DNA. This epigenetic change usually occurs in CpG islands of gene-promoting regions such as deleted in liver cancer 1, tissue factor pathway inhibitor 2, CDKN2A, and PTEN[30].

Pancreatic cancers

The etiology of PDAC is mainly related to genetic predisposition, environmental factors such as smoking, obesity, and poor nutritional diet. These factors lead to chromosomal instability, affecting cell cycle pathways, chromatin remodeling, WNT, MYC, NOTCH signaling, and DNA damage repairs[35,59]. Among the mutated genes, the one that appears most frequently is KRAS[60]. It is also possible to highlight mutations in MLH1, MSH2, PMS2, and MSH6 responsible for Lynch Syndrome and mutations in the germ lines of PALB26, 11, 12, and ATM7, 12, 13[35].

Pancreatic cancer genome analyses showed a homogenous profile with somatic mutations in a few genes shared KRAS, TP53, CDKN2A, and SMAD4. However, other less frequent genes are also involved including mitogen-activated protein kinase kinase 4 (MAP2K4), lysine demethylase 6A, ring finger protein 43, ARID1A, transforming growth factor beta receptor 2 (TGFβR2), GNAS, Ras responsive element binding protein 1, and Polybromo 1[61-63]. These mutations can vary, and it is observed that non-silent mutations, gene amplification (> 8 copies, deletions, and structural variants)[63]. The set of genes that appear often mutated in pancreatic cancer plays a role in oncogenes, DNA damage repair, and chromatin modification[61,64]. The pancreatic cancer genome has chromosomal rearrangements classified into four subtypes: stable, locally rearranged, scattered, and unstable[61]. The mutation event more frequent is non-silent single nucleotide variants and copy number change (loss)[61]. The pancreatic cancer stable subtype was found in 20% of samples and had very few structural rearrangements (< 50 structural rearrangements) and more chromosomal mutations (aneuploidy). The locally rearranged subtype was found in 30% of samples with a high number of structural rearrangements (> 200) in a few chromosomes (three or fewer chromosomes), and there is more gene amplification. The scattered subtype is the most frequent (36% of samples) and has 50-200 structural rearrangements. Besides, the mutation type gene amplification is more frequent than in the other subtypes. The unstable subtype is less frequent (14% of the samples) and has the highest number of structural rearrangements (> 200 structural rearrangements), such as intrachromosomal, translocations, inversion, deletions, and duplication. Besides the frequent mutation described in pancreatic cancer, the unstable subtype is also associated with BReast CAncer gene 1 (BRCA) pathway mutations (BRCA1, BRCA2, and PALB2)[61].

CRC

Most CRC cases are sporadic (70%), and only 30% are inherited[38]. The genes most affected are DNA mismatch-repair genes, APC, or mutY DNA glycosylase[39,40]. The DNA mismatch-repair proteins malfunctioning creates the condition of genetic mutation accumulation and tumor cells rising.

The CRC has three genetic subtypes based on their genomic alterations. The genomic alterations are chromosome or microsatellite instability or epigenetic changes of CpG islands (CpG island methylator phenotype - CIMP)[65,66]. Chromosomal instability is the most frequent in CRC, present in 71%-85%[65,66]. The genetic differences also lead to overall survival differences in CRC. The CIMP subtype is associated with poor prognosis, followed by chromosome instability, and microsatellite instability showed the best survival[66-68]. The CIMP's poor prognosis indicates the importance of CpG methylation dysregulation in CRC tumorigenesis. The methylation dysregulation might affect the proto-oncogenes and tumor-suppressor genes. The worst prognosis in the CIMP subtype indicates that a different approach is necessary to deal with molecular modifications. Epigenetic modifications can also be therapeutic targets to improve the treatment.

The genetic/genomic diversity in GI cancers shows the importance of molecular characterization to improve the treatment and prognosis.

PATHWAYS

The cellular pathways show the main activities and functions present in a cell when proteins work together. The cancer pathways are responsible for the cell's behavior, allowing unlimited cell replication, survival, and tissue invasion. The pathways also are responsible for the molecular changes driving tumorigenesis. Understanding how a set of proteins work together to develop a cancer cell might point to the target proteins to block these processes.

The pathways most present among the GI cancers discussed here are apoptosis, focal adhesion, and p21-activated kinase (PAK), PI3K/Akt, TGF-β, and Toll-like receptor (TLR) signaling pathways (Table 2)[69-93].

Apoptosis plays a role in maintaining the balance in cell division and death during development and life. The unbalance of apoptosis leads to survival and uncontrolled division in tumorigenesis[94]. The apoptosis pathway is triggered by irreparable DNA damage, and it has many proteins that can fail and be blocked to inhibit cell death. The intrinsic process is mediated by mitochondria releasing cytochrome C after BH3 proteins activate B-cell lymphoma 2 (Bcl-2)-associated X protein and Bcl-2 homologous antagonist/killer. The cytochrome C and apoptotic protease activating factor 1, and caspase-9 create the apoptosome to continue the apoptosis process. The extrinsic process has death receptor ligands (cluster of differentiation 95 ligand [CD95L], TNF-related apoptosis-inducing ligand, and TNFα), death receptors, and associated proteins (Fas-associated death domain and TNF receptor 1-associated death domain protein) that transduce the death signal until caspase-8. Both intrinsic and extrinsic processes act on caspase-3/6/7 to induce the apoptosis cascade. Cell death by apoptosis results in a non-inflammatory process, which attracts research to the development of therapies that use apoptosis to treat cancer[95-97].

The PAK1 signaling pathway has six members divided into two groups and induces proliferation, survival, and motility[98]. PAK1 participates in cancer tumorigenesis after being highly expressed. The crosstalk of PAK1 with the MAPK/extracellular signal-regulated kinase (ERK) and PI3K/Akt pathways induces proliferation and survival, respectively[99]. PAK1 also connects with the Wnt signaling pathway through CTNNB1 and continues to stimulate growth and metastasis[98]. PAK1 expression protects the cell from apoptosis after interaction with Raf, which inactivates Bcl-2 family members (BCL2 associated agonist of cell death [BAD]) in mitochondria[98,100].

TLRs are part of the family of pattern knowledge receptors and operate on innate immunity, participating in the body's first line of defense against invasion of microbial pathogens, tissue damage, and cancer. Its signaling pathway controls immune cell activation, maturation, and immune functions, especially the secretion of cytokines, influencing the tumor's metabolism, proliferation, and spread [101]. They are expressed by several immune cells such as macrophages, dendritic cells, B lymphocytes, natural killer cells, non-immune cells such as epithelial cells, and cancer-associated fibroblasts[102]. When expressed in the tumor, TLRs can release cytokines and chemokines into the tumor environment to recruit other immune cells to release more proinflammatory cytokines, pro-angiogenic factors, and growth factors[101].

The TGF-β signaling pathways are pleiotropic, regulating multiple functions such as cell growth, differentiation, apoptosis, angiogenesis, motility, invasion, and immune response. Modifications in this pathway might play an essential role in developing tumors and metastasis. These modifications can affect not only the tumor cells but also the environment. At this level, the TGF-β generates an environment conducive to tumor growth and metastasis at all carcinogenesis stages. TGF-β has a contradictory behavior at the cellular level, acting as a suppressor and a tumor promoter[103,104]. Initially, the TGF-β pathway promotes cell cycle arrest and apoptosis. It promotes cancer cell motility, invasion, tumor progression, and metastasis in advanced stages. Thus, the accumulation of mutations is

Table 2 Pathways enriched in transcriptional analyses in esophageal, gastric, liver, pancreas, and colorectal cancers

Pathway	CRC	EC	GC	HCC	PDAC	Ref.
Focal adhesion	X	X	X	X	X	[69-76]
Apoptosis	X	X	X	X	X	[71,72,77-79]
PAK pathway	X	X		X	X	[80-83]
PI3K/Akt signaling pathway	X	X	X			[71,84-86]
TGF-beta pathway		X	X	X	X	[75,76,87-90]
Toll-like receptor signaling pathway		X	X	X		[88,91-93]

CRC: Colorectal cancer; EC: Esophageal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; PAK: p21-activated kinase; PDAC: Pancreatic ductal adenocarcinoma; PI3K: Phosphoinositide 3-kinase; TGF: Transforming growth factor beta.

responsible for guiding the evolution from a suppressor pathway to a tumor promoter[105].

The HCC RNA sequencing study identified four subtypes of HCC using 212 samples. The pathway analyses using the expression data reveal the enriched pathways metabolism RNA processes such as RNA processing, binding, and splicing. Although all the samples are from HCC, this result indicates different gene expression, cell activity, and behaviors. These enriched processes are not shared by the four HCC groups funded. However, at least three groups shared translation, ribosome, metabolism of proteins, and cytoplasm ribosomal proteins[106]. The microarray analysis using 25 HCC samples identified thousands of differentially expressed genes, and the pathways of cell cycle response, DNA damage response, cell survival, and apoptosis were identified. In addition, it was also linked to pathway terms and poor prognosis clinical parameters. These results also agree with RNA sequencing study point transcriptional regulation, RNA processing, and cell cycle regulation. The single-cell RNA sequencing analysis indicates 119 genes associated with HCC. The pathways analysis using Gene Ontology showed an acute inflammatory response, oxidative stress, and humoral response. Simultaneously, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways indicate IL-17 and TNF signaling pathways, infectious disease, and rheumatoid arthritis. These samples present more immunological functions[107]. According to the OncoVar database, the KEGG pathways associated with HCC are mainly cancer pathways, viral infection, cell longevity (growth and death), antineoplastic drug resistance, and transduction signaling pathways (Wnt and Hippo signaling pathways)[108]. The molecular pathways in HCC are not entirely understood, and these results showed a notable variation of response in the differentially expressed genes working together to express a function.

Analysis combining CRC and endometrial cancer microarray samples identified 139 genes upregulated in both studies. These genes operate in the cellular functions of cell proliferation, Wnt signaling pathway, fatty acid beta-oxidation, transcription, exocytosis, dopaminergic neuron differentiation, and platelet degranulation. The KEGG pathways enriched were tight junctions, rheumatoid arthritis, renal cell carcinoma, and cancer pathways signaling. The rheumatoid arthritis pathway was enriched in more than one study with the genes (ATP6V0D1, ATP6V1D, CD28, CTLA4, CTSK, FOS, IL-18, and JUN)[109]. Other microarray meta-analysis studies using CRC samples point to also the KEGG pathways related to the cell cycle, pathways in cancer, and the Wnt signaling pathway. These pathways are linked; as a result, they share proliferation and block apoptosis[65]. Together, these processes induce the normal cell to convert to a tumor cell.

THE PROTEIN-PROTEIN INTERACTION IN CANCER

The number of GI cancer projects in different OMIC levels found many genes working in tumorigenesis. The GI cancers discussed here sum 178 different genes with associated mutations. The number of genes with mutations associated with GI cancers ranges from 41 to 89 genes in HCC and GC.

Each of these cancers has variation and can be classified into subtypes according to cell origin, chromosomal structural rearrangements, gene expression, and cell behaviors. However, there are 46 genes shared by at least two types of cancers. These genes should be investigated to understand better how they assist in the cell transformations to tumors, biomarkers of tumor cells, and potential drug or therapy targets. The genes present in all five types of cancers are activin A receptor type 2A, APC, ARID1A, and CTNNB1.

We used information from STRING database to check the protein-protein interaction (PPI) from these 178 genes. We used the experimental information only to build this PPI network. The PPI investigation allows for building a network with 111 genes connected (Figure 1)[110]. The number of nodes in the PPI network indicates that these genes work together in GI cancer tumorigenesis.

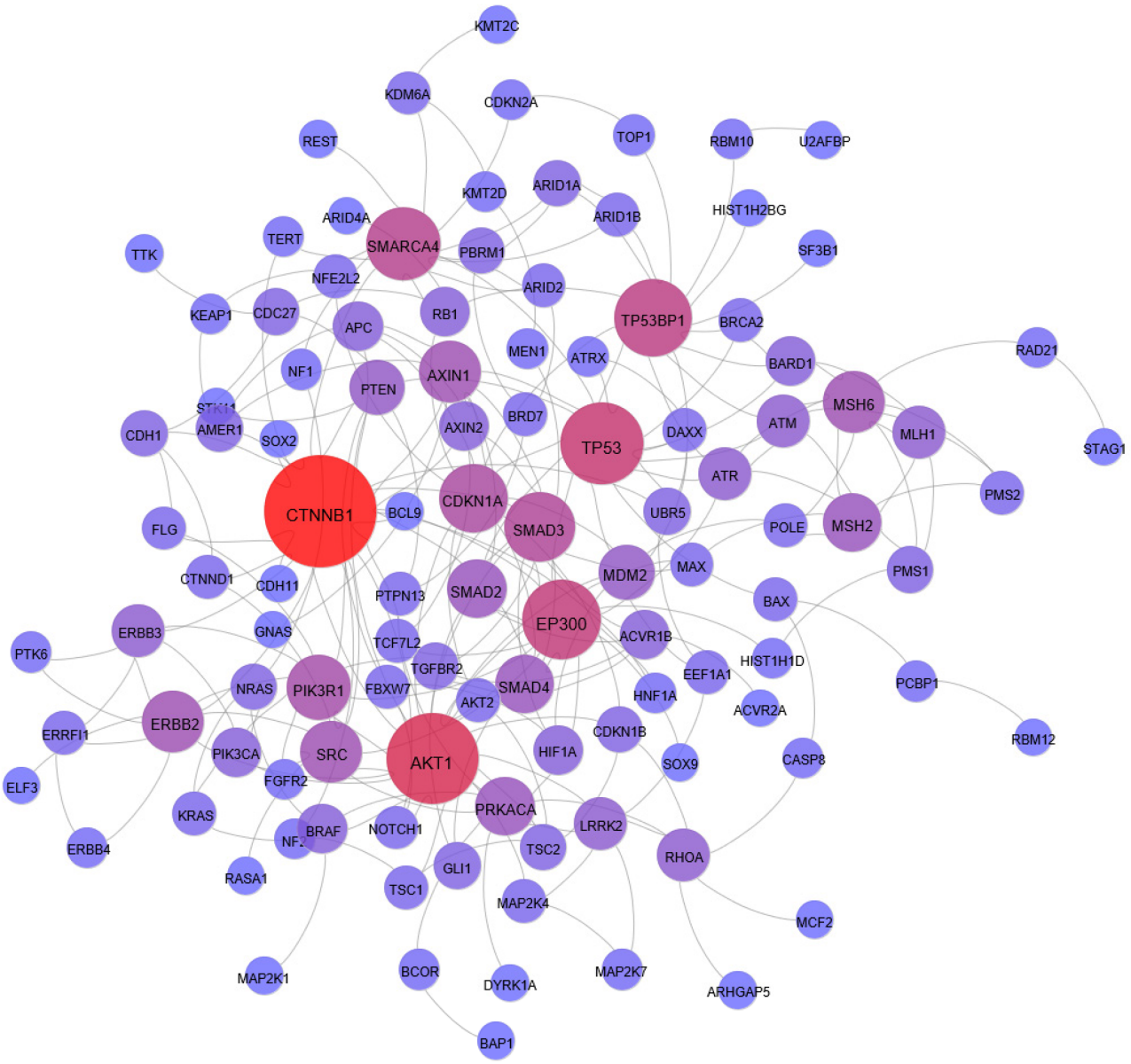

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Figure 1 Protein-protein interaction of genes with mutations associated with gastrointestinal cancers. The nodes represent the genes, and the edges represent the protein interactions. The network was built using information from experimental data only from the STRING database[110]. The node size represents the number of protein interactions (degree), indicating the node's centrality.

We analyzed the GI cancer network to identify in this PPI most connected protein (high degree) as central nodes. The proteins CTNNB1, Akt1, TP53, EP300, and TP53-binding protein 1 (53BP1) are the central nodes with the highest degree.

The CTNNB1 gene encodes a beta-catenin protein expressed in the adherens junctions[53]. The beta-catenin is a cytoplasm protein that works in the adhesion between cells. The beta-catenin binds the actin in the cytoskeleton and the E-cadherin protein in the cell membrane, connecting neighboring cells[111]. The beta-catenin is also a mediator in the Wnt signaling pathway. When activated, the Wnt signaling pathway induces the accumulation of beta-catenin in the nucleus, activating target genes' transcription [53]. The WNT protein binds the receptor in the membrane and induces beta-catenin to accumulate, promoting cell survival and proliferation[65]. The mutations in CTNNB1 gene are frequently found in HCC (13%)[112,113], CRC (6%)[114], and it is mutated in 4% of GC[47].

The Akt1 is a central protein in cell transduction signaling, which, when induced by PI3K, induces process cell proliferation, survival, and angiogenesis. The activation of the mammalian target of rapamycin (mTOR) complex by ATK is investigated as a drug target to treat PDAC[115-117]. The Epstein-Barr virus and *H. pylori* induce inflammation and the expression of Akt in GC. The outcome is cell proliferation and telomerase activation[118,119]. The investigation of blockage of Akt in GC resulted in suppression of growth and metastasis[120]. The investigation of critical proteins in HCC PPI identified several functions crucial in tumorigenesis, cell proliferation, anti-apoptosis, and metastasis.

The PPI network showed Akt1 as a potential drug target[104]. These results indicate Akt1 central position in tumorigenesis and a potential drug target.

The 53BP1 protein has a role in DNA damage response and cycle arrest, triggering the expression of p53; the malfunctioning of this protein might lead to the development of genomic instability and molecular diseases. The lack of function of 53BP1 is associated with poor prognosis, angiogenesis, and metastasis[121]. The decreased expression of 53BP1 in CRC induces radiotolerance and chemoresistance. Moreover, CRC cells with lower expression of 53BP1 have a higher proliferating rate, decreased apoptosis, and poor prognosis[122-124]. The 53BP1 also interacts with p53, as indicated in CRC and EC, when the reduction of 53BP1 induces the downregulation of p53[122,123,125]. The 53BP1 is expressed as soon as DNA damage treatment occurs in human pancreatic cells[126]. The 53BP1 might also influence tumor outcome in pancreatic cancer, as shown when the variation of 53BP1 expression changes the association of carbohydrate 19-9, a well-known pancreatic cancer marker, and overall survival[100].

The p300 protein (encoded by the *EP300* gene) is a histone acetyltransferase that participates in chromatin remodeling and interacts with basal transcriptional machinery to improve DNA binding, affecting gene transcription in normal and cancer cells[127]. The EP300 mutations are common in CRC and GC by frameshift in microsatellite regions[128]. The mutation in EP300 is frequent in EC (10%), and it correlates with a poor prognosis, associated with cell proliferation, migration, and invasion (metastasis)[129,130]. The role of p300 in remodeling the chromatin makes it appropriate to investigate epigenetic therapies, and the use of natural nutrients as potential prevention and treatment has already been discussed with GC[131].

ESSENTIAL GENES AND KAPLAN-MEIER SURVIVAL ANALYSIS

All GI cancers discussed here have a low 5-year survival rate, except CRC (Table 1). The esophagus, liver, and pancreas have the lowest 5-year survival rate. The late diagnosis, metastasis, and aggressive behavior are associated with a low 5-year survival rate. Many studies describe the poor prognosis as associated with gene expression[97,122,129,132-135].

The expression levels are crucial information that might work as a prognostic factor in GI cancers. The association between TP53BP1 expression and overall survival analyses in CRC indicate a connection with low expression and low survival in the I-IIA stage, T3-T4, and N0[122]. Again, this protein has an essential role in CRC, not only to a high degree but also as a prognostic marker. The EP300 gene has high expression associated with poor survival in ESCC[129]. The long non-coding RNAs (lncRNAs) have a critical role in cancer development, and the high expression of ANRIL and homeobox A11-antisense RNA (HOXA11-AS) lncRNA is associated with poor survival in GC[132,133]. The overexpression of lncRNA ANRIL is significantly associated with GC progression and can serve as an independent predictor of patient survival[136]. The high expression of ANRIL combined with polycomb repressive complex 2 significantly silences microRNA 99a (miR-99a) and miR-449a at the transcriptional level, which increases the expression of mTOR, CDK6, and E2 transcription factor 1[132]. The HOXA11-AS gene reduces the expression of suppressor tumor genes Krüppel-like Factor 2 (KLF2) and protease serine 8 at the transcriptional level[133]. KLF2 downregulation is associated with migration, invasion, and poor survival[137,138]. KLF2 inhibits growth and migration and induces pancreatic cancer cells to senescence.

ESCC has poor survival when low esophageal cancer-related gene 4 expression occurs compared to the high-expression group[139]. EAC has worse overall survival when IL11 expression increases. Poor survival is also observed in a low expression of neuronal pentraxin 1, inositol 1,4,5-trisphosphate receptor type 1, and platelet derived growth factor D[140].

PDAC analyses show that high expression of the centromere protein F, sciellin, serpin family B member 5, solute carrier family 2 member 1 (SLC2A1), SLC6A14, transmembrane channel like 7, and transmembrane serine protease 4 is associated with a lower probability of survival compared to the same genes in low expression[141].

We investigated the gene expression and overall survival of the central genes present in the PPI network (Figure 1). We used information from the Kaplan Meier plotter (https://kmplot.com)[142] to investigate the potential prognosis of the central genes. Three of the five genes investigated have gene expression associated with survival (Akt1, TP53, and CTNNB1) (Figure 2).

The high expression of Akt1 and TP53 in GC is associated with a poor prognosis. In contrast, low CTNNB1 expression is correlated with reduced survival. The expression values and survival curves for TP53 (mRNA) in the Kaplan Meier plotter agree with tumor protein p53 expression in GC[143,144]. The TP53 expression is low and has a short half-life in normal cells, whereas in tumor cells, this gene has high expression and a long half-file[145]. The higher expression of TP53 is indicative of the worst prognosis. Akt1 expression was not indicative of prognosis[146]. However, they found that EGFR and Akt1 expression are mutually exclusive and associated with poor survival. This result might be due to the two proteins acting in the same pathway. The phosphorylated Akt1 and CTNNB1 high expression are associated with poor survival[147,148].

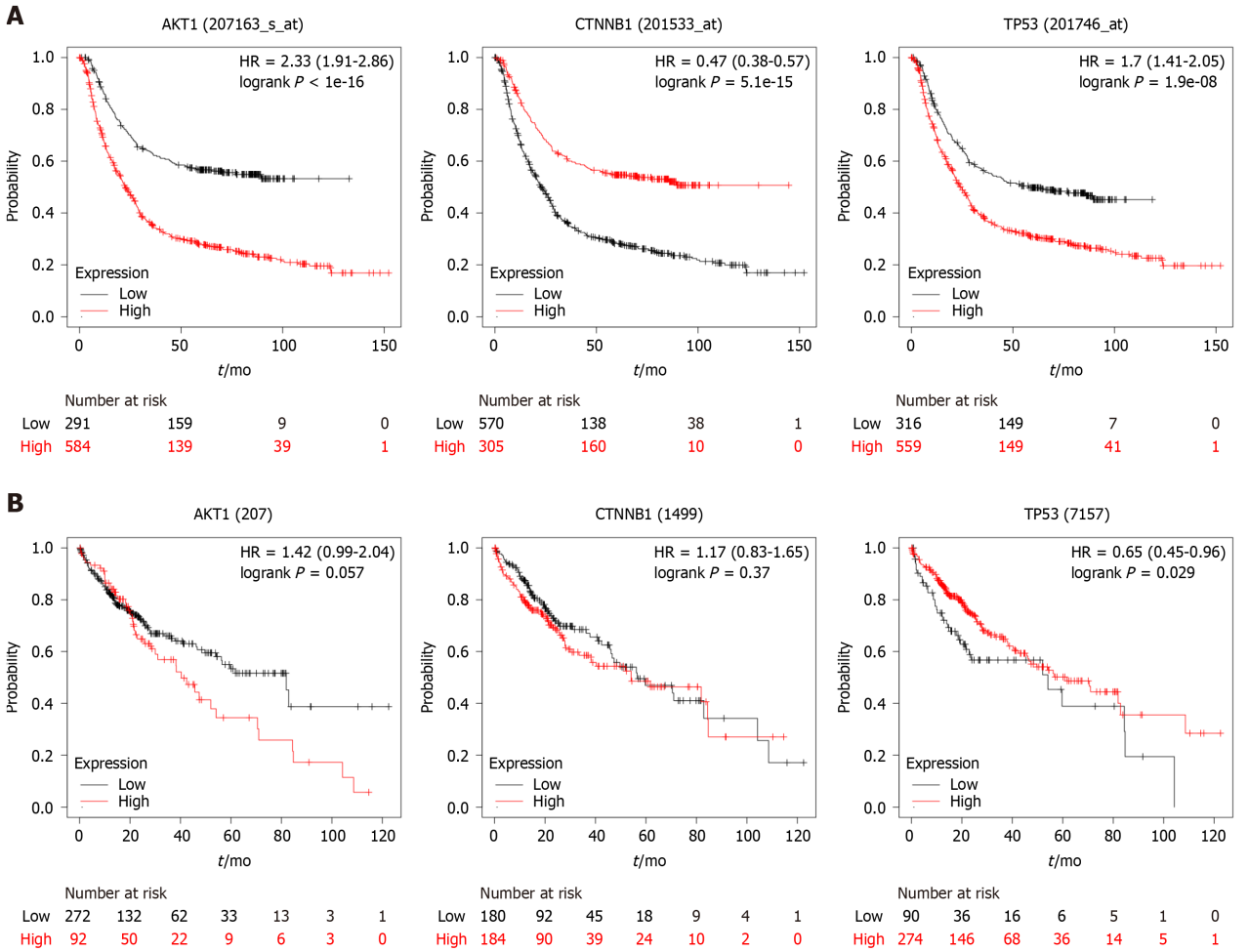

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Figure 2 Prognostic value of Akt1, catenin beta 1, tumor protein p53 for gastric cancer (A) and hepatocellular carcinoma (B) in Kaplan Meier plotter (https://kmplot.com)[142]. Kaplan-Meier survival curves for patients of gastric cancer and hepatocellular carcinoma with high and low indicated gene expression. CTNNB1: Catenin beta 1; TP53: Tumor protein p53.

There is no significant difference between Akt1 or CTNNB1 high and low expression groups in liver cancer. Regarding the TP53 gene, the differences in expression are not significant in the initial stage of carcinoma. However, this high expression predicts a poor prognosis and a higher mortality rate than a low expression. The results are not according to the TP53 gene expression for HCC, where TP53 high expression is present in poor prognosis groups[149].

However, the prognosis markers based on expression have limitations, and the result must be taken together with other markers.

CONCLUSION

The OMIC information about GI cancer is very complex, and each organ/region has subtypes and particularities. We presented information about and brought to light the most common genomic changes among these cancers. The pathways shared by these molecular diseases also point to the standard functions and the crosstalk of these pathways and the PAK1 pathway centrality, connecting to MAPK/ERK, PI3K/Akt, apoptosis, and Wnt signaling pathways. The PPI network pointed to five central genes, and the literature corroborates the crucial role in GI cancer with expression and poor prognosis association. This information might help in the target choice of drug and therapy research.

FOOTNOTES

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Country/Territory of origin: Brazil

ORCID number: Iasmin Moreira Costa Bispo 0000-0001-7500-619X; Henry Paul Granger 0000-0002-4889-8732; Palloma Porto Almeida 0000-0002-1588-8722; Patricia Belini Nishiyama 0000-0002-9495-6171; Leandro Martins de Freitas 0000-0003-4327-2922.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Somatic mutations in FAT cadherin family members constitute an underrecognized subtype of colorectal adenocarcinoma with unique clinicopathologic features

Liang-Li Wang, Wei Zheng, Xiu-Li Liu, Feng Yin

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Liang-Li Wang, Feng Yin, Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia, MO 65212, United States

Wei Zheng, Department of Pathology, Emory University School of Medicine, Atlanta, GA 30322, United States

Xiu-Li Liu, Department of Pathology and Immunology, Washington University, St. Louis, MO 63110, United States

Corresponding author: Feng Yin, MD, PhD, Assistant Professor, Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, One Hospital Drive, Columbia, MO 65212, United States. fengyin@health.missouri.edu

Abstract

BACKGROUND

The FAT cadherin family members (FAT1, FAT2, FAT3 and FAT4) are conserved tumor suppressors that are recurrently mutated in several types of human cancers, including colorectal carcinoma (CRC).

AIM

To characterize the clinicopathologic features of CRC patients with somatic mutations in FAT cadherin family members.

METHODS

We analyzed 526 CRC cases from The Cancer Genome Atlas PanCancer Atlas dataset. CRC samples were subclassified into 2 groups based on the presence or absence of somatic mutations in *FAT1*, *FAT2*, *FAT3* and *FAT4*. Individual clinicopathological data were collected after digital slide review. Statistical analysis was performed using *t* tests and chi-square tests.

RESULTS

This CRC study cohort had frequent mutations in the *FAT1* (10.5%), *FAT2* (11.2%), *FAT3* (15.4%) and *FAT4* (23.4%) genes. Two hundred CRC patients (38.0%) harbored somatic mutations in one or more of the *FAT* family genes and were grouped into the FAT mutated CRC subtype. The FAT-mutated CRC subtype was more commonly located on the right side of the colon (51.0%) than in the rest of

the cohort (30.1%, $P < 0.001$). It showed favorable clinicopathologic features, including a lower rate of positive lymph nodes (pN1-2: 33.5% *vs* 46.4%, $P = 0.005$), a lower rate of metastasis to another site or organ (pM1: 7.5% *vs* 16.3%, $P = 0.006$), and a trend toward an early tumor stage (pT1-2: 25.0% *vs* 18.7%, $P = 0.093$). FAT somatic mutations were significantly enriched in microsatellite instability CRC (28.0% *vs* 2.1%, $P < 0.001$). However, FAT somatic mutations in microsatellite stable CRC demonstrated similar clinicopathologic behaviors, as well as a trend of a better disease-free survival rate (hazard ratio = 0.539; 95% confidence interval: 0.301-0.967; log-rank $P = 0.073$).

CONCLUSION

FAT cadherin family genes are frequently mutated in CRC, and their mutation profile defines a subtype of CRC with favorable clinicopathologic characteristics.

Key Words: *FAT* cadherin family genes; Colorectal adenocarcinoma; Clinicopathologic features; Prognosis; The Cancer Genome Atlas

Core Tip: Colorectal carcinoma (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide. In this study, we aimed to characterize the clinicopathologic features of CRC patients with somatic mutations in FAT cadherin family members. CRC cases have frequent mutations in *FAT* family genes. The FAT-mutated CRC subtype is more commonly located on the right side of the colon and shows favorable clinicopathologic features, including a lower rate of positive lymph nodes and a lower rate of metastasis to another site or organ, suggesting that the *FAT* somatic mutation is a potentially independent prognostic factor in CRC.

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INTRODUCTION

Colorectal carcinoma (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide, with more than 1.9 million new cases and 935000 deaths in 2020[1]. Except for a few CRC cases (5%-10%) with inherited gene mutations, most CRC cases occur sporadically and exhibit chromosomal instability that leads to changes in chromosome numbers and structure, featuring aneuploidy, loss of heterozygosity, subkaryotypic amplification, and chromosomal rearrangement. Along with karyotypic abnormalities, mutations in specific tumor suppressor genes and oncogenes, such as the adenomatous polyposis (*APC*) gene, tumor protein p53 (*TP53*) and KRAS proto-oncogene GTPase, also contribute to CRC tumorigenesis. Notably, mutation of the *APC* gene, which leads to the activation of Wnt/β-catenin signaling, is an essential and early event in the development of CRC[2,3].

Despite the well-defined genetic and epigenetic alterations in CRC initiation and progression, recent studies have shown that the Hippo pathway may interact with Wnt/β-catenin signaling and play a crucial role in controlling intestinal stem cell proliferation and CRC development[4]. The Hippo pathway is an emerging tumor suppressor pathway. As a proposed upstream component of the Hippo pathway, the atypical cadherin FAT acts as a receptor to activate the Hippo pathway[5], and its mutation appears to be a recurrent event in human cancers in association with dysregulation of the Hippo pathway[6].

The human *FAT* cadherin gene family comprises the *FAT1*, *FAT2*, *FAT3* and *FAT4* genes[7-10]. The encoded proteins FAT1-4 are human homologs of Drosophila FAT, of which FAT1 and FAT4 have been reported to be involved in the regulation of planar cell polarity[11] and tumor suppression[12,13]. FAT1 also promotes actin-mediated cell migration[14,15] and plays a role in epithelial mesenchymal transition [16]. Somatic mutations of *FAT* family genes have been detected in different human cancers, including squamous cell carcinoma of the head and neck (*FAT1*, *FAT2* and *FAT4*)[17-20], breast cancer (*FAT1*)[21], melanomas (*FAT4*)[22], leukemia (*FAT1*)[23,24], hepatocellular cancer (*FAT1*, *FAT4*)[25,26], esophageal squamous cell carcinoma (*FAT1*)[27-29], pancreatic cancer (*FAT1*, *FAT3* and *FAT4*)[30,31], and gastric cancer (*FAT4*)[32,33]. Alterations in FAT family genes are associated with tumorigenesis and prognosis. For instance, upregulation of the *FAT1* gene is associated with poor prognosis and early relapse in acute

lymphoblastic leukemia patients[24] and invasive progression of ductal carcinoma *in situ*[21], while loss of *FAT4* is associated with invasiveness in gastric cancer[34]. Until now, the role of FAT family genes in CRC tumorigenesis has not been well studied. In this study, we characterized the clinicopathologic features of *FAT* family gene mutations in CRC patients.

MATERIALS AND METHODS

Study design

In total, 526 CRC cases were selected from The Cancer Genome Atlas (TCGA) PanCancer Atlas dataset. cBioPortal (https://www.cbioportal.org/) was used to download whole-exome somatic mutation data and clinical information. There are certain sample inclusion criteria for the TCGA PanCancer Atlas on colorectal adenocarcinoma. The biospecimens were collected from newly diagnosed colorectal adenocarcinoma patients undergoing surgical resection, regardless of histologic grade or tumor stage. The patients had not received prior chemoradiation therapy. The histological sections contained an average of 60% tumor cells with less than 20% necrosis[35].

In the TCGA PanCancer Atlas dataset, the somatic mutation profiles of *FAT1*, *FAT2*, *FAT3* and *FAT4* were analyzed for each tumor. Furthermore, the CRC cases were categorized into two groups based on their mutational status on FAT family genes: The cases with mutant *FAT1-4* and the cases with wild-type *FAT1-4*. Standard demographic and clinicopathological data were retrieved for each patient, including age, sex, tumor location, pT stage, pN stage, pM stage, differentiation grade, tumor type, lymphovascular invasion, month of disease-free survival (DFS) and overall survival (OS).

Statistical analyses

Demographic and clinicopathological details were stratified according to *FAT1-4* mutation. Quantitative and qualitative variables were expressed as the means ± SD and the frequencies. Comparisons between the groups were analyzed with *t* tests and chi-square tests. DFS and OS were analyzed using the Kaplan-Meier method, and the log-rank test was used to assess differences. The figure was prepared using GraphPad Prism 9 software (GraphPad Software, San Diego, California, United States). *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The study included 526 patients with CRC from TCGA PanCancer Atlas Dataset. The mean age of the patients was 65.8 years (SD 13.0 years; range: 31-90 years). Based on the available clinicodemographic information, two hundred fifty-two patients were female, and two hundred seventy-two patients were male. Of them, 254 (48.3%) patients had left-sided colon cancer, and 197 (37.5%) patients had right-sided colon cancer. The majority (72.4%) of the CRCs were moderately differentiated adenocarcinomas. The detailed demographics, histopathologic stage and features are summarized in Table 1.

Somatic mutations of FAT family genes in CRC

Among the 526 CRC cases, 200 (38.0%) patients harbored one or more somatic mutations of the FAT cadherin family genes, including mutations in the *FAT1* (10.5%), *FAT2* (11.2%), *FAT3* (15.4%), and *FAT4* (23.4%) genes. The somatic mutation types of the *FAT* family genes include missense mutation, nonsense mutation, splicing mutation, frameshift deletion, frameshift insertion and in-frame deletion, with missense mutation being the most common somatic mutation type (Table 2). Interestingly, these somatic mutations were significantly enriched in the extracellular cadherin domain (*FAT*1, 49.0%; *FAT*2, 63.4%; *FAT*3, 40.1%; *FAT*4, 57.8%) (Table 2).

Based on the presence or absence of somatic mutations in *FAT1-4* genes, these cases were subclassified into 2 groups in our study. The clinicopathologic features of these 2 subtypes are summarized in Table 3. In the FAT-mutated CRC subtype, the median patient age was 66.5 years (range: 33-90 years), and 102 (51.0%) patients were male. Compared with the rest of the cohort, the FAT-mutated CRC subtype was more commonly located on the right side of the colon (51.0% *vs* 30.1%, $P < 0.001$) and more commonly associated with favorable histopathologic features, including lower pathological nodal stage (pN0: 66.5% *vs* 52.8%, $P = 0.005$), lower rate of metastasis to another site or organ (pM1: 7.5% *vs* 16.3%, $P = 0.006$), and a trend of lower pathological tumor stage (pT1-2: 25.0% *vs* 18.7%, $P = 0.093$).

FAT somatic mutations are enriched in microsatellite-instable CRC

Human *FAT* family genes encode large atypical cadherin proteins with a large number of cadherin repeats. Given the overlapping features found in the FAT-mutated CRC subtype and microsatellite-instable (MSI) CRC (right sided with favorable clinicopathological features), we further explored the association between *FAT* mutations and MSI. Interestingly, FAT somatic mutations were significantly

Table 1 Clinicodemographics and histologic features in 526 patients with colorectal adenocarcinoma (PanCancer Atlas)

Feature	Level	Number	MSS number
Age (yr), mean ± SD		65.8 ± 13.0	65.4 ± 12.7
Gender	Female	252 (47.9%)	218 (47.1%)
	Male	272 (51.7%)	243 (52.5%)
	Unknown	2 (0.4%)	2 (0.4%)
Histopathologic differentiation	Well	19 (3.6%)	18 (3.9%)
	Moderate	381 (72.4%)	351 (75.8%)
	Poor	114 (21.7%)	83 (17.9%)
	Unknown	12 (2.3%)	11 (2.4%)
Tumor location	Left	254 (48.3%)	248 (53.6%)
	Right	197 (37.5%)	149 (32.2%)
	Left and right	3 (0.6%)	3 (6.5%)
	Unknown	72 (13.7%)	63 (13.6%)
Tumor staging (pT)	T1	18 (3.4%)	17 (3.7%)
	T2	94 (17.9%)	83 (17.9%)
	T3	355 (67.5%)	310 (67.0%)
	T4	57 (10.8%)	52 (11.2%)
	TX	2 (0.4%)	2 (0.4%)
Nodal staging (pN)	N0	305 (58.0%)	255 (55.1%)
	N1	128 (24.3%)	120 (25.9%)
	N2	90 (17.1%)	85 (18.4%)
	NX	3 (0.6%)	3 (6.5%)
Metastasis (pM)	M0	388 (73.8%)	338 (73.0%)
	M1	68 (12.9%)	66 (14.3%)
	MX	70 (13.3%)	59 (12.7%)
Lymphovascular invasion	Present	178 (33.8%)	157 (33.9%)
	Absent	230 (43.7%)	202 (43.6%)
	Unknown	118 (22.4%)	104 (22.5%)
Ethnicity	Caucasian	273 (51.9%)	236 (51.0%)
	African-American	60 (11.4%)	51 (11.0%)
	Asian	12 (2.3%)	11 (2.4%)
	Unknown	181 (34.4%)	165 (35.6%)
Subtype	CIN	328 (62.4%)	
	MSI	63 (12.0%)	
	GS	58 (11.0%)	
	POLE	10 (1.9%)	
	Unknown	57 (10.8%)	
Total		526	463

CIN: Chromosomal instability; MSI: Microsatellite instability; GS: Genomically stable; POLE: Polymerase epsilon mutation; MSS: Microsatellite stable.

enriched in MSI CRC (28.0% *vs* 2.1%, $P < 0.001$) (Table 3).

Table 2 Genetic mutation types and numbers in FAT family genes in colorectal adenocarcinoma (PanCancer Atlas)

Gene	Missense mutation	Nonsense mutation	Splicing mutation	Frame shift deletion	Frame shift insertion	Inflame deletion	Total mutation	Mutation in Cadherin domains
FAT1	85	5	2	3	2	1	98	48 (49.0%)
FAT2	90	2	3	5	1	0	101	64 (63.4%)
FAT3	124	6	0	5	2	0	137	55 (40.1%)
FAT4	198	19	0	10	4	0	230	133 (57.8%)

To control for confounding in the analysis, we focused on cases of microsatellite-stable (MSS) CRC. As shown in Table 1, the MSS CRC cases showed similar clinicodemographic and histologic features as the entire cohort. We also categorized the MSS CRC cases into 2 groups based on the mutation status of *FAT* family genes. Similar to the entire cohort we described earlier, the FAT-mutated MSS CRC subtype was also more commonly located on the right side of the colon (39.6% *vs* 28.8%, P = 0.038) and more commonly associated with favorable histopathologic features, such as a lower rate of metastasis to another site or organ (pM1: 9.0% *vs* 16.6%, P = 0.038). It also showed a trend of lower pathological tumor stage (pT1-2: 26.4% *vs* 19.1%, P = 0.083) and lower pathological nodal stage (pN0: 60.4% *vs* 52.7%, P = 0.079) (Table 3). Therefore, even though it is enriched in MSI CRC, the FAT somatic mutation is a potentially independent prognostic factor in CRC.

The median DFS for CRC patients was 26.0 mo (0.5-148.0 mo), and the OS was 21.0 mo (0-148.0 mo). Consistent with the favorable pathologic features, the FAT-mutated MSS CRC subgroup showed a trend toward a better DFS rate [hazard ratio (HR) = 0.539; 95% confidence interval (CI): 0.301-0.967; log-rank P = 0.073]. However, FAT mutation status did not show a significant impact on the OS rate (HR = 1.198; 95%CI: 0.770-1.864; log-rank P = 0.440) (Figure 1).

DISCUSSION

To our knowledge, this is the first study to assess the impact of somatic mutations in *FAT* family genes on clinicopathologic features, with an emphasis on prognosis in CRC patients. Our study shows that somatic mutations in *FAT* family genes are associated with favorable clinicopathologic features, including a lower rate of lymph node and distal metastasis. It also showed a trend toward a lower tumor stage with a relatively favorable DFS.

In addition to the *APC-β-catenin* pathway, which represents the most prominent signaling pathway in CRC, components of the Hippo pathway have been reported to be involved in CRC tumorigenesis[36-40] and have been proposed as prognostic factors in CRC[41-44]. As an upstream organizer and activator of the Hippo pathway[6], *FAT* family genes have emerged as an important mechanism that orchestrates epithelial development as well as human cancer initiation and progression. The *FAT* family genes (*FAT1-4*) encode atypical cadherins that contain multiple extracellular cadherin repeats, laminin G motifs and EGF-like motifs[45]. Among these, *FAT*1 and *FAT*4 are relatively well studied. Loss of *FAT*4 expression has been reported in some primary breast cancers and breast cancer cell lines[46]. Low *FAT*4 expression was also observed in gastric cancers and was associated with a poor prognosis, including high pathologic T stage, an increase in perineural invasion, high lymph node metastasis and reduced DFS[47]. Similarly, a study reported recurrent *FAT1* mutations in multiple human cancers, including glioblastoma, CRC, and head and neck cancer, and *FAT1* mutations affected patient survival by promoting Wnt signaling and tumorigenesis[48]. Our study demonstrates that somatic mutations in FAT family genes are frequent recurrent events in CRC and that FAT mutations are associated with favorable clinicopathologic features. These somatic mutations are highly enriched in the extracellular cadherin domains (Table 2). FAT proteins are large single transmembrane receptors characterized by 32-34 extracellular cadherin repeats. These cadherin repeats contain highly conserved binding sites for proteins, such as beta-catenin and p120-catenin, which are important for the FAT protein to execute its role in migration, polarity and cell adhesion by linking it to the actin cytoskeleton.

Our study also revealed the significant enrichment of FAT-mutated CRC (28.0%) in the MSI subgroup. However, the clinicopathologic characteristics in FAT-mutated MSS CRC are quite compatible with the entire FAT-mutated CRC cohort in our study, suggesting that MSI only partially contributes to its pathologic features and clinical outcomes. Interestingly, FAT-mutated MSS CRC cases showed a trend of favorable DFS but not OS. The underlying mechanisms of this discrepancy are currently unclear. Notably, DFS does not always correlate with OS in CRC, such as in the case of liver-only metastatic CRC[49].

Similar to the findings in our study, Wang *et al*[33] reported a superior prognosis in gastric adenocarcinoma with *FAT* family gene mutations. In their study, *FAT* gene mutations were significantly associated with better progression-free survival and OS, which was likely attributed to the significantly

Table 3 Association of clinicopathologic features with FAT somatic mutations in colorectal adenocarcinoma (PanCancer Atlas)

Clinicopathologic features	Mutated FAT genes	Wildtype FAT genes	*P* value	Mutated FAT genes (MSS)	Wildtype FAT genes (MSS)	*P* value
Mean age (mean ± SD)	66.5 ± 12.9	65.3 ± 13.0	0.912	65.6 ± 12.1	65.3 ± 12.9	
Sex			0.689			0.825
Female	98 (49.0%)	154 (47.2%)		67 (46.5%)	151 (47.3%)	
Male	102 (51.0%)	170 (52.1%)		77 (53.5%)	166 (52.0%)	
Location			< 0.001[a]			0.038[a]
Left side	65 (32.5%)	181 (55.5%)		70 (48.6%)	178 (55.8%)	
Right side	102 (51.0)	98 (30.1%)		57 (39.6%)	92 (28.8%)	
pT stage			0.093			0.083
pT1-2	50 (25.0%)	61 (18.7%)		38 (26.4%)	61 (19.1%)	
pT3-4	150 (75.0%)	263 (80.7%)		106 (73.6%)	256 (80.3%)	
pN stage			0.005[a]			0.079
pN0	133 (66.5%)	172 (52.8%)		87 (60.4%)	168 (52.7%)	
pN1	44 (22.0%)	84 (25.8%)		39 (27.1%)	81 (25.4%)	
pN2	23 (11.5%)	67 (20.6%)		18 (12.5%)	67 (21.0%)	
pM stage			0.006[a]			0.038[a]
pM0	153 (76.5%)	235 (72.1%)		110 (76.4%)	228 (71.5%)	
pM1	15 (7.5%)	53 (16.3%)		13 (9.0%)	53 (16.6%)	
Differentiation grade			0.332			0.172
G1-2	145 (72.5%)	255 (78.2%)		117 (81.3%)	252 (79.0%)	
G3	47 (23.5%)	67 (20.6%)		20 (13.9%)	63 (19.7%)	
Subtype			< 0.001[a]			
CIN	92 (46.0%)	236 (72.4%)				
MSI	56 (28.0%)	7 (2.1%)				
GS	25 (12.5%)	33 (10.1%)				
Lymphovascular invasion			0.313			0.516
Positive	61 (30.5%)	117 (35.9%)		44 (30.6%)	113 (35.4%)	
Negative	90 (45.0%)	140 (42.9%)		63 (43.8%)	139 (43.6%)	
Total	200 (38.0%)	326 (62.0%)		144 (31.1%)	319 (68.9%)	

[a]$P < 0.05$.

CIN: Chromosomal instability; MSI: Microsatellite instability; GS: Genomically stable; MSS: Microsatellite stable.

higher tumor mutational burden and an inflamed tumor microenvironment[33]. Whether the tumor microenvironment plays a similar role in CRC still awaits further investigation.

Our study has several limitations. First, our findings were obtained from a bioinformatics study on somatic mutation profiles through the TCGA PanCancer Atlas dataset. The protein expression levels of individual FAT family members were not systemically examined in the study, and the underlying molecular mechanisms related to the prognostic role of the FAT family in colorectal cancer need further experimental validation. Second, all the patients in the study were untreated, with no therapy response data and a short follow-up. Therefore, the evaluation of advanced-stage CRC is relatively limited. Third, we tried to address the impact of MSI status, a confounding factor, by analyzing the MSS samples. However, there are still additional potential confounding factors, such as histopathological subtypes, *TP53* mutation status, and intratumoral spatial and temporal heterogeneity. The ability of our study to address these potential confounding factors is hampered by intrinsic limitations of the TCGA database, the landmark cancer program heavily focused on cancer genomics datasets. A randomized, large-scale clinical cohort is necessary to validate our conclusion and to establish somatic mutations in *FAT* family

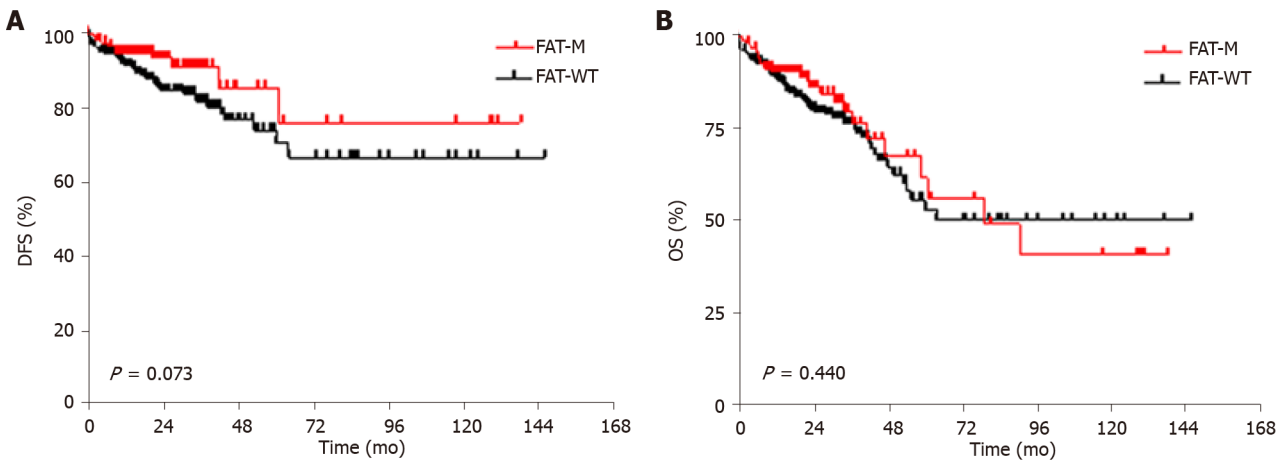

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Figure 1 Kaplan-Meier curves of disease-free survival and overall survival in microsatellite-stable colorectal adenocarcinoma patients without and with FAT family gene mutations. A: Disease-free survival; B: Overall survival. FAT-M: FAT mutated; FAT-WT: Wild-type FAT; DFS: Disease-free survival; OS: Overall survival.

genes as independent prognostic factors for CRC in future studies.

CONCLUSION

In summary, our study shows that somatic mutations in *FAT* family genes are recurrent genetic events detected in approximately 38% of CRC cases and therefore represent an underrecognized subtype of CRC. The FAT-mutated CRC subtype shows unique clinicopathologic features, including a right-side location, a lower rate of positive lymph nodes, a lower rate of metastasis to another site or organ, and a trend toward favorable DFS. Our study suggests that somatic mutations in *FAT* family genes are potential prognostic biomarkers for CRC.

ARTICLE HIGHLIGHTS

Research background

The human *FAT* cadherin gene family comprises the *FAT*1, *FAT*2, *FAT*3 and *FAT*4 genes. Somatic mutations of *FAT* family genes have been detected in different human cancers.

Research motivation

Until now, the role of *FAT* family genes in colorectal carcinoma (CRC) tumorigenesis has not been well studied. In this study, we characterized the clinicopathologic features of *FAT* family gene mutations in CRC patients.

Research objectives

In total, 526 CRC cases were selected from The Cancer Genome Atlas PanCancer Atlas dataset.

Research methods

CRC cases were categorized into two groups based on their mutational status on *FAT* family genes: The cases with mutant *FAT1-4* and the cases with wild-type *FAT1-4*. Standard demographic and clinicopathological data were retrieved for each patient, including age, sex, tumor location, pT stage, pN stage, pM stage, differentiation grade, tumor type, lymphovascular invasion, month of disease-free survival and overall survival.

Research results

The FAT-mutated CRC subtype is more commonly located on the right side of the colon and shows favorable clinicopathologic features, including a lower rate of positive lymph nodes and a lower rate of metastasis to another site or organ.

Research conclusions

FAT cadherin family genes are frequently mutated in CRC, and their mutation profile defines a subtype of CRC with favorable clinicopathologic characteristics.

Research perspectives

FAT somatic mutation is a potentially independent prognostic factor in CRC.

FOOTNOTES

Author contributions: Wang LL, Zheng W, Liu XL and Yin F collected and analyzed the data, made the tables and figures, and wrote and finalized the manuscript; and all authors have approved the final manuscript.

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Country/Territory of origin: United States

ORCID number: Liang-Li Wang 0000-0002-8145-0243; Wei Zheng 0000-0003-3193-2655; Xiu-Li Liu 0000-0001-5791-2017; Feng Yin 0000-0002-8444-1123.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Outcomes after natural orifice extraction *vs* conventional specimen extraction surgery for colorectal cancer: A propensity score-matched analysis

Isaac Seow-En, Lionel Raphael Chen, Yi-Xin Li, Yun Zhao, Jing-Hui Chen, Hairil Rizal Abdullah, Emile Kwong-Wei Tan

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Isaac Seow-En, Lionel Raphael Chen, Yun Zhao, Emile Kwong-Wei Tan, Department of Colorectal Surgery, Singapore General Hospital, Singapore 169608, Singapore

Yi-Xin Li, Department of Surgery, Duke-NUS Graduate Medical School, Singapore 169857, Singapore

Jing-Hui Chen, Hairil Rizal Abdullah, Department of Anaesthesiology, Singapore General Hospital, Singapore 169608, Singapore

Corresponding author: Isaac Seow-En, FRCS (Ed), MBBS, MMed, Assistant Professor, Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608, Singapore. isaac.seow.en@gmail.com

Abstract

BACKGROUND

Natural orifice specimen extraction (NOSE) *via* the anus or vagina replaces conventional transabdominal specimen retrieval *via* the transabdominal route through a limited mid-line laparotomy or Pfannenstiel incision. Reducing the number of laparoscopic ports further decreases operative abdominal wall trauma. These techniques reduce the surgical wound size as well as the risk of incision-related morbidity.

AIM

To compare short-term outcomes following 3-port NOSE surgery with a matched cohort of conventional non-NOSE colorectal cancer surgery.

METHODS

Patients who underwent elective 3-port laparoscopic colorectal NOSE surgery between February to October 2021 were identified. Selection criteria for NOSE surgery was adapted from the 2019 International Consensus on Natural Orifice Specimen Extraction Surgery for colorectal cancer. Patients with clinical T4 or N2 tumors on staging computed tomography were also excluded. The propensity score-matched cohort was identified amongst patients who underwent conventional laparoscopic colorectal surgery from January 2019 to December 2020. Matching was performed in the ratio of 1:4 based on age, gender, type of resec-

tion, and p - tumor node metastasis staging.

RESULTS

Over the eight-month study duration, 14 consecutive cases (nine female, five male) of elective 3-port laparoscopic surgery with NOSE were performed for colorectal cancer. Median age and body mass index were 70 (range 43-82) years and 24.1 (range 20.0-31.7) kg/m^2 respectively. Six patients underwent transanal NOSE and eight had transvaginal NOSE. Median operative time, intraoperative blood loss and postoperative length of stay were 208 (range 165-365) min, 30 (range 10-150) mL and 3 (range 2-6) d respectively. Two (14%) suffered minor postoperative compilations not attributable to the NOSE procedure. Median follow-up duration was 12 (range 8-15) mo. No instances of mortality, local or distant disease recurrence were recorded in this cohort. Compared to the conventional surgery cohort of 56 patients, the 3-port NOSE cohort had significantly quicker mean return of bowel function (2.6 *vs* 1.2 d, $P < 0.001$), reduced postoperative pain and patient-controlled analgesia use, and decreased length of hospital stay (6.4 *vs* 3.4 d, $P < 0.001$). There were no statistical differences in surgical duration and perioperative complication rates between the NOSE and non-NOSE cohorts.

CONCLUSION

3-port laparoscopic colorectal surgery with NOSE is a feasible technique, augmenting the minimally invasive nature of surgery and producing good outcomes. Appropriate patient selection and expertise in conventional laparoscopy are required.

Key Words: 3-port laparoscopy; Colorectal surgery; Natural orifice specimen extraction; Transanal; Transvaginal; Minimally invasive surgery

Core Tip: This paper demonstrates the benefit of reduced port laparoscopic colorectal surgery with natural orifice specimen extraction compared to conventional laparoscopic colorectal surgery. This technique represents a natural progression towards scarless surgery - the holy grail of minimally invasive surgery.

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INTRODUCTION

Minimal access abdominopelvic surgery has come a long way since the advent of laparoscopic colorectal surgery in the early 90 s. New technologies and platforms have been introduced, including robotic and transanal minimally invasive surgery. The primary objective remains the same - complete tumor extirpation along with the draining lymphatic tissue. Without deviating from the principles of surgical oncology, increasing experience and expertise of laparoscopic surgeons has encouraged continued surgical innovation, resulting in improved operative technique and patient outcomes.

Natural orifice specimen extraction (NOSE) is a logical progression in the evolution of minimally invasive colorectal surgery. Removal of the surgical specimen *via* a natural bodily orifice such as the vagina or anus replaces the need for conventional specimen extraction (CSE) *via* the transabdominal route through a limited mid-line laparotomy or Pfannenstiel incision. This greatly reduces the surgical wound size as well as the risk of incision-related morbidity.

The first use of NOSE in colorectal surgery was reported in 1993 by Franklin *et al*[1], who described laparoscopic colectomy with transanal specimen retrieval. There has been continued interest in this technique almost three decades later. Three meta-analyses comparing laparoscopic colorectal resection with NOSE *vs* CSE have been published in the last two years[2-4]. These studies consistently demonstrate the benefits of NOSE, in terms of overall complications, incision-related complications, intraoperative blood loss, postoperative pain, return of gastrointestinal function and length of hospital stay. However, NOSE required a longer operating time than CSE. No significant differences were observed for cancer-specific outcomes, including local and distant recurrences, 3- and 5-year disease-free survival and overall survival[2-4].

Furthermore, patients who underwent NOSE colectomy were found to have better perception of body image and cosmetic appearance compared to CSE at a median follow-up of approximately 3-years after surgery[5]. Quality of life and gastrointestinal function following NOSE were also found to be superior to a propensity score-matched cohort of CSE at 3-mo post-surgery[6]. We recently demonstrated the feasibility of NOSE following combined colectomy and liver resection[7].

Conventional laparoscopic colorectal surgery is performed using 4 or 5 ports: 1 camera port, 2 operator ports and 1 or 2 assistant ports. Reducing the number and size of the ports further decreases the operative trauma to the abdominal wall. 3-port colorectal surgery with 1 camera port and 2 operator working ports has previously been demonstrated to be feasible[8-10]. A recent study showed equivalent long-term oncologic outcomes with 3-port right hemicolectomy compared to the conventional 5-port technique; the former was also associated with significantly less operative blood loss[11].

Logically, the minimally invasive nature of surgery is augmented utilizing 3-port surgery in addition to NOSE, enhancing the overall benefit to the patient. In this study we aimed to compare the short-term outcomes following 3-port NOSE surgery with a matched cohort of conventional laparoscopic non-NOSE surgery across a variety of colorectal cancer resection types. We also discuss the in-depth technical approach to NOSE surgery.

MATERIALS AND METHODS

From 1 February to 1 October 2021, all cases of elective 3-port laparoscopic colorectal surgery with NOSE for colorectal cancer were included in the study. Selection criteria for NOSE surgery was adapted from the 2019 International Consensus on Natural Orifice Specimen Extraction Surgery for colorectal cancer[12]. Colectomy for benign diagnoses were excluded from the analysis. Patients with clinical T4 or N2 tumors on staging computed tomography were also excluded. Final decision to proceed with the NOSE procedure was only made following laparoscopic assessment.

The propensity score-matched cohort was identified amongst anonymized subjects who underwent elective laparoscopic colorectal surgery with CSE for colorectal cancer from January 2019 to December 2020. Matching was performed in the ratio of 1:4 based on age, gender, type of resection, and p - tumor node metastasis staging. Statistical analysis was performed using R statistical software (version 4.1.2). Continuous variables were compared with the Mann-Whitney U test and independent t-test, while dichotomous variables with compared using chi-squared test.

Ethics approval for the study was granted by the SingHealth centralized institutional review board (reference number 2022/2114), conforming to the provisions of the Declaration of Helsinki. All patients who underwent NOSE surgery provided written informed consent for participation in the study.

Surgical technique

The 3-port laparoscopic NOSE technique involves 3 phases: (1) Standard laparoscopic bowel mobilization and oncologic resection; (2) Natural orifice specimen extraction; and (3) Intestinal reconstruction. We utilized the port placements and operative set-up as shown in Figure 1.

NOSE procedure: For left-sided resections, transanal NOSE was the only possible natural orifice extraction method in males, and preferable over transvaginal NOSE in females to avoid an additional vaginal incision. The transvaginal route *via* a posterior vaginotomy was chosen to allow retrieval of larger specimens due to the increased elasticity of the vagina[11]. For both transanal and transvaginal NOSE, the specimen was delivered through an extra small Alexis® dual-ring wound protector with the inner ring inserted fully into intraperitoneal space and the outer ring opened against the perineum to shorten the length of the channel (Figure 2). Reducing the length of the channel for extraction is of particular importance for sigmoid cancer surgery where the full length of the rectum is preserved.

For right-sided resections, only females were selected for the NOSE procedure. All specimens were thus extracted transvaginally. We recently reported our technique for 3-port laparoscopic D3 right hemicolectomy with transvaginal NOSE[13]. Transanal NOSE has been successfully performed and described following right-sided colonic surgery, in both male and female patients[14,15]. However, this approach requires an additional rectal incision and was avoided in our cohort, due to the added risk of luminal content spillage.

Care was taken to ensure surgical specimens were delivered complete (Figure 2) and did not tear or rupture during the extraction process. Following transvaginally delivery, the posterior vaginotomy was closed continuously with a barbed suture (Figure 2).

Intestinal reconstruction: Restoration of intestinal continuity following left-sided NOSE surgery requires management of the proximal and distal bowel ends prior to anastomosis, which was performed with a circular stapler.

Two methods were used to secure the anvil to the proximal bowel. The first involved transanal or transvaginal colonic pull-through to allow extracorporeal anvil application (Figure 3). This required complete mobilization of splenic flexure for length. In our cohort, medial-to-lateral splenic flexure takedown did not require additional port placement. The second technique involved securing the anvil

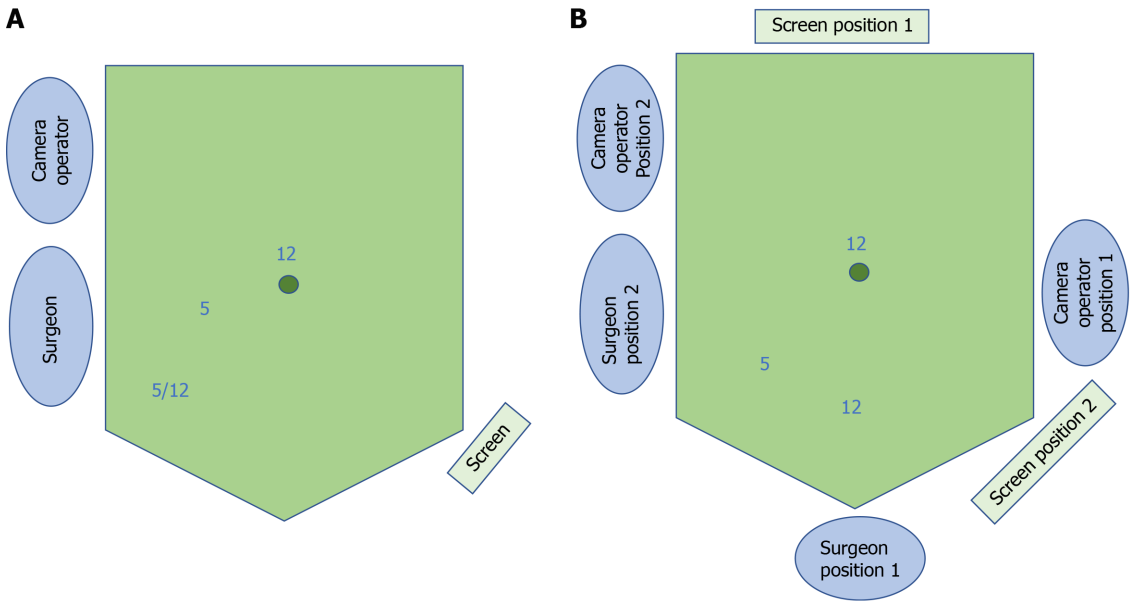

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Figure 1 Schematic of 3-port natural orifice specimen extraction surgery port positioning and operative set-up. A: For left-sided colorectal resection; the right iliac fossa port can be 5 or 12 mm depending on whether a linear stapler is used; B: For right-sided or subtotal/total colectomy, comprising position 1 for the initial phase of surgery and position 2 for the natural orifice specimen extraction procedure.

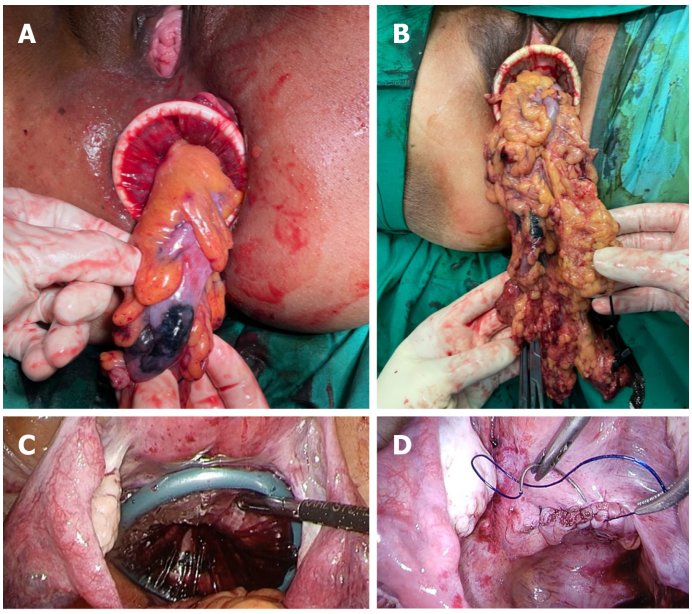

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Figure 2 Operative images of the natural orifice specimen extraction procedure. A: Transanal extraction; B: Transvaginal extraction; C: Intraperitoneal application of the dual-ring wound protector with the uterus hitched to the anterior abdominal wall; D: Closure of the posterior vaginotomy.

to cut end of the proximal bowel using an intracorporeal purse-string suture (Figure 3). This approach required less colonic mobilization but had a theoretical risk of luminal content spillage in a poorly bowel-prepped patient.

Rectal stump closure was performed using several techniques. The first was conventional distal transection with a linear stapler, where transvaginal NOSE was planned. A linear stapler was also used to seal the open rectal stump following transanal NOSE (Figure 4). Otherwise, a purse-string suture could be applied to the rectal stump and anchored to the spike of circular stapler. For high anastomoses, the purse-string could be applied laparoscopically. For low rectal anastomoses, transanal application of the purse-string was preferred, with the aid of a transanal minimally invasive surgery access device (Figure 4).

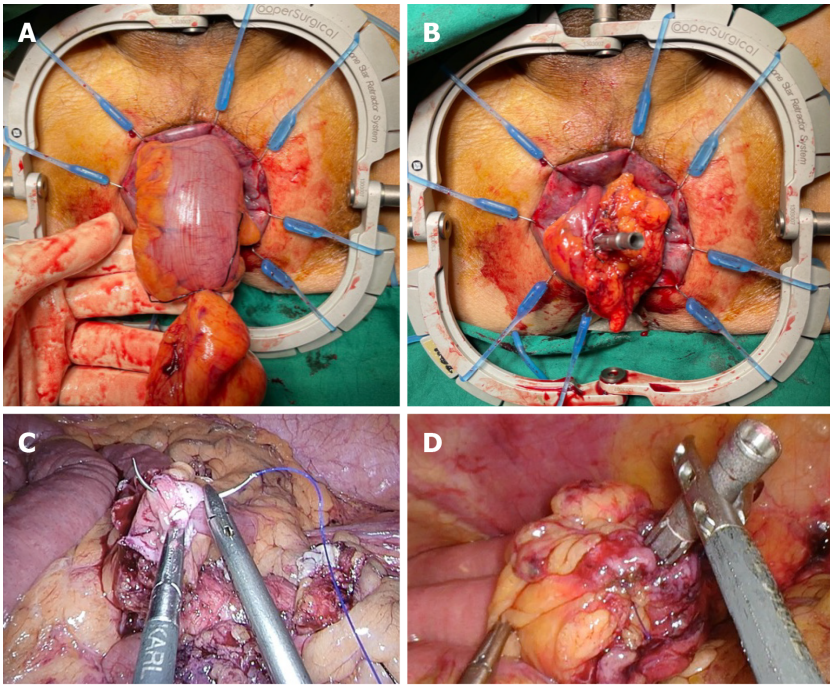

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Figure 3 Methods of securing the circular stapler anvil to the proximal bowel. A and B: Bowel pull-through and extracorporeal anvil application; C and D: Securing the anvil with an intracorporeal purse-string suture.

The hypothetical advantage of rectal purse-string closure is the creation of a double purse-string single-stapled anastomosis (Figure 4). This method eliminates the "dog-ears" of the anastomosis, with theoretical points of weakness at the corners of the linear staple line and the cross-stapled junctions between the linear and circular staple lines[16]. Furthermore, the double purse-string anastomosis enabled the use of a smaller 5 mm port instead of 12 mm, as a linear stapler was not required (Figure 1).

Ileocolic anastomoses following right-sided resections were performed in an antiperistaltic side-to-side fashion, with the linear stapler introduced *via* the 12mm suprapubic port (Figure 1). This was previously demonstrated in a video correspondence[13].

RESULTS

Over the eight-month study duration, 14 consecutive cases (nine female, five male) of elective 3-port laparoscopic colorectal surgery with NOSE were performed by a single surgeon. Patient and surgical characteristics of these are shown in Table 1. Six patients underwent transanal NOSE and eight had transvaginal NOSE. Median age and body mass index (BMI) were 70 (range 43-82) years and 24.1 (range 20.0-31.7) kg/m^2 respectively. All patients with left-sided resections underwent pre-operative bowel preparation with 2 L polyethylene glycol. No bowel preparation was administered for right-sided resections.

Operative data and postoperative outcomes are given in Table 2. Median operative time, intraoperative blood loss and postoperative length of stay were 208 (range 155-365) min, 30 (range 10-150) mL and 3 (range 2-6) d respectively. All patients recovered gastrointestinal function within the first two postoperative d, defined as passage of flatus and non-mucoid stool. All surgical margins were clear (R0) and all had more than 12 harvested lymph nodes.

Overall complication rate was 14% (n = 2), although both were minor without requiring return to the operating theatre. One patient had low-volume chylous ascites (Clavien-Dindo grade I) and the other had high ileostomy output requiring antimotility agents (Clavien-Dindo grade II); the latter was re-admitted to hospital on postoperative day 18 for dehydration. Neither complication was attributable to the natural orifice extraction or reconstruction technique. Postoperative abdominal appearance following 3-port NOSE surgery is shown in Figure 5. Median follow-up duration was 12 (range 8-15) mo. No instances of mortality, local or distant disease recurrence were recorded.

Propensity score matching identified 56 patients from an anonymized, prospectively maintained, retrospective database, who underwent conventional laparoscopic colorectal surgery at our unit from 2019 to 2020. Comparisons of characteristics and perioperative outcomes between the NOSE and non-NOSE cohorts are shown in Table 3 and Table 4 respectively. Due to inconsistent documentation in the non-NOSE group, operative blood loss was not compared between the cohorts.

Table 1 Patient and surgical characteristics for patients who underwent 3-port laparoscopic colorectal surgery with natural orifice specimen extraction

Patient	Age	ASA	Sex	BMI (kg/m²)	Surgery	Indication
1	80	3	F	29.1	Anterior resection, transvaginal NOSE	Sigmoid cancer pT3N1M0
2	59	1	F	20.0	Left hemicolectomy, transvaginal NOSE	Splenic flexure cancer pT3N1M0
3	82	3	F	22.4	Anterior resection, transvaginal NOSE	Sigmoid cancer pT3N0M0
4	43	2	F	31.7	Anterior resection, transanal NOSE	Sigmoid cancer pT1N0M0
5	78	3	F	21.6	Right hemicolectomy (D3), transvaginal NOSE	Transverse colon cancer pT3N1M0
6	63	2	F	28.0	Right hemicolectomy (D3), transvaginal NOSE	Hepatic flexure cancer pT1N0M0
7	77	2	M	20.3	Anterior resection with DI, transanal NOSE	Mid rectal cancer pT3N1M0
8	50	2	F	28.0	Anterior resection, transvaginal NOSE	Sigmoid cancer pT3N0M0
9	77	2	M	24.3	Anterior resection with DI, transanal NOSE	Mid rectal cancer pT3N1M0
10	79	3	M	24.3	Anterior resection, transanal NOSE	Upper rectal cancer pT3N1M0
11	73	3	M	22.4	Anterior resection, transanal NOSE	Sigmoid cancer pT4N2M1
12	58	2	F	23.5	Anterior resection, transvaginal NOSE	Sigmoid cancer pT2N0M0
13	67	2	M	27.6	Anterior resection, transanal NOSE	Sigmoid cancer pT2N1M0
14	58	2	F	23.8	Left hemicolectomy, transvaginal NOSE	Splenic flexure cancer pT1N0M0

ASA: American Society of Anesthesiologists score; BMI: Body mass index; M: Male; F: Female; NOSE: Natural orifice specimen extraction; DI: Defunctioning ileostomy.

Table 2 Intraoperative data and postoperative outcomes for patients who underwent 3-port laparoscopic colorectal surgery with natural orifice specimen extraction

Patient	Operative time (min)	Blood loss (mL)	Time to first flatus/ BO (d[a])	Postoperative LOS (d[a])	Postoperative complications
1	235	30	1/1	4	Nil
2	170	20	1/2	3	Nil
3	210	30	2/2	3	Nil
4	200	20	1/1	3	Nil
5	260	100	2/1	3	Nil
6	255	50	2/2	5	Chylous ascites
7	265	80	1/1	3	Nil
8	175	10	1/1	3	Nil
9	300	150	1/1	6	High stoma output
10	365	100	1/1	3	Nil
11	205	20	1/2	3	Nil
12	155	30	1/2	2	Nil
13	205	10	2/2	3	Nil
14	180	50	1/2	3	Nil

[a]Postoperative days. BO: Bowel opening; LOS: Length of stay.

There were no statistical differences in surgical duration and perioperative complication rates between the NOSE and non-NOSE cohorts. The 3-port NOSE group had significantly quicker return of bowel function, reduced postoperative pain and analgesia use, with a mean use of zero mg of patient-controlled morphine on the second postoperative day. Notably, the average length of hospital stay was

Table 3 Comparison of characteristics between laparoscopic 3-port colorectal natural orifice specimen extraction surgery with a propensity score-matched cohort of conventional surgery

Characteristic	NOSE, *n* = 14 Frequency (%)	Non-NOSE, *n* = 56 Frequency (%)	*P* value
Age, mean ± SD (yr)	67.4 ± 12.4	73.1 ± 10.2	0.182
Gender			
Male	5 (35.7)	21 (37.5)	0.765
Female	9 (64.3)	35 (62.5)	
BMI, mean ± SD (kg/m^2)	24.8 ± 3.5	24.0 ± 4.1	0.526
ASA score			
1	1 (7.1)	1 (1.8)	0.265
2	8 (57.1)	43 (76.8)	
3	5 (35.7)	12 (21.4)	
Tumor location			
Caecum to transverse colon	2 (14.3)	18 (32.1)	0.219
Splenic flexure to sigmoid	9 (64.3)	22 (39.3)	
Rectum	3 (21.4)	16 (28.6)	
Surgery			
Anterior resection	7 (50.0)	23 (41.1)	0.576
Low anterior resection	3 (21.4)	13 (23.2)	
Left hemicolectomy	2 (14.3)	3 (5.4)	
Right hemicolectomy	2 (14.3)	17 (30.4)	
Defunctioning stoma creation			
Yes	3 (21.4)	9 (16.1)	0.634
No	11 (78.6)	47 (83.9)	
AJCC pT stage			
T1	4 (28.6)	7 (12.5)	0.527
T2	2 (14.3)	10 (17.9)	
T3	7 (50)	33 (58.9)	
T4	1 (7.1)	6 (10.7)	
AJCC pN stage			
N0	6 (42.9)	33 (58.9)	0.236
N1	7 (50.0)	15 (26.8)	
N2	1 (7.1)	8 (14.3)	
M stage			
M0	13 (92.9)	55 (98.2)	0.282
M1	1 (7.1)	1 (1.8)	
Stage			
I	4 (28.6)	13 (23.2)	0.162
II	1 (7.1)	20 (35.7)	
III	8 (57.1)	22 (39.3)	
IV	1 (7.1)	1 (1.8)	

NOSE: Natural orifice specimen extraction; ASA: American Society of Anesthesiologists score; BMI: Body mass index; SD: Standard deviation, AJCC:

American Joint Committee on Cancer Staging 8th Edition.

Table 4 Comparison of perioperative outcomes between laparoscopic 3-port colorectal natural orifice specimen extraction surgery with a propensity score-matched cohort of conventional surgery

Outcome	NOSE *n* = 14 Frequency (%)	Non-NOSE *n* = 56 Frequency (%)	*P* value
Duration of surgery, mean ± SD (min)	227 ± 55	261 ± 96	0.463
Intraoperative complications			
Yes	0 (0)	2 (3.6)	0.473
No	14 (100)	54 (96.4)	
30-day postoperative complications			
Yes	2 (14.3)	13 (23.2)	0.466
No	12 (85.7)	43 (76.8)	
Clavien-Dindo classification			0.202
1	1 (7.1)	5 (8.9)	
2	1 (7.1)	7 (12.5)	
3	0	0	
4	0	1 (1.8)	
5	0	0	
Time to first bowel movement, mean ± SD (d)	1.2 ± 0.4	2.6 ± 2.0	<0.001
Length of hospitalization stay, mean ± SD (d)	3.4 ± 1.0	6.4 ± 5.3	<0.001
POD 1 highest pain score[a], mean ± SD	1.5 ± 1.9	3.0 ± 2.0	0.012
POD 2 highest pain score[a], mean ± SD	0.7 ± 1.5	1.8 ± 2.2	0.066
POD 1 PCA total morphine use, mean ± SD (mg)	1.4 ± 3.3	6.7 ± 8.1	0.002
POD 2 PCA total morphine use, mean ± SD (mg)	0	2.5 ± 5.1	0.005

[a]Measured using visual analog scale. NOSE: Natural orifice specimen extraction; SD: Standard deviation; POD: Postoperative day; PCA: Patient-controlled analgesia.

almost twice as long in the non-NOSE group compared to the NOSE group.

DISCUSSION

As recommended by the international NOSE surgery consensus, the maximum tumor dimension for transanal and transvaginal NOSE are 3 cm and 5 cm respectively[12]. While tumor size can be estimated on preoperative imaging, the decision to proceed with the NOSE procedure can often only be established intraoperatively, due radiological limitations on assessment of peritumoral desmoplastic reaction and mesocolic or mesorectal bulkiness, which may add considerably to the overall specimen diameter.

Moreover, while absolute diameter is an important consideration, the relative size of the specimen to the width of the pelvic outlet as well as the laxity of the chosen bodily orifice may be more crucial in determining the success or failure of the procedure. As illustrated by a recent series of NOSE following sigmoidectomy for volvulus, surgery for benign colorectal disease without a physical mass is ideal for NOSE[17].

BMI limits of 30 kg/m^{2}and 35 kg/m^2 were suggested for transanal and transvaginal NOSE respectively[12]. Obese patients often possess a bulkier mesocolon or mesorectum which increases the difficulty of extraction. Nonetheless, the benefits of reduced incision may be more apparent in a patient with a thicker abdominal wall, who is at an increased risk of wound complications including infection and herniation. We previously demonstrated a successful transvaginal NOSE technique in a patient with BMI of 37 kg/m^2[18]. A large retrospective Australian study also demonstrated the feasibility of NOSE in obese patients[19].

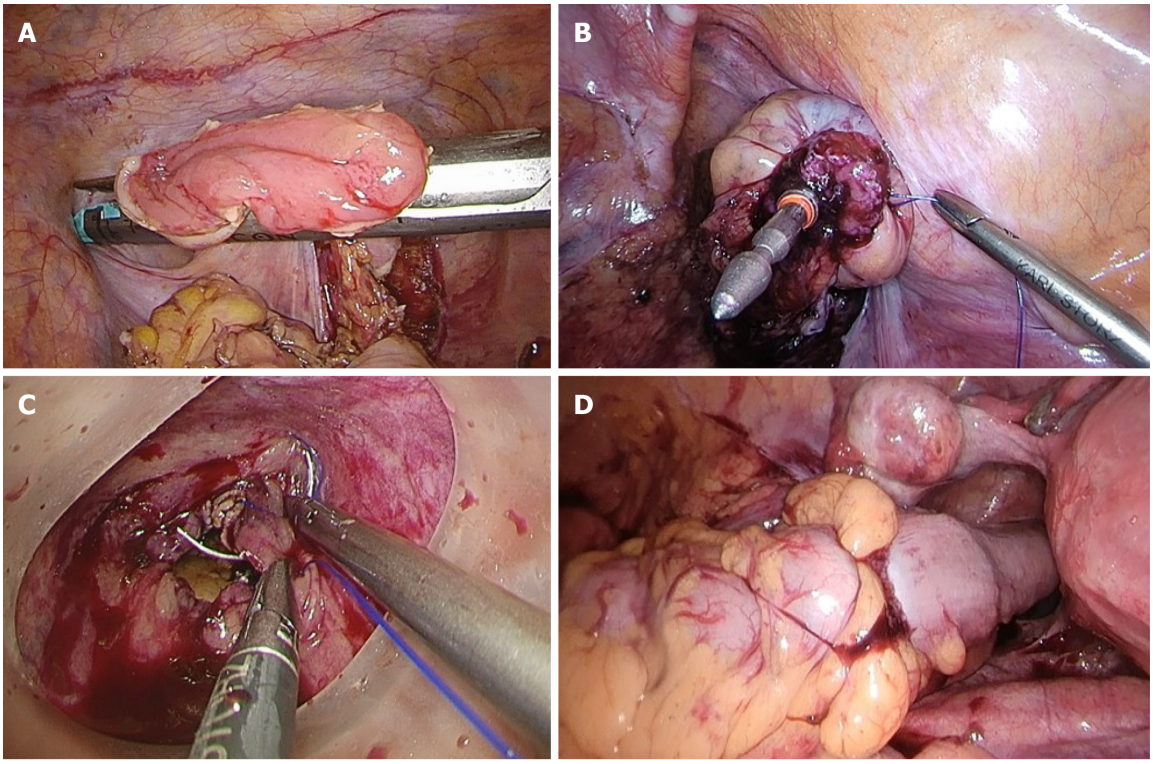

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Figure 4 The hypothetical advantage of rectal purse-string closure is the creation of a double purse-string single-stapled anastomosis. A and B: Methods of rectal stump closure linear-stapled closure, intracorporeal purse-string suture onto the fully extended spike of the circular stapler; C: Transanal purse-string suture with a transanal access device; D: A double purse-string single-stapled anastomosis.

Unlike prior reports, NOSE did not significantly add to operative time in our experience, even with the removal of assistant ports[2-4]. Following our findings, routine postoperative patient-controlled opioid anaesthesia (PCA), a feature of our unit's enhanced recovery program, was discontinued for NOSE patients in view of minimal use[20]. Furthermore, postoperative ileus was virtually eliminated in the studied cohort. This may be explained by the relative lack of extracorporeal bowel exposure, as well as quicker patient mobilization. There were also no infective complications recorded, despite known concerns regarding contamination during transanal specimen extraction[21].

While the reduction of several laparoscopic ports may ostensibly offer only minor improvement over traditional 4- or 5-port surgery, reduced-port colorectal surgery represents another incremental step towards the holy grail of scarless surgery. In the modern era of minimally invasive surgery, an accumulation of several small gains may be required to make meaningful clinical differences to patient outcomes. In our opinion, the reduced-port technique is synergistic with natural orifice specimen extraction techniques to further minimize abdominal wall trauma. Another advantage of reduced-port surgery is the removal of dependence on a surgical assistant, particularly in the setting of limited manpower resources.

Single incision laparoscopic surgery (SILS), and 2-port laparoscopic surgery (using a SILS multi-channel umbilical port and one separate working port), have been demonstrated in colorectal surgery [22-24]. While these techniques reduce the number of ports even further, a larger umbilical incision is generally required for insertion of a multi-channel access device, which offsets the decrease in overall number of ports. Considerable operative challenges can also be anticipated with a SILS access device, including clashing of the laparoscopic instruments with the endoscope, and operator discomfort due to awkward surgical posture. In our experience, the 3-port technique provides the optimal balance between minimizing abdominal trauma and allowing operator as well as cameraman comfort by enabling adequate optical and working port triangulation.

A technical learning curve exists for 3-port NOSE surgery, and the 3-port technique and natural orifice extraction each present with a separate set of challenges. The issue of lack of tissue traction by an assistant can be overcome *via* positional changes of the operating table. The uterus should be hitched to the anterior abdominal wall for all female patients (Figure 2), facilitating pelvic visualization during rectal mobilization or the NOSE procedure. Additional assistant ports should be used if difficulties are encountered. In event of a problematic natural orifice extraction, transabdominal specimen extraction can be performed instead of NOSE with minimal added detriment to the patient. Operators should be proficient in conventional laparoscopic colorectal surgery before attempting the 3-port NOSE technique.

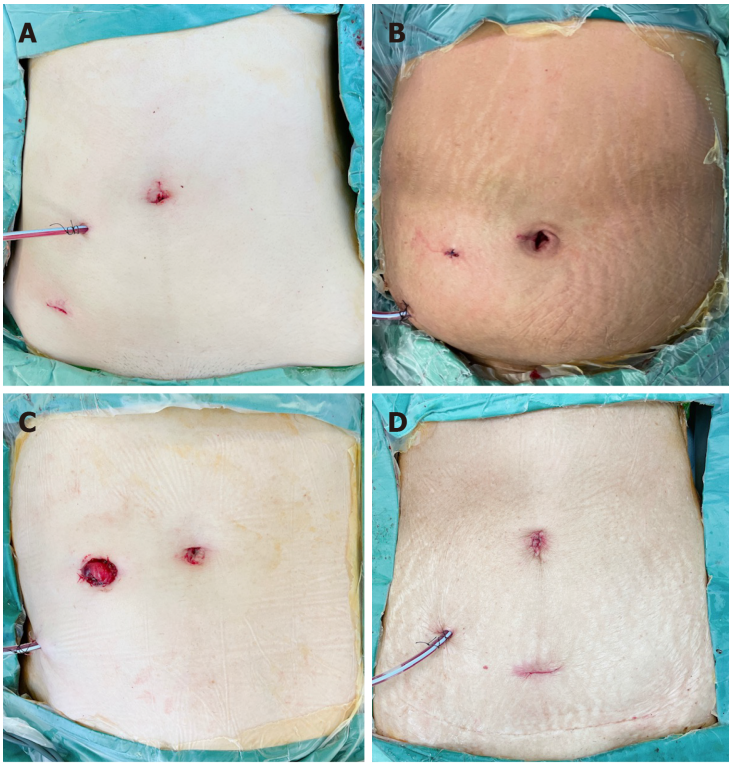

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Figure 5 Postoperative abdominal incisions and appearance. A: Anterior resection with transvaginal natural orifice specimen extraction (NOSE); B: Anterior resection with transanal NOSE; C: Low anterior resection and defunctioning ileostomy with transanal NOSE; D: D3 right hemicolectomy with transvaginal NOSE.

Our study is limited by the small sample size in the NOSE cohort. Furthermore, the benefits shown in the 3-port NOSE group may have been largely contributed by the reduced abdominal incision, consistent with the findings from previous studies, rather than the reduced number of ports used[2-4]. Nonetheless, the feasibility and clinical applicability of the 3-port NOSE technique is still demonstrated across a range of colorectal resection types, with considerable improvements in short-term outcomes compared to conventional laparoscopy.

CONCLUSION

3-port laparoscopic colorectal surgery with NOSE is a feasible and safe technique, and together augment the minimally invasive nature of surgery producing excellent cosmesis and good outcomes. Appropriate patient selection and expertise in conventional laparoscopy are required. Larger studies are necessary to draw conclusive results.

ARTICLE HIGHLIGHTS

Research background

Natural orifice specimen extraction (NOSE) *via* the anus or vagina replaces conventional transabdominal specimen retrieval *via* the transabdominal route through a limited mid-line laparotomy or Pfannenstiel incision. Reducing the number of laparoscopic ports further decreases operative abdominal wall trauma. These techniques reduce the surgical wound size as well as the risk of incision-related morbidity.

Research motivation

To our knowledge, the technique of 3-port colorectal cancer surgery with NOSE has never been evaluated or described in-depth.

Research objectives

To compare short-term outcomes following 3-port NOSE surgery with a matched cohort of conventional non-NOSE colorectal cancer surgery.

Research methods

This was a retrospective cohort study of patients who underwent elective 3-port laparoscopic colorectal NOSE surgery between February to October 2021. The propensity score-matched cohort was identified amongst patients who underwent conventional laparoscopic colorectal surgery from January 2019 to December 2020. Matching was performed in the ratio of 1:4 based on age, gender, type of resection, and p - tumor node metastasis staging.

Research results

Our results showede no statistical differences in surgical duration and perioperative complication rates between the NOSE and non-NOSE cohorts. As hypothesized, the 3-port NOSE cohort had significantly quicker mean return of bowel function (2.6 *vs* 1.2 d, $P < 0.001$), reduced postoperative pain and patient-controlled analgesia use, and decreased length of hospital stay (6.4 *vs* 3.4 d, $P < 0.001$), compared to the conventional surgery cohort.

Research conclusions

3-port laparoscopic colorectal surgery with NOSE is a feasible technique, augmenting the minimally invasive nature of surgery and producing good outcomes.

Research perspectives

Studies with larger patient numbers are necessary to draw definitive conclusions. A defined criteria should be evaluated for more objective selection of patients who are considered for colorectal NOSE surgery.

FOOTNOTES

Author contributions: Seow-En I conceived the research and study design; Seow-En I, Chen LR, Li YX, and Tan EKW contributed to data acquisition and analysis; Zhao Y performed the statistical analysis; all authors were involved in interpretation of data and writing of the manuscript, as well as editing and revision of the article, read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the SingHealth Institutional Review Board.

Informed consent statement: All natural orifice specimen extraction study participants provided informed written consent prior to study enrolment.

Conflict-of-interest statement: All authors declare no conflict-of-interest.

Data sharing statement: No additional data are available.

STROBE statement: All authors have read the STROBE Statement - checklist of items, and the manuscript was prepared and revised according to the STROBE Statement - checklist of items.

Country/Territory of origin: Singapore

ORCID number: Isaac Seow-En 0000-0001-8287-6812; Lionel Raphael Chen 0000-0002-6541-7099; Yi-Xin Li 0000-0001-9256-6391; Yun Zhao 0000-0003-4093-4695; Jing-Hui Chen 0000-0002-2769-1089; Hairil Rizal Abdullah 0000-0003-1916-0832; Emile Kwong-Wei Tan 0000-0002-0771-5063.

Corresponding Author's Membership in Professional Societies: Society of Colorectal Surgeons (Singapore).

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ORIGINAL ARTICLE

Retrospective Study

Oncology and reproductive outcomes over 16 years of malignant ovarian germ cell tumors treated by fertility sparing surgery

Muangloei Rungoutok, Prapaporn Suprasert

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Muangloei Rungoutok, Prapaporn Suprasert, Department of Obstetrics and Gynecology, Chiang Mai University, Muang 50200, Chiang Mai, Thailand

Corresponding author: Prapaporn Suprasert, MD, Associate Professor, Department of Obstetrics and Gynecology, Chiang Mai University, 110 Inthawarorod Road, Muang 50200, Chiang Mai, Thailand. psuprase@gmail.com

Abstract

BACKGROUND

Malignant ovarian germ cell tumors (MOGCT) are rare and frequently occur in women of young and reproductive age and the oncologic and reproductive outcomes after fertility-sparing surgery (FSS) for this disease are still limited.

AIM

To evaluate the oncology and reproductive outcomes of MOGCT patients who underwent FSS.

METHODS

All MOGCT patients who underwent FSS defined as the operation with a preserved uterus and at least one side of the ovary at our institute between January 2005 and December 2020 were retrospectively reviewed.

RESULTS

Sixty-two patients were recruited for this study. The median age was 22 years old and over 77% were nulliparous. The three most common histology findings were immature teratoma (32.2%), dysgerminoma (24.2%), and yolk sac tumor (24.2%). The distribution of stage was as follows; Stage I, 74.8%; stage II, 9.7%; stage III, 11.3%; and stage IV, 4.8%. Forty-three (67.7%) patients received adjuvant chemotherapy. With a median follow-up time of 96.3 mo, the 10-year progression-free survival and overall survival were 82.4% and 91%, respectively. For reproductive outcomes, of 43 patients who received adjuvant chemotherapy, 18 (41.9%) had normal menstruation, and 17 (39.5%) resumed menstruation with a median time of 4 mo. Of about 14 patients who desired to conceive, four were pregnant and delivered good outcomes. Only one case was aborted. Therefore, the successful pregnancy rate was 28.6%

CONCLUSION

The oncology and reproductive outcomes of MOGCT treated by FSS are excellent.

Many patients show a long survival time with normal menstruation. However, the obstetric outcome is not quite satisfactory.

Key Words: Malignant ovarian germ cell tumor; Fertility-sparing surgery; Oncology outcome; Reproductive outcome; Pregnancy rate; Survival rate

Core Tip: The oncology and reproductive outcomes of malignant ovarian germ cell tumors treated by fertility-sparing surgery were satisfying. Even though most patients developed normal menstruation, nearly 1/3 were successfully pregnant and delivered.

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INTRODUCTION

Malignant ovarian germ cell tumors (MOGCT) account for about 5% of all ovarian cancer cases and approximately 70% develop in young women[1]. With the introduction of chemotherapy consisting of bleomycin, etoposide, and cisplatin (BEP) for MOGCT treatment after surgery, the outcome of this malignancy is excellent even in the advanced stage[2]. The cure rate of MOGCT in the early stage and the advanced stage was 100% and 75%, respectively[3]. Therefore, in patients who were of young and reproductive age, the role of fertility-sparing surgery (FSS) defined as cytoreductive surgery with preservation of the contralateral adnexa and uterus is the standard treatment for these patients[4]. We previously reported a 10-year overall survival (OS) rate as high as 86.2% but did not focus on the patients who underwent FSS[5]. Therefore, with the limited data on oncology and reproductive outcomes of FSS especially in Southeast Asia, this study was conducted to identify these outcomes of MOGCT patients who were treated by FSS.

MATERIALS AND METHODS

Study population

After the protocol was approved by the local ethics committees, the medical records of the MOGCT patients who underwent FSS defined as surgical cytoreduction with preservation of the uterus and unilateral adnexa at Chiang Mai University Hospital from January 2005 through December 2020 were reviewed. The patients who developed other histologic types arising in germ cell tumors were excluded. The basic clinical data, histology, staging, type of surgery, chemotherapy regimen, and outcomes were identified. All pathology specimens were examined by gynecologic pathologists in our institute. The decision of treatment depended on the preference of the physicians.

Oncology outcome

After complete treatment, the surveillance schedule was set every 3 mo in the first year, every 4 mo in the second year, every 6 mo in the third to fifth year, and annually thereafter. At that time, all of the patients were examined for a blood test for MOGCT and were examined by gynecologic oncologists. Pelvic ultrasonography was done at each visit for unmarried patients. Other imaging modalities such as CT were utilized when clinically indicated or with a rising of tumor markers.

Progression-free survival (PFS) was defined as the time between the month of the primary surgery and the month of tumor progression or recurrence detection or last contact, whereas OS was defined as the similar starting time of PFS to the month of patient death or last contact. The death data was also sought from the Thai Civil registration system *via* the National identification card number. Both PFS and OS were estimated by the Kaplan-Meier method using the SPSS for Windows program (Version 22; IBM Corporation, Armonk, New York, United States). Descriptive data of all studied patients are presented as the mean with range and discrete data are reported as numbers and percentages.

Reproductive outcome

The reproductive outcome after FSS was identified by collecting the data on the menstrual status during and after treatment, the number of pregnancies and childbirth before and after treatment, the present marital status, the childbearing desire, the method of pregnancy, gestational age at delivery, birth weight of the baby, and obstetrical complications from the medical records and direct contact with the patients by phone for more information.

RESULTS

Among 98 MOGCT, 62 patients underwent FSS in the studied period. The clinical data are presented in Table 1. The median age of these patients was 22 with a range of 4-34 years old. Over 77% of them were nulliparous and the three most common presentations were pelvic mass, abdominal pain, and abdominal distension. Approximately 54.8% of the tumors were located on the right side and 41.9% on the left side.

The details of FSS are as follows: Unilateral salpingo-oophorectomy (SO) in 49 cases, unilateral ovarian cystectomy in four, and unilateral SO with contralateral ovarian cystectomy in the rest. A frozen section was done in 26 cases. About staging procedures, peritoneal cytology was done in 39 cases with ten cases revealing positive malignancy cells, while omentectomy was done in 44 cases and lymphadenectomy was performed in 30, with four cases each having positive results. Half of the studied patients underwent an appendectomy. Regarding the surgical outcomes, 75.8% had complete resections.

The three leading histology types were immature teratoma (32.3%), dysgerminoma (24.2%), and yolk sac tumor (24.2%). The majority of the patients were in stage I (74.2%) and about 4.8% were in stage IV. Nearly 70% of the patients were given adjuvant chemotherapy. All except one was BEP regimen. Only one case was given etoposide + methotrexate + actinomycin D + cyclophosphamide + vincristine (EMACO). This case was diagnosed with stage IV choriocarcinoma. About one-third of the patients received four to six cycles of chemotherapy. Concerning the long-term side effects of chemotherapy, numbness occurred in three cases, lung fibrosis occurred in two, and hearing problems in two. Five patients died; two died from neutropenic sepsis and the rest from the progression of the disease.

Oncology outcome

With a median follow-up time of 96.3 mo, the 10-year PFS and OS were 82.4% and 91% as shown in Figures 1 and 2, respectively. However, 62.9% did not continue regular follow-ups.

Four cases developed progression after primary FSS. The details of these patients are summarized in Table 2. One of them lived while the others died from the disease progression during treatment. The surviving case was a 17-year-old with stage IC1 grade 2 immature teratoma. The primary surgery was right SO and appendectomy with pelvic recurrence developing 1 mo after the operation. She underwent tumor debulking and received six cycles of the BEP regimen. She is still alive without disease with an overall survival of 109 mo. The other three cases had stage IV disease. The histology was yolk sac tumor in two cases with choriocarcinoma in the remainder. All of them underwent FSS and received multiple chemotherapy regimens with unfavorable outcomes and died of disease after primary surgery at 16, 28, and 30 mo. One case developed lung fibrosis after being administered two cycles of the BEP regimen.

Regarding four patients who underwent only a cystectomy, the pathology was immature teratoma in two cases (stage IA grade 2 and stage IC grade 1), papillary thyroid cancer arising from mature teratoma (1), and carcinoid tumor (1). Only one case of stage IA grade 2 immature teratoma received four cycles of BEP regimen while the other received only an operation. All of them are still alive at present with an overall survival of 44-173 mo.

Reproductive outcome

Of 62 patients, 43 received adjuvant chemotherapy with BEP in 41 cases and EMACO in the rest. The menstrual history of these patients is summarized in Table 3. Forty-two percent of the patients had menstruation while receiving chemotherapy, while 39.5% resumed menstruation after complete treatment with a median resumption time of 4 mo. One case was five years old at the treatment time with menarche at age 12 (seven years later).

Eight patients were without menstruation after chemotherapy. The one case without menarche at presentation was 12 years old. She was diagnosed with stage I mixed MOGCT and received six cycles of BEP regimen after undergoing right SO at 5 years of age. She was followed regularly with no evidence of recurrence. The remaining seven patients developed premature menopause. One case was diagnosed as having a stage IIA endodermal sinus tumor at 29 years old. She received six cycles of BEP regimen after undergoing right SO and omentectomy on January 1, 2017. One year after that, she developed a left ovarian tumor measuring 10 cm × 15 cm and received a hysterectomy with left SO. The final pathology revealed grade 1 endometrioid CA. The patient was given six cycles of carboplatin with a disease-free survival of 61 mo and received estradiol valerate 2 mg as hormonal therapy. The other two patients underwent FSS and received three and six cycles of BEP, respectively. Both cases did not resume menstruation after completing treatment. One case received hormonal therapy. However, both cases

Table 1 Clinical data (*n* = 62)

	n (%)
Median age (range; yr)	22.0 (4-34)
Parity before surgery	
0	48 (77.4)
1	8 (12.9)
2	6 (9.7)
Presentation	
Pelvic mass	24 (38.7)
Abdominal pain	18 (29.0)
Abdominal distension	15 (24.2)
Others[1]	5 (8.1)
Tumor side	
Right	34 (54.8)
Left	26 (41.9)
Bilateral	2 (3.2)
Detail of FSS	
Unilateral SO	49 (79.0)
Unilateral cystectomy	4 (6.5)
Unilateral SO & cystectomy	9 (14.5)
Frozen section	26 (41.9)
Cytology	
Not done	23 (37.1)
Negative	29 (46.8)
Positive	10 (16.1)
Omentectomy	
Not done	18 (29.0)
Negative	40 (64.5)
positive	4 (6.5)
Lymphadenectomy	
Not done	32 (51.6)
Negative	26 (41.9)
Positive	4 (6.5)
Appendectomy	32 (51.6)
Surgical outcome	
No residual	47 (75.8)
Optimal	5 (8.1)
Suboptimal (residual tumor > 1 cm)	10 (16.1)
Histology	
Dysgerminoma	17 (27.4)
Immature teratoma	20 (32.3)
Yolk sac tumor	15 (24.2)
Mixed type	5 (8.1)

Others[2]	5 (8.1)
Stage	
I	46 (74.2)
II	6 (9.7)
III	7 (11.3)
IV	3 (4.8)
Adjuvant chemotherapy	
None	19 (30.6)
BEP	42 (67.7)
EMACO	1 (1.6)
Cycles of chemotherapy	
1-3	6
4-6	33
> 6	4
Long-term side effect	
None	46 (74.2)
Numbness	3 (4.8)
Lung fibrosis	2 (3.2)
High-frequency hearing loss	1 (1.6)
Tinnitus	1 (1.6)
Progression of disease	4 (9.5)
Death	5 (8.1)
Alive	55 (88.7)
Missing data	2 (3.2)

[1]Others: Amenorrhea (2), anti-NMDAR (N-methyl D-aspartate receptors) encephalitis (1), incidental finding during cesarean section (1), and hyperthyroidism (1).
[2]Others: Struma ovarii (1), carcinoid (1), chorioCA (1), steroid cell tumor (1), and papillary thyroid CA arising in teratoma (1).
Death: SN 43, 52, 74, 108, and 110. SO: Salpingo-oophorectomy; BEP: Bleomycin etoposide cisplatin; EMACO: Etoposide methotrexate actinomycin D cyclophosphamide vincristine.

were followed for only 1 year after FSS. Four cases died, two from neutropenic sepsis, and two from disease progression after multiple chemotherapy regimens. The details of these patients are summarized in Table 4.

Regarding 19 patients who underwent only FSS without adjuvant chemotherapy, one was lost to follow-up since surgery while the remaining 18 had no problem with menstruation. One case was diagnosed with stage I immature teratoma and received left SO with omentectomy and appendectomy at 4 years old. At 15 years old, her menarche occurred.

For pregnancy outcomes, the data was available in 30 patients and revealed that 14 cases attempted to become pregnant and four of them (28.6%) succeeded in delivering a term baby after 1 year for two cases and 6 years for one case. One patient was known to give one term birth due to unavailable contact details. Three cases underwent unilateral SO and the rest received a unilateral ovarian cystectomy. The histology of these four cases was grade 1 carcinoid tumor neuroendocrine tumor (1), dysgerminoma (2), and grade 1 immature teratoma (1). Moreover, one case developed a spontaneous abortion 2 years after treatment and was never pregnant again. She was diagnosed with a steroid cell tumor. None of the patients who attempted to conceive actively tried to become pregnant by going to an infertility clinic. The details of these patients are shown in Table 5.

Table 2 Progression cases (*n* = 4)

SN	Year	Age	Stage	Histology	Chemotherapy	Cycle	Site	Primary surgery	Note
50	2013	17	IC1	Immature teratoma grade 2	None	-	Right	Right SO and appendectomy	PFS 3 mos →pelvic recurrence → debulking tumor and BEP × 6 cycles → alive without disease DFS 103 mos, overall survival 109 mo
52	2013	15	IV	Yolk sac tumor	BEP	8	Right	Right SO and left cystectomy and omentectomy	Progression after BEP × 8: Liver & lung metastasis → TIP x 2 → PT × 1 → ifosfamide × 1 → progression → death (overall survival 16 mo)
74	2010	18	IV	Choriocarcinoma	EMACO	6	Left	Left SO and omentectomy and appendectomy and PAN sampling	EMACO × 6 → progression (PFS 7 mos) → cisplatin and ifosfamide × 5 → paclitaxel × 1 → Act D and 5 FU × 1 → VAC × 1 → TAH and right SO (19/4/2011) → EMA/EP × 9 → TP/TE × 1 → BEP × 2 → palliative treatment → death 5/7/2012 overall survival 28 mo
110	2005	16	IV	Yolk sac tumor	BEP × 2 → EP × 11	12	Right	Right SO and appendectomy	Progression after EP × 11 → ifosfamide × 1 → EMA × 1 → single paclitaxel × 1 → palliative RT 25/1/2006 → VAC × 1 → Death 4/7/2007,OS 30 mo (lung fibrosis after BEP × 2)

PFS: Progression-free survival; DFS: Disease-free survival; SO: Salpingo-oophorectomy; PAN: Para-aortic lymph node; BEP: Bleomycin etoposide cisplatin; EMACO: Etoposide methotrexate actinomycin D cyclophosphamide vincristine; TIP: Paclitaxel ifosfamide cisplatin; PT: Paclitaxel carboplatin; Act D; actinomycin d; EMA/EP: Etoposide methotrexate actinomycin D etoposide cisplatin; 5FU: Fluorouracil; VAC: Vincristine dactinomycin and cyclophosphamide; TP/TE: Paclitaxel cisplatin/paclitaxel etoposide; TAH: Total abdominal hysterectomy; EP: Etoposide cisplatin, palliative; RT: Radiotherapy.

Table 3 Menstrual data of studied patients who received chemotherapy (*n* = 43)

	n (%)
No menstruation after treatment	8 (18.6)
No menarche[1]	1
Premature menopause	7
Resume menstruation[2]	17 (39.5)
1 mo	2
2 mo	2
3 mo	2
4 mo	3
5 mo	1
6 mo	6
Median 4 mo (1-6)	
Menstruation during and post-treatment	18 (41.9)

[1]SN 4, no menarche at age 12 years old.
[2]SN 64, menarche at age 12.

DISCUSSION

Oncology outcome

The outcome of 62 MOGOT patients who were treated by FSS in the present study was excellent with the 10-year PFS and OS being 82.4% and 91%, respectively. These results were close to the previous reports. Zamani *et al*[6] studied 79 MOGCT over 15 years and showed the 10-year OS as 94.4%. This study recruited only stages I-III while our study recruited all stages including three progressed cases of

Table 4 Details of premature menopausal patients (*n* = 7)

SN	Year	Age	Stage	Histology	Chemotherapy	Cycle	Site	Primary surgery	Note
25	2017	29	IIA	Yolk sac tumor	BEP	6	Right	Right SO and omentectomy January 6, 2017	16/1/18 abdominal pain and pelvic mass size 10 cm × 15 cm, solid and cystic, movable AFP 2.2 → TAH and left SO 19/1/18 → endometrioid CA IA → carboplatin × 6 → complete response → DFS 61 mo, HRT
43	2014	16	III	Dysgerminoma	BEP	4	Bilateral	Left SO and omentectomy	Partial response during BEP, overall survival of 3 mo, death from sepsis (neutropenia)
52	2013	15	IV	Yolk sac tumor	BEP	8	Right	Right salpingo-oophorectomy with left ovarian cystectomy	PFS 15 mo → TIP × 2 cycles → PT × 1 → ifosfamide × 1 cycle → death OS 16 mo
87	2008	28	I	Dysgerminoma	BEP	3	Left	Left SO	HRT icycloprogynova lost to follow up since 2009, unknown status
108	2005	15	III	Yolk sac tumor	BEP	6	Right	Right SO	Febrile neutropenia → sepsis → death 2005 OS 9 mo
110	2005	16	IV	Yolk sac tumor	BEP × 2 → EP × 11	12	Right		Progression after EP × 11 → ifosfamide × 1 → EMA × 1 → single paclitaxel × 1 → palliative RT January 25, 2006 → VAC × 1 → Death July 4, 2007, OS 30 mo (lung fibrosis after BEP × 2)
114	2005	23	II	Dysgerminoma	BEP	6	Right	Right SO	Alive, loss after 12 mo since start treatment, no HRT

BEP: Bleomycin etoposide cisplatin; SO: Salpingo-oophorectomy; TAH: Total abdominal hysterectomy; AFP: Alpha-fetoprotein; DFS: Disease free survival; HRT: Hormonal replacement therapy; PFS: Progression free survival; TIP: Paclitaxel ifosfamide cisplatin; PT: Paclitaxel carboplatin; OS: Overall survival; EP: Etoposide cisplatin; EMA: Etoposide methotrexate + actinomycin D; palliative RT: Radiotherapy.

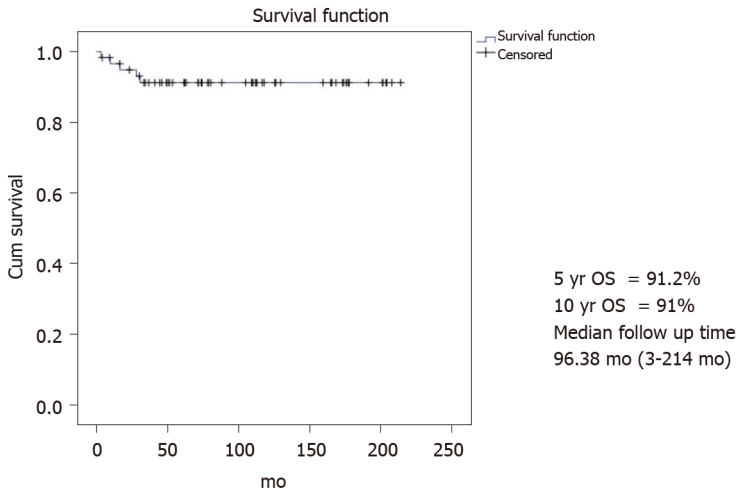

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Figure 1 Overall Survival. 5-year overall survival (OS) = 91.2%, 10-year OS = 91%, and median follow-up time = 96.38 mo (3-214 mo). OS: Overall survival.

stage IV. Another study from Korea[1] studied 171 MOGCT patients who underwent FSS for 23 years (1992-2015). They reported the 5-year PFS and OS as 86% and 97%, respectively. About 14.6% developed recurrent disease and the death rate of disease was 2.9%. This recurrence rate was higher than our study which showed the progression of the disease at only 1.6%. However, due to over 2/3 of our patients without regular follow-up, the actual number of recurrence patients might be missed. However, the death rate of this disease in our study was 4.8%, which is near the Korean report. In addition, Beiner *et al* [7] reviewed eight retrospective studies comparing FSS with the conventional operation for MOGCT patients and found that both types of surgery were not significant for recurrence.

Regarding ovarian cystectomy in MOGCT, although this operation was not the standard of FSS, Tamauchi *et al*[8] showed an excellent outcome in eight patients who were diagnosed with early-stage

Table 5 Pregnancy outcomes

SN	Year	Age Dx	Age Preg	Stage	Histology	Site	Chemotherapy	Cycle	Parity	Primary surgery	Pregnancy outcome
19	2018	30	31	IA	Carcinoid tumor neuroendocrine tumor grade 1 arising in mature cystic teratoma	Left	None	-	1001	Laparoscopic left ovarian cystectomy June 1, 2018	1 Term pregnancy, GA 39 wk, NL August 1, 2019, BW 3030 gm
53	2013	21	27	IC	Dysgerminoma	Right	BEP	4	-	Right SO and omentectomy and appendectomy June 15, 2013	1 Term pregnancy, C/S GA 38 wk April 23, 2019, BW 2780 gm, ompholocele 9 cm × 8 cm, and atrial septal defect → surgical correction
84	2008	19	21	IA	Steroid cell tumor	Right	None	-	-	Right SO and omentectomy and PNS and PAS December 18, 2008	1 spontaneous abortion 31/1/2010
92	2005	34	35	IA	Immature teratoma grade[1]	Left	None	-	1001	Left SO	1 Term pregnancy, GA 38 wk, NL 10/12/2006, BW 2700 gm
94	2007	24	26	IA	Dysgerminoma	Left	None	-	1001	Left SO and omentectomy October 9, 2007	1 Term pregnancy with no available data of birth date, GA, and BW

[1]Parity before primary surgery.

NB: 14 of 30 patients who could be contacted for this information revealed an attempt to conceive. GA: Gestational age; BW: Birth weight; BEP: Bleomycin etoposide cisplatin; SO: Salpingo-oophorectomy; C/S: Cesarean section; PNS: Pelvic lymph node sampling; PAS: Para-aortic lymph node sampling.

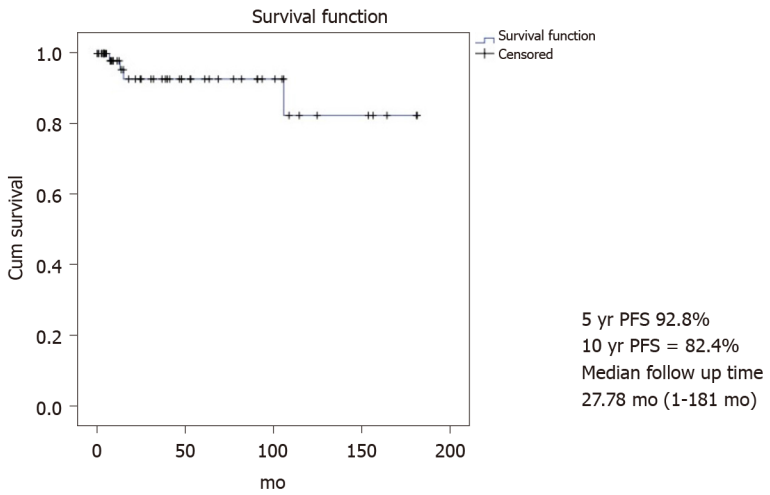

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Figure 2 Progression free survival. 5-year progression free survival (PFS) = 92.8%, 10-year PFS = 82.4%, and median follow-up time = 27.78 mo (1-181 mo). PFS: Progression-free survival.

immature teratoma treated by ovarian cystectomy. Five patients received chemotherapy. With a median follow-up time of 4.7 years, all patients were still free of disease. The authors suggested that cystectomy followed by adjuvant chemotherapy showed impressive outcomes for early-stage MOGCT, especially in immature teratoma. For our study, four cases underwent ovarian cystectomy with one case of stage IA grade 2 immature teratoma and received adjuvant chemotherapy. All of them were still alive at a duration time of 44-173 mo after surgery.

Reproductive outcome

The 70.8% of patients who had no menstruation during treatment by FSS and chemotherapy in this study resumed menstruation with a median time of 4 mo. The true premature ovarian failure from chemotherapy occurred in only two (3.2%) cases. Both underwent unilateral SO with three and six cycles of the BEP regimen. Turkmen *et al*[9] used the Tokai Ovarian Tumor Study Group database on ovarian cancer patients and selected 110 MOGCT patients who received FSS with a median follow-up

period of 10.4 years for the study. In this Japanese report, 63.9% of the patients received the BEP regimen and about 30.6% received the cisplatin + vincristine + bleomycin regimen. They revealed premature menopause which was close to our study of 2.9%.

Regarding the obstetric outcome, our study reported that the rate of term pregnancy was 28.6%. This result was different from that of a Japanese study[9]. The authors revealed that 45 patients attempted to become pregnant with 40 patients succeeding in deliveries with total pregnancies as term deliveries in 54 (83.1%) cases, preterm delivery in two (3.2%), and abortion in 12 (18.5%). Seven cases received fertility treatment. A publication from Iran reported that 19 of 26 (73%) MOGCT patients who underwent FSS were successful in delivery without infertility treatment[6]. In addition, Mikuš *et al*[10] reported that the pregnancy rate in 20 German patients with MOGCT who desired to become pregnant of their series was 50%. The pregnancy rate from previous studies was higher than that of our study, which showed the successful pregnancy rate was only 28.6%. The difference might be from the current trend of Thai culture to have fewer children, the missing data from the patients unable to be contacted, and those non-actively who tried to conceive in our patients.

The strength of our study was the real-world series of patients with MOGCT treated by FSS in a single institute to show the oncology and reproductive outcomes. However, with the limitation of the retrospective study, about 2/3 of the patients were not followed for a long time. Therefore, some data were missed.

CONCLUSION

In conclusion, the oncology and reproductive outcomes of MOGCT treated by FSS were good. Many patients showed a long survival time with normal menstruation. However, the obstetric outcome in patients who attempted to conceive was not quite as high.

ARTICLE HIGHLIGHTS

Research background

Malignant ovarian germ cell tumors (MOGCT) are rare and frequently occur in women of young and reproductive age. Fertility-sparing surgery (FSS) is the main treatment for these patients. However, oncologic and reproductive outcomes after FSS for this disease are still limited.

Research motivation

Due to the limited data on oncology and reproductive outcomes of FSS especially in Southeast Asia, this study was conducted to identify these outcomes of MOGCT patients who were treated by FSS.

Research objectives

To evaluate the oncology and reproductive outcomes of MOGCT who underwent FSS.

Research methods

All MOGCT patients who underwent FSS defined as the operation with a preserved uterus and at least one side of the ovary at our institute between January 2005 and December 2020 were retrospectively reviewed.

Research results

Sixty-two patients were reviewed in this study. The median age was 22 years old and over 77% were nulliparous. The three most common histology findings were immature teratoma (32.2%), dysgerminoma (24.2%), and yolk sac tumor (24.2%). The distribution of stage was as follows: Stage I, 74.8%; stage II, 9.7%; stage III, 11.3%; stage IV, 4.8%. About 2/3 of the patients received adjuvant chemotherapy. With a median follow-up time of 96.3 mo, the 10-year progression-free survival and overall survival were 82.4% and 91%, respectively. For reproductive outcomes, of 43 patients who received adjuvant chemotherapy, 18 (41.9%) had normal menstruation and 17 (39.5%) resumed menstruation with a median time of 4 mo. Of about 14 patients who desired to conceive, four were pregnant and delivered good outcomes. Only one case was aborted. Therefore, the successful pregnancy rate was 28.6%.

Research conclusions

The oncology and reproductive outcomes of MOGCT treated by FSS were excellent. Many patients showed a long survival time with normal menstruation. However, the obstetric outcome was not quite high.

Research perspectives

The strength of our study was the real-world series of patients with MOGCT treated by FSS in a single institute to show the oncology and reproductive outcomes. However, with the limitation of the retrospective study, about 2/3 of the patients were not followed for a long time. Therefore, some data were missed. A good plan follow-up is needed in the future.

FOOTNOTES

Author contributions: Rungoutok M and Suprasert P contributed equally to this work; Suprasert P designed the research study; Rungoutok M and Suprasert P performed the research and contributed analytic tools; Suprasert P analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study was approved by Chiang Mai University Ethic Committees (Research ID: 7736; Study Code: OBG-2563-07736).

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

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Country/Territory of origin: Thailand

ORCID number: Muangloei Rungoutok 0000-0002-1124-0662; Prapaporn Suprasert 0000-0002-0205-2280.

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ORIGINAL ARTICLE

Clinical Trials Study

Clinical relevance of the use of Dentoxol® for oral mucositis induced by radiotherapy: A phase II clinical trial

Sebastián Solé, Sergio Becerra, Claudia Carvajal, Piero Bettolli, Hernán Letelier, Alejandro Santini, Lorena Vargas, Alexander Cifuentes, Francisco Larsen, Natalia Jara, Jorge Oyarzún, Eva Bustamante, Benjamín Martínez, David Rosenberg, Tomas Galván

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Sebastián Solé, Lorena Vargas, Francisco Larsen, Natalia Jara, Department of Radiotherapy, Radiomedicine Institute, Américo Vespucio Norte 1314 Vitacura, 7630370, Santiago, Chile

Sergio Becerra, Claudia Carvajal, Alexander Cifuentes, National Institute of Cancer, Santiago, Servicio de Salud Metropolitano Norte, Av Profesor Zañartu 1010, Independencia, 8380455, Santiago, Chile

Piero Bettolli, Eva Bustamante, Oncologic Institute Arturo López Pérez Foundation, José Manuel Infante 805, Providencia, 7500691, Santiago, Chile

Hernán Letelier, Jorge Oyarzún, Hospital Base Valdivia, Bueras 1003 s/n XIV Región, 5100238, Valdivia, Chile

Alejandro Santini, Oncologic Center of Antofagasta, Los Pumas 10255, Antofagasta, 1267348, Antofagasta, Chile

Benjamín Martínez, Universidad Mayor, Santiago, Av Libertador Bernardo O´Higgins 2013, 8340585, Santiago, Chile

David Rosenberg, Tomas Galván, Ingalfarma, Dr Manuel Barros Borgoño 71, Oficina 1308, Providencia, 7500593, Santiago, Chile

Corresponding author: Sebastián Solé, MD, Assistant Professor, Department of Radiotherapy, Radiomedicine Institute, Américo Vespucio Norte 1314 Vitacura, 7630370, Santiago Chile, Santiago, Chile. sebasole@gmail.com

Abstract

BACKGROUND

Severe oral mucositis associated with cancer therapy is a frequent complication that may affect a patient's systemic condition, resulting in interruption and/or prolongation of cancer therapy. Dentoxol® is a medical solution in the form of a mouthwash that has been shown to result in statistically significant improvement in the prevention of severe oral mucositis. However, knowing the measures of the clinical significance of this therapy is important for accurate decision-making.

AIM

To describe the clinical impact of Dentoxol® use in severe oral mucositis.

METHODS
Clinical significance was measured using the results obtained in a randomized controlled clinical trial previously conducted by the same group of researchers. The measures of clinical significance evaluated were the absolute risk or incidence, relative risk, absolute risk reduction, relative risk reduction, number needed to treat, and odds ratio.

RESULTS
The data obtained show that the impact of Dentoxol® on reducing the severity of oral mucositis has important clinical relevance.

CONCLUSION
The results of this study justify the incorporation of Dentoxol® mouth rinse into clinical protocols as a complement to cancer therapy to prevent and/or treat oral mucositis secondary to radiotherapy.

Key Words: Clinical trial; Dentoxol; Oral mucositis; Prevention; Radiotherapy; Treatment

Core Tip: Oral mucositis associated with cancer therapy is a frequent complication. Dentoxol® is a medical solution that has been shown to prevent severe oral mucositis. The clinical significance of Dentoxol® was measured using the results obtained in a randomized controlled clinical trial previously conducted by the same group of researchers. The data obtained show that the clinical impact of Dentoxol® on oral mucositis justifies its incorporation into clinical protocols as a complement to cancer therapy to prevent and/or treat oral mucositis.

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INTRODUCTION

Oral mucositis is a complication that arises from cancer treatment (chemotherapy and/or radiotherapy) and manifests as erythematous and ulcerative lesions of the oral mucosa. These lesions cause considerable pain and functional impairment that can compromise nutritional status and prevent adequate oral hygiene in patients, increasing the risk of local infection and systemic spread. Additionally, in some cases, it can limit the dose or continuity of cancer therapy[1-3].

The available scientific evidence indicates that between 94%-96% of patients treated with head and neck radiotherapy develop some degree of oral mucositis, while 66% present with severe oral mucositis [4,5].

The pain caused by lesions often compromises a patient's ability to eat, frequently leading to the need for *via* nasogastric or gastrostomy tubes, which can impact the general condition of the patient due to weight loss 5%[6] as well as the overall cost of therapy by requiring hospitalization. Approximately 16% of patients with head and neck radiotherapy require hospitalization due to oral mucositis. In addition, 11% of patients who received radiotherapy for head and neck cancer had unplanned interruptions in radiotherapy due to severe oral mucositis[7].

The pathogenesis of oral mucositis is complex and involves different pathways. One of the events involved in the development of mucositis is the inflammatory response of tissues to cancer therapy[8,9]. Within these tissues, the participation of proinflammatory cytokines such as TNF- and IL-1 plays key roles in both the onset of tissue damage and acceleration of the process[10-13]. Likewise, these cytokines induce the expression of cyclooxygenase-2, which is responsible for the production of proinflammatory prostanoids such as prostaglandin E2 and prostacyclin I2 and for tissue injury and pain at the inflammation site[14-16].

Additionally, ulcers caused by oral mucositis can be colonized by bacteria from the patient's own oral flora. This secondary colonization may aggravate the clinical picture of mucositis through the release of bacterial products (lipopolysaccharides) capable of generating greater tissue damage and inhibiting the

healing process[13]. Sobue *et al*[17] evaluated the growth of and inflammatory responses against *Candida albicans, Candida glabrata,* and 2 streptococcal species of the mitis group (*S. oralis and S. mitis*), which are frequently associated with oral mucositis, in an organotypic model to represent chemotherapy-induced mucositis. Although a nonsignificant increase in growth was observed for the species studied, the authors reported an exacerbated proinflammatory response to *C. albicans, C. glabrata*, and *S. oralis*[17]. Recently, a positive correlation was found between ≥ grade 2 oral mucositis and the presence of *Bacteroidales G2*, *Capnocytophaga, Eikenella, Mycoplasma*, *Sneathia,* and the periodontopathogens *Porphyromonas* and *Tannerella*. Additionally, a large amount of *Fusobacterium, Haemophilus, Tannerella, Porphyromonas*, and *Eikenella* on buccal mucosa influenced oral mucositis susceptibility[18]. Bacteriome disturbance has been shown to have a strong and independent association with oral mucositis severity through decreases in commensal organisms such as those belonging to the *Streptococcus, Actinomyces, Gemella, Granulicatella,* and *Veillonella* genera and increases in gram-negative bacteria such as *Fusobacterium nucleatum* and *Prevotella oris*[19].

The complex nature of oral mucositis requires a comprehensive preventive and therapeutic approach that can address the different pathways involved to achieve a successful outcome[20]. Managing only inflammation or overinfection is not sufficient for efficient and adequate control.

In this context, Dentoxol®, an aqueous solution used as a mouthwash, whose main mode of action is mechanical sloughing of the superficial epithelial cell layer of the oral mucosa, thus stimulating local regeneration of the epithelium, was developed. The interaction of its components (purified water, xylitol, sodium bicarbonate, eugenol, camphor, parachlorophenol, and peppermint essence) in specific concentrations sloughs and eliminates cells damaged by radio/chemotherapy as well as particles and detritus present in the oral cavity, such as bacteria and organic debris. The clinical effect observed is a result of the interaction of its components acting on the different aspects of the physiopathogenesis of oral mucositis (antioxidant, bacteriostatic, bactericidal, anti-inflammatory, and moisturizing properties and mucosal regenerative stimulation). As a result, Dentoxol® can prevent oral mucositis by physically moisturizing and lubricating the oral mucosa to provide flexibility and resistance. Accordingly, it affects several pathways that influence the severity of oral mucositis[21].

Recently, a randomized controlled clinical trial conducted by this research team evaluated the effect of Dentoxol® mouthwash on the prevalence of severe oral mucositis and found statistically significant results regarding the prevention and reduction in the severity of oral mucositis[21]. Many clinical studies present their results based on statistical significance. However, clinical measures of significance are essential for evaluating the relevance and usefulness of a therapy in daily clinical practice[22].

Considering the high incidence of oral mucositis in patients undergoing head and neck cancer therapy as well as the relevant impact of this pathology on patient morbidity and quality of life, in addition to the associated economic costs, the clinical significance of an agent that can successfully treat oral mucositis needs to be analyzed. The aim of the present study is to objectively and clearly present the clinical impact of Dentoxol® on affected tissues based on statistical results obtained in a previously conducted clinical trial, with the aim of providing a clearer picture of the impact that clinicians responsible for managing this pathology should expect in their daily work when using this preventive and therapeutic tool to manage and control oral mucositis.

MATERIALS AND METHODS

Definition

Severe oral mucositis: Grade 3 or 4 mucositis based on the scale described by the World Health Organization (Table 1).

A descriptive study was conducted on the clinical significance of Dentoxol® in treating oral mucositis based on results obtained in a randomized controlled clinical trial with a parallel arm design (1:1) evaluating the effect of Dentoxol® mouthwash (test group) versus a placebo mouthwash (control group) on the incidence of severe oral mucositis associated with cancer therapy. The full methodology of the clinical trial was previously published by Lalla *et al*[21].

A total of 108 patients older than 18 years (Dentoxol® group = 55 and control group = 53) participated in the study.

Once the statistical results of the clinical trial were obtained, clinical significance measures such as the absolute risk (AR), relative risk (RR), absolute risk reduction (ARR), relative risk reduction, number necessary to treat (NNT), and odds ratio were calculated using a contingency table (Table 2).

RESULTS

Patient selection

A total of 108 patients were considered for the analysis of the outcomes of the randomized controlled clinical trial evaluating the use of Dentoxol®.

Table 1 Absolute frequencies and percentages of patients with and without severe oral mucositis by follow-up week

Week	Dentoxol® (*n* = 55)				Control (*n* = 53)				
	No severe oral mucositis		Severe oral mucositis		No severe oral mucositis		Severe oral mucositis		*P* value
	n	%	*n*	%	*n*	%	*n*	%	
1	49	94.2	3	5.8	49	98.0	1	2.0	0.327
2	49	100	0	0.0	42	95.5	2	4.5	0.131
3	47	95.9	2	4.1	30	76.9	9	23.1	0.007[a]
4	42	91.3	4	8.7	29	70.7	12	29.3	0.013[a]
5	33	73.3	12	26.7	19	52.8	17	47.2	0.055
6	29	64.4	16	35.6	15	46.9	17	53.1	0.125
7	22	57.9	16	42.1	11	44.0	14	56.0	0.280
8	11	57.7	6	35.3	4	44.4	5	55.6	0.320

[a]Statistically significant.

Table 2 Odds ratio were calculated using a contingency table

	Severe oral mucositis	No severe oral mucositis	Total
Dentoxol®	a	b	a + b
Control	c	d	c + d
Total	a + c	b + d	a + b + c + d

a: Number of patients who presented severe oral mucositis and received Dentoxol® treatment; b: Number of patients who did not present severe oral mucositis and received Dentoxol® treatment; a + b: Total number of patients in the Dentoxol® group; c: Number of patients who presented severe oral mucositis and received control treatment; d: Number of patients who did not present severe oral mucositis and received control treatment; c + d: Total number of patients in the control group.

Oral mucositis severity

Table 1 shows the number and percentage of patients who presented with severe oral mucositis in each treatment group. The Dentoxol® and control groups showed a progressive increase in the frequency of severe oral mucositis, with a peak at seven weeks.

Compared with the control group, the Dentoxol® group presented a lower number of patients with severe oral mucositis every week except for the first week, with a statistically significant difference observed at weeks 3 and 4 of the follow-up (see Table 1).

Clinical relevance

Table 2 shows the measures of clinical significance. The ARs of severe oral mucositis in the Dentoxol® group were 0.04 and 0.09 or 4% and 9% for weeks 3 and 4, respectively, versus 0.23 and 0.29 or 23% and 29%, respectively, in the control group. Additionally, from week 2 onward, the relative risk of severe oral mucositis in the Dentoxol® group was less than 1, indicating that Dentoxol® use acted as a protective factor.

Dentoxol® use was positively associated with a reduction in severe oral mucositis from week 2 onward, showing ARR values greater than 0. The values at weeks 3 and 4, ARR = 0.19 or 19% and 0.21 or 21%, respectively, indicate that if 100 patients were treated with Dentoxol®, 19 and 21, respectively, fewer cases of severe mucositis would occur compared to the control group. Likewise, during weeks 3 and 4, when statistically significant differences between the groups were noted, 5 patients (NNT) would need to be treated with Dentoxol® to prevent 1 additional case of severe oral mucositis (Table 3).

DISCUSSION

Measures of clinical significance allow making well-founded decisions when evaluating a therapy and can be applied in daily clinical practice and especially in recommendations for massive clinical protocols because through these measures, expected results with a real impact on the population can be obtained.

Table 3 Measures of clinical significance for the effect of Dentoxol® on severe oral mucositis

Week	AR		RR (95%CI)	ARR	RRR	NNT	OR (95%CI)
	Dentoxol (%)	Control (%)	Dentoxol®	Dentoxol® (%)	Dentoxol® (%)	Dentoxol®	Dentoxol®
1	5.77	2	2.88 (0.31-26.82)	-4	-188	-27	3 (0.30-29.85)
2	0	4.55	-	5	100	22	-
3	4.08	23.08	0.18 (0.04-0.77)	19	82.31	5	0.14 (0.03-0.70)
4	8.7	29.27	0.3 (0.1-0.85)	21	70.29	5	0.23 (0.07-0.78)
5	26.67	47.22	0.56 (0.31-1.02)	21	43.53	5	0.41 (0.16-1.03)
6	35.56	53.13	0.67 (0.4-1.12)	18	33.07	6	0.49 (0.29-1.23)
7	42.11	56	0.75 (0.45-1.25)	14	24.81	7	0.57 (0.21-1.58)
8	35.29	55.56	0.64 (0.27-1.52)	20	36.47	5	0.44 (0.08-2.27)

ARR: Absolute risk reduction; RR: Relative risk; RRR: Relative risk reduction; NNT: Number necessary to treat; OR: Odds ratio.

In the present study, the group that used Dentoxol® showed a lower incidence (AR) of severe oral mucositis than the control group (Figure 1) from the 2nd week of evaluation to the 4th week, representing the greatest difference between the groups (Table 2). The results shown in Table 2 demonstrate the strong potential of Dentoxol® to lower treatment complications. Treating 5 patients with Dentoxol® will prevent 1 additional case of severe oral mucositis that may need percutaneous endoscopic gastrostomy tubes, liquid diet supplements, pain medications, *etc*. Moreover, the results in Table 1 show that Dentoxol® delayed the onset of severe mucositis such that even patients with a severe grade who received it had the complication for a shorter period, with benefits on cost and quality of life.

Another important conclusion of the clinical trial was that the most beneficial effects of therapy with Dentoxol® are observed in patients who follow the instructions to rinse 4 times a day (Figure 1). Therefore, following the recommended instructions specifying that more frequent rinses yield better clinical results is important. Furthermore, the rinsing time should be longer than 1 min to allow the product to exert its effects on the oral mucosa. This is not a minor point because cancer patients very often have nausea and vomiting, which should be controlled to allow rinses at the appropriate frequency and time. A clinically recognized effective strategy is to begin with rinses days or ideally weeks before starting cancer therapy to prepare the mucosa for toxic effects and their consequences and thus more effectively prevent the onset of mucositis. Therefore, continuing to study different clinical protocols based on the experience of clinicians regarding this aspect through well-designed controlled clinical trials is essential.

With respect to the latter, the literature contains multiple studies evaluating different products and protocols to reduce the onset and severity of oral mucositis[23-25]. Properly designed studies allow their results to be comparable in terms of clinical effectiveness for correct decision-making. In this sense, 1 multicenter clinical trial evaluated the ability of Caphosol®, an electrolyte solution with concentrated calcium phosphate, to reduce oral mucositis in patients who received radiotherapy for head and neck cancer[26]. When observing the percentages of severe oral mucositis, 29.3% and 42.4% of grade 3 mucositis occurred during the 3rd and 4th weeks, respectively, and 8.6% and 18.6% of grade 4 mucositis occurred during the same weeks. If we compare these results with those obtained in the Dentoxol® trial, at the 3rd and 4th weeks, only 4.1% and 8.7% of patients who rinsed with Dentoxol® had severe oral mucositis, respectively (grades 3 and 4, respectively). Another more recent clinical trial showed no reduction in the incidence or duration of severe oral mucositis with Caphosol® use in patients with head and neck cancer versus the control group (64.1% *vs* 65.4%)[24]. Given the results obtained in these studies, the benefit of Caphosol® is not clear. On the other hand, Dentoxol® showed a statistically significant clinical benefit for patients undergoing radiotherapy for head and neck cancer.

Systematic reviews are also useful for comparing the different applications and clinical effectiveness of multiple therapeutic alternatives. Accordingly, a 2017 Cochrane Library review evaluated the effect of cytokines and growth factors in the prevention of oral mucositis[25]. The main agent evaluated was keratinocyte growth factor (KGF). The results indicated that KGF decreased the risk of severe oral mucositis in patients undergoing head and neck cancer therapy, with an RR = 0.79 and a 95% confidence interval (CI) = 0.69-0.90 (obtained from 3 studies), and that 7 patients (95%CI = 5-15) would need to be treated to prevent 1 case of severe mucositis[25]. If we compare those findings with the results for Dentoxol®, the latter agent had a lower RR from the 3rd week of follow-up, with RR values = 0.18 to 0.75, and between 5 and 7 patients (depending on the week of follow-up) would be required to prevent an additional case of severe oral mucositis. Although these results may seem similar, notably, KGF is a drug with important limitations: it is not indicated for solid tumors because it may enhance their growth; the cost is much higher; and it must be administered by IV infusion. Other products used for

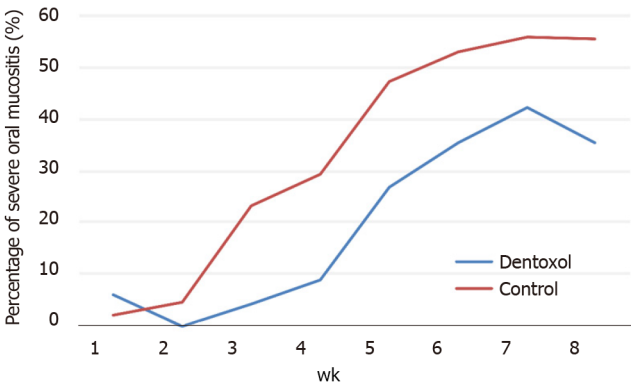

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Figure 1 Line graph for the absolute risk (%) by treatment group.

similar clinical conditions could be considered for comparative evaluations[27].

To better present the results of the Dentoxol® study and to facilitate comparisons with other results, we must note that the placebo used in the clinical trial from which the analysis of the present study was performed was not a totally inactive agent. Due to ethical reasons, the control group could not be deprived of minimum protection; therefore, the placebo used was a mouthwash composed of an aqueous solution of sodium bicarbonate and xylitol, thus reducing the actual difference between the Dentoxol® group and the control group. Therefore, the benefit provided by rinses with Dentoxol® is even greater in reality.

In conclusion, more well-designed controlled clinical trials are needed to increase scientific evidence and test different clinical protocols and therapeutic strategies to offer patients effective solutions based on scientific evidence. To facilitate comparisons with other interventions, the type of cancer presented by the patients, the type of therapy (chemo- and/or radiotherapy), the frequency, dose, starting point, and duration of therapy for oral mucositis, *etc.*, should be considered. Additionally, the timing of evaluation considering the pathogenesis of mucositis is also an important factor.

CONCLUSION

In this study, the safety and clinical efficacy of Dentoxol® were demonstrated for the prevention and treatment of severe oral mucositis, an unwanted pathology that is a complication of treatments for much more serious diseases, including cancer. However, this complication can impact the costs and continuity of cancer treatment and, above all, the quality of life of patients. In this study, the effects of Dentoxol® were clinically evident and detectable in a small number of treated patients; therefore, the inclusion of Dentoxol® in clinical protocols is highly recommended for the management and control of the side effects of cancer treatments, which is as important as the other components of the therapeutic arsenal for cancer.

ARTICLE HIGHLIGHTS

Research background

Oral mucositis is a complication that arises from cancer treatment (chemotherapy and/or radiotherapy) and manifests as erythematous and ulcerative lesions of the oral mucosa. The pathogenesis of oral mucositis is complex and involves different pathways. One of the events involved in the development of mucositis is the inflammatory response of tissues to cancer therapy The complex nature of oral mucositis requires a comprehensive preventive and therapeutic approach that can address the different pathways involved to achieve a successful outcome. Managing only inflammation or overinfection is not sufficient for efficient and adequate control. In this context, Dentoxol®, an aqueous solution used as a mouthwash, whose main mode of action is mechanical sloughing of the superficial epithelial cell layer of the oral mucosa, thus stimulating local regeneration of the epithelium, was developed. Recently, a randomized controlled clinical trial conducted by this research team evaluated the effect of Dentoxol® mouthwash on the prevalence of severe oral mucositis and found statistically significant results regarding the prevention and reduction in the severity of oral mucositis.

Research motivation

Many clinical studies present their results based on statistical significance. However, clinical measures of significance are essential for evaluating the relevance and usefulness of a therapy in daily clinical practice.

Research objectives

The aim of the present study is to objectively and clearly present the clinical impact of Dentoxol® on affected tissues based on statistical results obtained in a previously conducted clinical trial, with the aim of providing a clearer picture of the impact that clinicians responsible for managing this pathology should expect in their daily work when using this preventive and therapeutic tool to manage and control oral mucositis.

Research methods

Once the statistical results of the clinical trial were obtained, clinical significance measures such as the absolute risk (AR), relative risk (RR), absolute risk reduction (ARR), relative risk reduction, number necessary to treat (NNT), and odds ratio were calculated using a contingency table.

Research results

The ARs of severe oral mucositis in the Dentoxol® group were 0.04 and 0.09 or 4% and 9% for weeks 3 and 4, respectively, versus 0.23 and 0.29 or 23% and 29%, respectively, in the control group. Additionally, from week 2 onward, the relative risk of severe oral mucositis in the Dentoxol® group was less than 1, indicating that Dentoxol® use acted as a protective factor. Dentoxol® use was positively associated with a reduction in severe oral mucositis from week 2 onward, showing ARR values greater than 0. The values at weeks 3 and 4, ARR = 0.19 or 19% and 0.21 or 21%, respectively, indicate that if 100 patients were treated with Dentoxol®, 19 and 21, respectively, fewer cases of severe mucositis would occur compared to the control group. Likewise, during weeks 3 and 4, when statistically significant differences between the groups were noted, 5 patients (NNT) would need to be treated with Dentoxol® to prevent 1 additional case of severe oral mucositis.

Research conclusions

In this study, the effects of Dentoxol® were clinically evident and detectable in a small number of treated patients; therefore, the inclusion of Dentoxol® in clinical protocols is highly recommended for the management and control of the side effects of cancer treatments, which is as important as the other components of the therapeutic arsenal for cancer.

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FOOTNOTES

Author contributions: Solé S contributed to the conception, design, investigation, supervision, clinical data acquisition, and interpretation and critically revised the manuscript; Becerra S, Carvajal C, Bettolli P, Letelier H, Santini A, Vargas L, Cifuentes A, Larsen F, Jara N, Oyarzún J, and Bustamante E contributed to the conception, investigation, and clinical data acquisition; Martínez B and Galván T contributed to critically revising the manuscript; Rosenberg D contributed to the investigation and interpretation and drafted the manuscript.

Institutional review board statement: The study was reviewed and approved by the Chilean Institute of Public Health.

Clinical trial registration statement: ClinicalTrials.gov Identifier, No. NCT02885376.

Informed consent statement: All the participants have read and understood the provided information and have had the opportunity to ask questions. All authors understand that their participation is voluntary and that they were free to withdraw at any time, without giving a reason and without cost. All authors understand that they will be given a copy of this consent statement.

Conflict-of-interest statement: Rosenberg D and Galván T have a stock/ownership interest in Ingalfarma SpA. The authors declare that they have no conflicts of interest.

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ORCID number: Sebastián Solé 0000-0002-9291-2319; Sergio Becerra 0000-0001-9977-6869; Hernán Letelier 0000-0001-8968-8144; Alexander Cifuentes 0000-0002-0031-7257; David Rosenberg 0000-0002-0911-0471.

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SYSTEMATIC REVIEWS

Neutrophil-to-lymphocyte ratio as a prognostic factor for survival in patients with colorectal liver metastases: A systematic review

Menelaos Papakonstantinou, Stylianos Fiflis, Gregory Christodoulidis, Mariano Cesare Giglio, Eleni Louri, Savvas Mavromatidis, Dimitrios Giakoustidis, Vasileios N Papadopoulos, Alexandros Giakoustidis

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Menelaos Papakonstantinou, Stylianos Fiflis, Eleni Louri, Savvas Mavromatidis, Dimitrios Giakoustidis, Vasileios N Papadopoulos, Alexandros Giakoustidis, Department of Surgery, General Hospital Papageorgiou, Aristotle University of Thessaloniki, Thessaloniki 56429, Greece

Gregory Christodoulidis, Department of General Surgery, University Hospital of Larissa, Larissa 41110, Greece

Mariano Cesare Giglio, Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples 80138, Italy

Corresponding author: Gregory Christodoulidis, MD, PhD, Consultant Physician-Scientist, Department of General Surgery, University Hospital of Larissa, Mezourlo, Larissa 41110, Greece. gregsurg@yahoo.gr

Abstract

BACKGROUND

The inflammatory response to tumor has been proven to be closely related to the prognosis of colorectal cancer. Neutrophil to lymphocyte ratio (NLR) is a widely available inflammatory biomarker that may have prognostic value for patients with colorectal liver metastasis (CRLM).

AIM

To assess the role of NLR as a prognostic factor of survival and tumor recurrence in patients with CRLM.

METHODS

A systematic literature search of PubMed, Cochrane Library and clinicaltrials.gov was conducted by two independent researchers in order to minimize potential errors and bias. Conflicts were discussed and settled between three researchers. Studies including patients undergoing different types of medical interventions for the treatment of CRLM and evaluating the correlation between pretreatment NLR and disease-free survival (DFS) and overall survival (OS) were included in the review. Nineteen studies, involving 3283 patients matched our inclusion criteria.

RESULTS

In the studies included, NLR was measured before the intervention and the NLR thresholds ranged between 1.9 and 7.26. Most studies used 5 as the cut-off value.

Liver metastases were treated with hepatectomy with or without chemotherapy regimens in 13 studies and with radiofrequency ablation, radioembolization, chemoembolization or solely with chemotherapy in 6 studies. High NLR was associated with decreased OS and DFS after liver resection or other medical intervention. Moreover, high NLR was associated with poor chemosensitivity. On the contrary, CRLM patients with low pretreatment NLR demonstrated improved OS and DFS. NLR could potentially be used as a predictive factor of survival and tumor recurrence in patients with CRLM treated with interventions of any modality, including surgery, chemotherapy and ablative techniques.

CONCLUSION

NLR is an inflammatory biomarker that demonstrates considerable prognostic value. Elevated pretreatment NLR is associated with poor OS and DFS in patients with CRLM who are submitted to different treatments.

Key Words: Neutrophil-to-lymphocyte ratio; Colorectal liver metastasis; Prognosis; Survival

Core Tip: Colorectal cancer is the third most common cancer globally and liver is the most common site of metastasis. Even though surgery and chemotherapy are the main treatment options, prognostic markers are also essential for the progress and future management of the disease. Neutrophil-to-lymphocyte ratio (NLR) is a promising biomarker that has been recently proposed as an indicator for the survival and recurrence of various malignancies. In our review we assess the role of NLR in the overall survival of patients with colorectal liver metastases.

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INTRODUCTION

According to GLOBOCAN 2020 Data, colorectal cancer (CRC) is the third most frequent cancer in both men and women with an estimated 1931500 new cases and 935173 deaths worldwide in 2020. The liver is the most common site of metastasis in patients with CRC as almost 50% of these patients will develop liver metastases (LM) during the course of their disease of whom 15%-25% have LM at initial diagnosis. The remaining 18%-25% will have metachronous LM in the next 5 years[1,2]. The management of patients with colorectal liver metastases (CRLM) consists of different treatment options such as tumor resection, radiofrequency ablation (RFA), which can destroy the tumor by the use of high-frequency electromagnetic current and can be applied in unresectable CRLM, or microwave ablation. Other treatment options include systemic therapy, such as Irinotecan-loaded drug-eluting beads and radioembolization (RE), that administer high doses of chemotherapy and radiation, respectively, and chemotherapy. The intra-arterial techniques aim specifically at the tumor's vasculature, thus minimizing systemic toxicity, and may be an option in patients not eligible for surgery or ablation[3]. Different treatment methods are selected depending on the patient's clinical and radiological data[4]. Advancements in treatment for patients with CRLM have resulted in improved 5-year survival rates as high as 46%; however, survival remains low in patients where all sites of disease are not surgically resectable[5]. The low 5-year overall survival (OS) and the fact that recurrences occur in more than half of CRLM patients, highlights the need for more prognostic factors that could be easily applied to predict OS as well as disease-free survival (DFS)[6].

Many studies have examined the prognostic role of neutrophil to lymphocyte ratio (NLR) in CRLM patients. NLR is a widely available, low-cost prognostic index that is calculated by dividing the number of neutrophils by the number of lymphocytes and reflects the inflammatory response of the patient against the tumor, which is correlated with tumor development and poor outcomes[7,8]. Neutrophils play a role in cancer development and metastases, while lymphocytes mediate an immune response against the malignancy, consequently an elevated NLR value could indicate a protumorigenic status.

In this systematic review we investigated the association between NLR and the prognosis of CRLM in patients treated with interventions of any modality including surgery, chemotherapy and ablative techniques[9,10]. High NLR was associated with poor survival in CRLM patients in the systematic

review and meta-analysis by Tang *et al*[11], which included 8 studies and in the systematic review by Haram *et al*[12] which also included 8 studies. Our systematic review includes 19 studies thus making the analysis results more robust. It consists of 12 studies including 2442 patients treated surgically, 6 studies including 641 patients treated with RFA or RE or solely chemotherapy and 1 study (Kishi *et al* [15]) including 200 patients treated surgically and 90 different patients treated with RFA. We studied the different impact of pretreatment NLR as a prognostic factor depending on the medical intervention and we present the analysis results in two categories. The first category included 2642 patients who were treated surgically and the second category included 731 patients who were treated with ablative techniques or solely chemotherapy. All the studies included demonstrated that CRLM patients with low pretreatment NLR had better survival and DFS in comparison to high pretreatment NLR patients regardless of the medical intervention received.

MATERIALS AND METHODS

Data extraction and risk of bias

A systematic literature search of PubMed and the Cochrane Library was performed using the following search terms: "Neutrophil to Lymphocyte Ratio and liver metastas* and survival", "NLR and liver metastas* and survival", "NLR and liver metastasis and prognostic factor", "NLR and liver metastas*" and "NLR". The same search strategy was used for the trial registry "ClinicalTrials.gov" in order to minimize publication bias by identifying unpublished studies.

The titles of the articles were screened and relevant abstracts were assessed for eligibility. After excluding duplicates, eligible articles were further evaluated and then the references of those studies were also checked. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is shown in Figure 1.

In order to minimize possible errors and bias, two independent researchers blindly reviewed the literature and extracted data using the method of completely independent data extraction. After that, any potential differences were cleared up through discussion between them and a third reviewer. The following data were extracted from each study: (1) Patients' clinicopathological characteristics; (2) The treatment modalities used to treat CRLM; (3) The median survival, 3-year and 5-year OS, 3-year and 5-year DFS; and (4) The univariate and multivariate analysis outcomes.

Inclusion and exclusion criteria

In order to be included in the analysis, the studies must meet all of the following criteria: (1) Include patients older than 18 years of age diagnosed with CRLM; (2) Define NLR as the absolute number of neutrophils divided by the absolute number of lymphocytes in the peripheral blood; (3) Clearly stated pretreatment NLR values and NLR thresholds; and (4) Analyzing the correlation between pretreatment NLR value and OS outcome and/or DFS. The following exclusion criteria were applied: (1) Not specifically reported colorectal metastasis to the liver; (2) Patients with liver metastases originating from outside the colorectum; (3) Pre-clinical studies; and (4) Studies published in a language other than English.

Definitions

NLR was defined as the absolute number of neutrophils divided by the absolute number of lymphocytes in the peripheral blood. OS was defined as the time between treatment (hepatectomy, RFA, RE, chemotherapy) and death or last follow-up. DFS was defined as the time between the treatment and the first detection of disease recurrence, including local tumor recurrence, intrahepatic recurrence and extrahepatic metastases. Progression-free survival (PFS) was defined as the duration between primary tumor resection and disease progression.

RESULTS

NLR is a predictor of survival after hepatectomy with neoadjuvant or adjuvant chemotherapy. Eleven studies assessed the prognostic significance of NLR for patients undergoing hepatectomy for CRLM after neoadjuvant chemotherapy. Details on patient demographics and the different NLR thresholds are shown in Tables 1 and 2. Five studies that included 902 patients in total, used 5 as the cut-off value for the NLR. Elevated NLR was significantly associated with worse OS[13-17]. Peng *et al*[18] used 4.63 as the NLR threshold in 59 patients who received neoadjuvant chemotherapy yielded the same results. Elevated NLR was also significantly correlated with poor OS when the threshold was 1.9, 2.3, 2.4, 2.5, 2.6 or 7.26[19-23].

Ninety-eight patients in 3 studies received only adjuvant chemotherapy after metastasectomy. Elevated NLR was associated with significantly worse DFS[19,24,25]. The OS was also significantly shorter with elevated preoperative NLR in two of the studies[19,24]. However, the NLR cut-off value

Table 1 Patient demographics, neutrophil to lymphocyte ratio cut-off value, follow-up time and time of sample acquisition for patients after hepatectomy

Ref.	Number of patients	Sex	Mean age (years)	NLR threshold	Follow up (mo), mean (range)	Sample acquisition
Erstad *et al*[13]	151	84 M, 67 F	58	5	41.3 ± 36.7 (2-186)	Within 6 mo prior to surgery and prior to chemotherapy
Halazun *et al*[14]	440	289 M, 151 F	64 (32-88)	5	24 (11-97)	1 d prior to surgery
Kishi *et al*[15]	290	Resection group 132 M, 68 F; non resection group 61 M, 29 F	Resection, 57; non resection, 56	5	28 (2-102)	Resection group: Before chemotherapy and before resection
Neal *et al*[16]	302	192 M, 110 F	64.8 (26-85)	5	29.5 (4-96)	Prior to surgery
Hand *et al*[17]	322	205 M, 117 F	252 p < 70 yr; 70 p > 70 yr	5	41	On admission; the night prior to or on the morning of surgery
Peng *et al*[18]	150	97 M, 53 F	58 (20-82)	4.63	36 (2-126)	Within 7 d prior to surgery
Kim *et al*[19]	83	62 M, 21 F	59.5	1.94	NS	Within 1 wk prior to surgery
Mao *et al*[20]	183	123 M, 60 F	67 p > 60 yr	2.3	36.3	Within 10 d before chemotherapy and surgery
Neofytou *et al*[21]	140	88 M, 52 F	78% < 70 yr	2.4	33 (1-103)	Within 10 d prior to surgery
Giakoustidis *et al*[22]	169	104 M, 65 F	135 p < 70 yr, 34 p > 40 yr	2.5	34.6	10 d prior to surgery - after preoperative chemotherapy
Dupré *et al*[23]	343	236 M, 107 F	65.8 ± 10.9	2.5, 2.6 and 7.26[1]	49	Within 1 wk prior to surgery
Hamada *et al*[24]	29	20 M, 9 F	63 ± 11.6 (41-83)	4.1	51 (2-97)	NS
Zeman *et al*[25]	130	70 M, 60 F	60 (33-82)	5	39.3	NS

[1]Cut-off values that reached statistical significance.
M: Male; F: Female; p: Patients; NS: Not stated.

was different in each cohort (4.1, 1.94 and 5)[19,24,25]. Further information on the OS and DFS, the tumor characteristics as well as the results of univariate and multivariate analyses for the studies mentioned above are shown in Tables 3 and 4.

Non-surgical methods (RFA, RE, only chemotherapy)

Five studies included 494 patients who underwent RFA or RE or intraarterial therapy and they investigated the correlation between NLR and OS or DFS.

Chang *et al*[26] and Zhang *et al*[27] included 190 patients with CRLM without concomitant metastases outside of the liver. Patients were treated with RFA and both studies showed that preoperative high NLR (> 2.5) was associated with worse OS and DFS. Weiner *et al*[28] and Tohme *et al*[29] enrolled 235 patients, 100 of whom had extrahepatic metastases and an unspecified number of patients had unresected primary CRC both of which affect NLR and its correlation to OS. All of the patients underwent RE and high NLR was significantly associated with reduced OS. The fifth study investigated the correlation between NLR and OS in CRLM patients with unresectable CRC who were treated with Irinotecan drug-eluting beads against a control group and high NLR was significantly associated with reduced OS[30].

Two studies included 145 patients with unresectable or potentially resectable liver-only metastases from CRC and all of them were treated with primary tumor resection followed by chemotherapy. Both studies revealed that high NLR was significantly associated with worse survival and that prolonged survival was anticipated when NLR was normalized after chemotherapy. Wu *et al*[31] demonstrated that the normalization of high NLR was significantly associated with better PFS[15,31]. More details of patient demographics, medical treatments provided to the patients and survival outcomes are shown in Tables 5 and 6.

Table 2 Survival and disease characteristics

Ref.	Median Survival	5-year OS	5-year DFS	Extrahepatic Disease	Primary Tumor	Chemotherapy
Erstad *et al* [13]	3.1 yr, NLR > 5; 6.3 yr NLR < 5	28.7%, NLR > 5; 59.6%, NLR < 5	NS	No	Previous resection of rectum or colon	Neoadjuvant
Halazun *et al* [14]	NS	22%, NLR > 5; 43%, NLR < 5	12%, NLR > 5; 42%, NLR < 5	No disseminated or unresectable EHD	Previously resected	Neoadjuvant
Kishi *et al*[15]	34 mo, NLR > 5; 45 mo, NLR < 5	26%, NLR > 5; 36%, NLR < 5	NS	No	Previously resected	Neoadjuvant, *n* = 200; Without resection, *n* = 90
Neal *et al*[16]	27.8 mo, NLR > 5; 39.8 mo, NLR < 5	18.5% NLR > 5; 30.6% NLR < 5	22.3%, NLR > 5; 35.2%, NLR < 5[2]	NS	Rectum *n* = 149, Colon *n* = 153	Adjuvant, *n* = 126
Hand *et al*[17]	59 mo	Chemotherapy group, 50.8%; No chemotherapy group, 42.5%	NS	NS	No	Neoadjuvant, *n* = 202
Peng *et al*[18]	NS	18.8%, NLR > 4.63; 46.7%, NLR < 4.63	NS	No	58% colon, 42% rectum	Neoadjuvant, *n* = 59
Kim *et al*[19]	NS	NS	NS	No	NS	Neoadjuvant, *n* = 24
Mao *et al*[20]	31.1 mo NLR > 2.3 43.1 mo NLR < 2.3	NS	NS	No	Colon *n* = 104	Neoadjuvant, *n* = 183
Neofytou *et al* [21]	55 mo, NLR > 2.4; Not reached, NLR < 2.4	42%, NLR > 2.4; 69%, NLR < 2.4	Total 27%. 14%, NLR > 2.4; 40%, NLR < 2.4	No	Resection prior to hepatectomy in 81%	Neoadjuvant
Giakoustidis *et al*[22]	75 mo	51%, NLR > 2.5; 74% NLR < 2.5	NS	No	Synchronous resection, *n* = 26; 'liver first', *n* = 7	Neoadjuvant, *n* = 169
Dupré *et al* [23]	50.3, NLR < 2.5; 38.4, NLR > 2.5; 44.8, NLR < 7.26; 25.4, NLR > 7.26	NS	11.6, NLR < 2.5; 9.7, NLR > 2.5; 10.3, NLR < 7.26; 6.3, NLR > 7.26[1]	Resectable EHD in 36 patients	Synchronous, *n* = 169; Right colon, *n* = 73; Left colon, *n* = 126; Rectum, *n* = 142; Multiple, *n* = 2	Neoadjuvant, *n* = 198
Hamada *et al* [24]	NS	NS	NS	Yes, *n* = 5	NS	Adjuvant, *n* = 15
Zeman *et al* [25]	Resection group, 56 mo	46.6%, resection group; 9.5%, RFA group	30.5%, resection group, 21 mo median	No	Rectum *n* = 60, colon *n* = 70	Adjuvant, *n* = 25

[1]PFS: Progression-Free Survival.
[2]CSS: Cancer-Specific Survival.
OS: Overall survival; DFS: Disease-free survival; NLR: Neutrophil to lymphocyte ratio; NS: Not stated; EHD: Extra-hepatic disease.

DISCUSSION

Many studies have shown the significance of elevated NLR as a prognostic marker in various cancers and the role of NLR in predicting survival remains unanimous across diverse studies that included different cancer types, disease stages and sites[32]. In the studies we analyzed, the NLR cut-off values were determined either by using receiver operating characteristic (ROC) curve analysis that assigned patients in high and low NLR groups or arbitrarily by the authors based on previous studies or the decision-making for the threshold was not mentioned. There is currently no perfect cut-off value that could be used for all CRLM patients as the NLR is greatly affected by chemotherapy regimens, other inflammatory conditions and the tumor burden of each patient. The most frequently used cut-off values in CRLM patients are 2.5 and 5 but further research is needed in order to establish the ideal NLR threshold.

Association between NLR - inflammation - cancer

NLR is an inexpensive and easily calculated marker by dividing the total count of neutrophils by the total count of lymphocytes in peripheral blood as measured in a complete blood count (CBC) examination[11,12]. NLR is also immediately available as CBC is part of the routine examinations in patients with cancer.

Table 3 Univariate and multivariate analysis results after hepatectomy

Ref.	Univariate analysis	Multivariate analysis
Erstad *et al*[13]	NLR > 5 was significantly associated with reduced OS (P = 0.001)	NLR > 5 associated with reduced OS (P = 0.032)
Halazun *et al*[14]	NLR > 5 was associated with reduced OS (P < 0.0001); NLR > 5 was the sole positive predictor of recurrence (P < 0.0001)	NLR > 5 was associated with reduced OS (P < 0.0001)
Kishi *et al*[15]	NLR > 5 predicted worse survival (P = 0.011)	NLR > 5 predicted worse survival using variables available before surgery (P = 0.016) and after surgery (P = 0.048)
Neal *et al*[16]	NLR > 5 was significantly associated with worse OS (P = 0.001) and CSS (P < 0.001) following metastasectomy	NLR > 3 was associated with shorter survival (P < 0.001); NLR > 3 was associated with adverse outcomes regarding CSS (P < 0.001)
Hand *et al*[17]	Following index hepatectomy, patients with NLR > 5 had a median survival of 55 mo *vs* 70 mo when NLR < 5 (P = 0.027); Following neoadjuvant chemotherapy, no association between NLR and survival was demonstrated (P = 0.93); NLR > 5 had no impact on prognosis following repeat hepatectomy	There is an independent association between elevated preoperative neutrophil count and shortened overall survival (P = 0.001); no such association was found for NLR
Peng *et al*[18]	Patients with NLR > 4.63 were more likely to present multiple hepatic metastases than those with low NLR (68.8% *vs* 40.3%, P = 0.030); 5-year RFS and OS for high NLR were significantly inferior to those for low NLR (RFS: 12.5% *vs* 38.5%, P = 0.015; OS: 18.8% *vs* 46.7%, P = 0.004)	NLR was not identified as an independent inflammatory factor for better RFS
Kim *et al*[19]	NLR > 1.94 was a prognostic factor for poor OS (P = 0.035) and DFS; High NLR was associated with recurrence (P = 0.031)	NLR > 1.94 was an independent prognostic factor for OS (P = 0.01) and prognostic factor for poor DFS; High NLR was associated with recurrence (P = 0.006)
Mao *et al*[20]	Pre- and post-chemotherapy NLR > 2.3 was associated with decreased OS (P = 0.012)	NLR > 2.3 was a significant predictor both for worse OS (P < 0.001) and for RFS (P = 0.017)
Neofytou *et al*[21]	NLR > 2.4 was associated with decreased DFS (P = 0.033) and OS (P = 0.007)	No significant correlation was found between NLR and OS/DFS
Giakoustidis *et al*[22]	NLR > 2.5 was associated with decreased OS (P = 0.009) and decreased DFS (P = 0.09)	High NLR remained a significant prognostic factor for poor OS (P = 0.012)
Dupré *et al*[23]	NLR of 2.5 was an independent prognostic factor for OS and PFS	High NLR was significantly associated with decreased OS (P < 0.002)
Hamada *et al*[24]	NLR > 4.1 was significantly correlated with better CSS (P = 0.026)	Only univariate analysis was performed
Zeman *et al*[25]	NLR > 5 was significantly associated with DFS (P = 0.044); OS was significantly affected by the preoperative number of leukocytes (P = 0.0014) and neutrophils (P = 0.0036) but not by the NLR.	NLR > 5 was significantly associated with DFS (P = 0.03); Leukocyte number was significantly associated with OS (P = 0.0014); no effect of NLR was demonstrated on OS

NLR: Neutrophil to lymphocyte ratio; OS: Overall survival; CSS: Cancer-specific survival; RFS: Recurrence-free survival; DFS: Disease-free survival.

The association between high NLR and worse prognosis in CRLM patients is complicated and is being rigorously studied. Inflammation plays a significant role in tumor initiation, promotion and progression through pro-inflammatory cytokines, growth factors, chemokines and pro-angiogenic factors. Neutrophils promote tumorigenesis through several mechanisms. They induce DNA damage and mutations by producing toxic substances such as reactive nitrogen species, they promote neoangiogenesis and tumor progression by releasing matrix metalloproteinase-9 (MMP-9) followed by the release of vascular endothelial growth factor. Moreover, neutrophils release a granule protein, called Arg-1, which restricts CD3-cell mediated T cell activation, thus establishing an immunosuppressive microenvironment that contributes to cancer growth. Therefore, a high neutrophil count could indicate worse prognosis in patients with cancer[33,34]. On the contrary, a low lymphocyte count is associated with poorer tumor infiltration and insufficient cell immunity and therefore with worse prognosis in patients with cancer[32]. Consequently, high NLR as a result of increased neutrophils and/or decreased lymphocytes could be an indicator of poor host against tumor response and poor prognosis.

It is plausible that NLR could have an impact in clinical practice as it represents a readily-available biomarker which could potentially assist in the decision-making with prognostic significance. In the studies included in our literature review, patients were treated with different interventions such as surgery with or without adjuvant or neo-adjuvant chemotherapy and other patients were treated with RFA or RE or solely chemotherapy. High NLR was associated with worse OS and DFS in all of the studies.

Table 4 Patient demographics, NLR cut-off value, follow up and time of sample acquisition for patients treated with radio-frequency ablation, radioembolization or solely chemotherapy

Ref.	Number of patients and procedure	Sex	Mean age (yr)	NLR threshold	Follow up (mo)	Sample acquisition
Tohme *et al*[29]	104 RE	69 M, 35 F	60.8 ± 12.2, NLR > 5, 66.4 ± 12.2, NLR < 5	5	100 patients died during follow up	Same day before RE
Chang *et al* [26]	98 RFA	56 M, 42 F	62 (28-92)	2.5	35.2 ± 21.89	1 d before RFA - 1 mo after RFA
Zhang *et al* [27]	92 RFA	51 M, 41 F	59 (43-78)	5	27.1 ± 9.8 (range 5-62)	Preoperatively as part of the routine workup. 1-3 d before RFA
Weiner *et al*[28]	131 RE	84 M, 47 F	59	5	117 deaths during follow up	NS
Kishi *et al* [15]	90 chemotherapy	61 M, 29 F	56	5	28 (2-102)	
Wu *et al* [31]	55 chemotherapy	35 M, 20 F	59	4	Complete clinical records (no exact mention)	Preoperatively and before 2nd cycle of chemotherapy
Philips *et al*[30]	71	-	-	5	-	-

RE: Radioembolization; RFA: Radiofrequency ablation; M: Male; F: Female; NLR: Neutrophil to lymphocyte ratio; NS: Not stated.

Table 5 Survival and disease characteristics of patients that were treated with radio-frequency ablation, radioembolization or solely chemotherapy

Ref.	Median Survival	5-year OS	5-year DFS	Extrahepatic disease	Primary tumor	Chemotherapy
Tohme *et al*[29]	5.6 m high NLR 10.6 m low NLR	-	-	40 (less than 10% of tumor burden)	Some patients had undergone CRC resection (number not mentioned)	All patients
Chang *et al*[26]	-	-	(Preoperative NLR) 11.1% high NLR 22.6% low NLR (NLR increase after RFA 8.6%) (No postoperative NLR increase 22.2%)	No	All patients had undergone CRC resection	No mention
Zhang *et al*[27]	-	18,4% high NLR 41.7% low NLR	9.5% high NLR 26.7% low NLR	No	All patients had undergone CRC resection	If necessary after primary tumor resection (number not mentioned)
Weiner *et al*[28]	7.9 m high NLR 13 low NLR	-	-	59	79% had undergone primary CRC resection	All patients
Kishi *et al*[15]	11 m high NLR 21 m low NLR	0% high NLR 14% low NLR	-	No	All patients had undergone CRC resection	All patients
Wu *et al* [31]	24 m high NLR 56 m low NLR	-	-	No	All patients had undergone CRC resection	All patients
Philips *et al*[30]	14.7 m high NLR 31.9 m low NLR	-	-	Liver dominant disease	Not mentioned	All patients

RFA: Radio-frequency ablation; RE: Radioembolization; OS: Overall survival; DFS: Disease-free survival; NLR: Neutrophil to lymphocyte ratio; CRC: Colorectal cancer.

Chemotherapy may affect NLR - Surgical candidates

Patients with CRLM have a poor prognosis if not treated appropriately. The current surgical approach when applicable is to resect the primary tumor followed by liver metastases resection 2-3 mo later with or without chemotherapy, but in certain cases there can be synchronous resection of the primary colon cancer and the hepatic metastases or the 'liver first approach'[35]. The role of systemic chemotherapy before or after a surgical procedure is well-established both for resectable and non-resectable disease, as

Table 6 Univariate and multivariate analysis outcomes for patients treated with radio-frequency ablation, radioembolization or solely chemotherapy

Ref.	Univariate analysis	Multivariate analysis
Tohme *et al*[29]	High NLR associated with decreased OS $P < 0.001$	High NLR associated with decreased OS (HR = 1.927, 95%CI: 1.202-3.089, $P = 0.006$)
Chang *et al*[26]	Preoperative high NLR and postoperative increase in NLR were associated with decreased DFS ($P = 0.044$ and $P = 0.022$, respectively)	Only postoperative NLR increase was associated with decreased DFS ($P = 0.029$)
Zhang *et al*[27]	High NLR associated with decreased OS ($P = 0.007$) and DFS ($P = 0.007$)	High NLR associated with decreased OS ($P = 0.039$, HR = 3.59, 95%CI: 1.54-9.67) and DFS ($P = 0.022$, HR = 3.19, 95%CI: 1.87-8.24).
Weiner *et al*[28]	High NLR associated with decreased OS (HR = 2.18, 95%CI: 1.45-3.28, $P = 0.0002$)	High NLR associated with decreased OS (HR = 2.22, 95%CI: 1.46-3.38, $P = 0.0002$)
Kishi *et al* [15]	High NLR associated with decreased OS (HR = 3.1, 95%CI: 1.7-5.9, $P < 0.001$)	High NLR associated with decreased OS (HR = 2.9, 95%CI: 1.5-5.5, $P = 0.001$).
Wu *et al* [31]	High NLR (HR = 3.182, 95%CI: 1.277-7.933, $P = 0.013$) associated with decreased OS and DFS (HR = 2.284, 95%CI: 1.156-4.498, $P = 0.017$). Patients with normalization of NLR had better DFS than those with high NLR that did not decrease ($P = 0.002$).	No association between NLR and survival
Philips *et al*[30]	High NLR associated with decreased OS $P = 0.067$ (statistically significant)	No association between NLR and survival

CI: Confidence interval; RFA: Radio-frequency ablation; RE: Radioembolization; OS: Overall survival; DFS: Disease-free survival; NLR: Neutrophil to lymphocyte ratio.

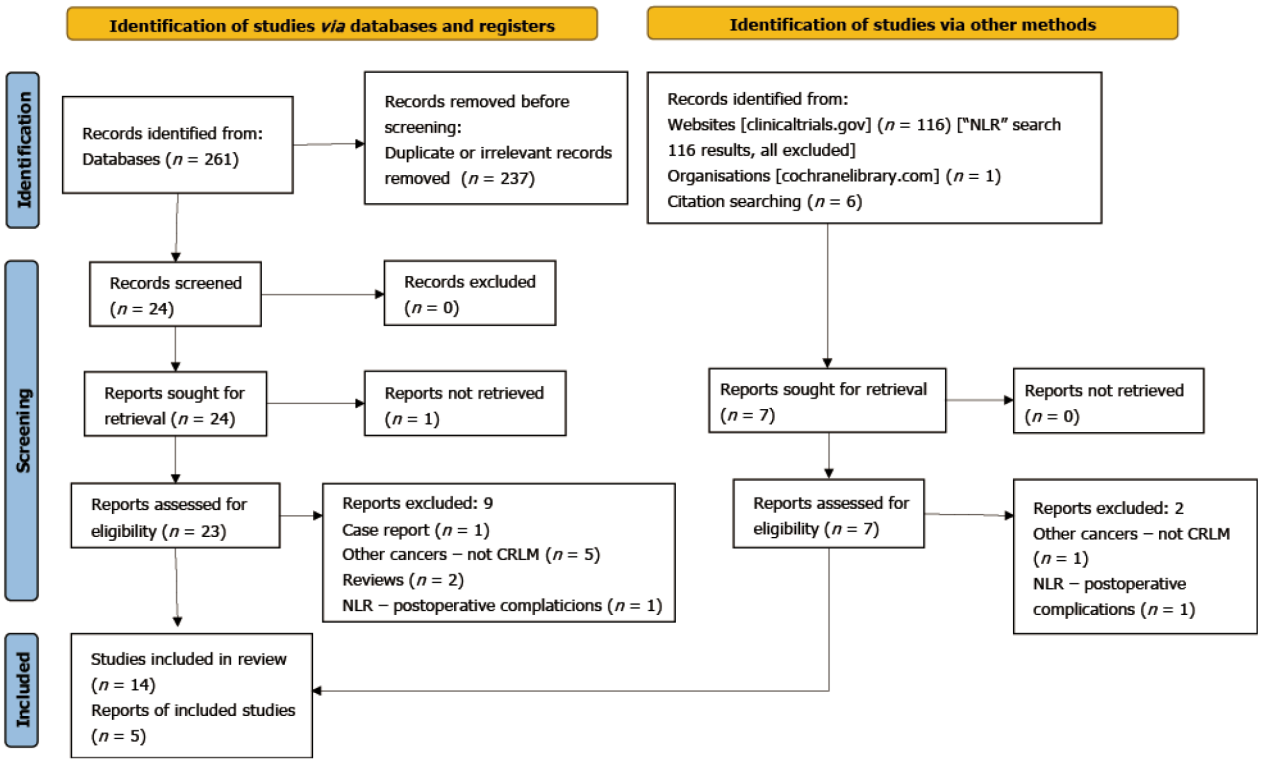

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Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

it can improve OS[36].

This systematic review points out the role of the NLR as a prognostic factor for the OS and DFS of patients with CRLM. Patients with low preoperative NLR value had better outcomes with longer OS. Similar results were presented by another systematic review which concluded that preoperative NLR calculation could contribute to the identification of patients who could benefit from adjuvant therapies [12]. Measurement of the NLR is inexpensive and easily applied with its value possibly being able to add to the management strategy for patients.

It would be of interest if we could clarify whether different types of chemotherapy affect the NLR or vice versa. In two of the studies included, some patients received adjuvant and others neoadjuvant chemotherapy. The results showed that an elevated NLR is indeed significantly associated with worse survival, but the patients who received neoadjuvant chemotherapy were not separated from the adjuvant group[14,16]. However, Kishi *et al*[15] showed that preoperative chemotherapy normalized the NLR in 68% of patients with elevated pretreatment NLR, who eventually had similar survival to those with normal pretreatment NLR. Of note, Hand *et al*[17] showed that OS was significantly shorter for chemotherapy-naive patients with elevated NLR, but not for those who received neoadjuvant chemotherapy. For the latter, the OS resembled that of the patients with normal NLR. Hand *et al*[17] did not measure the NLR after chemotherapy, but their results are consistent with the fact that neoadjuvant chemotherapy could normalize NLR. Finally, the role of chemotherapy was also investigated in the study by Mao *et al*[20]. They separated patients into four groups depending on pretreatment and presurgical NLR values. Simultaneous pretreatment and presurgical NLR > 2.3 was significantly associated with worse OS, and the authors hypothesized that high NLR may also indicate poor chemosensitivity[20]. Wu *et al*[31] included patients with synchronous CRLM who were treated with chemotherapy after primary tumor resection. They showed that patients with normalization of the NLR after one cycle of chemotherapy had better PFS than patients in whom the NLR remained high after chemotherapy and CRC resection. Consequently, the reduction of NLR could imply better chemosensitivity.

Non-surgical candidates

To this day, hepatectomy is the "gold standard" treatment in patients with CRLM offering the longest OS, but as a matter of fact only 25% of those patients are eligible for surgery mainly because their clinical condition does not allow them to be surgical candidates or sometimes they refuse surgical treatment[37].

In two studies where patients were treated with RE, the median OS ranged between 5.6 to 7.9 mo in the high NLR group and between 10.6 to 13 mo in the low NLR group. Zhang *et al*[27] and Chang *et al*[26] included 190 patients with liver-only CRC metastases. They showed that high NLR patients had worse 5-year DFS ranging between 9.5 to 11% whereas low NLR patients had better 5-year DFS ranging between 22.6 to 26.7%. Zhang *et al*[27] also showed that high NLR is associated with worse 5-year OS (18.4%) after RFA in comparison to 41.7% in low NLR patients.

It is plausible that the studies investigating the correlation between NLR and OS or DFS in patients with unresectable tumors will demonstrate worse OS or/and DFS compared to studies in surgically treated patients, since as mentioned before non-surgical candidates present a worse clinical condition in general which affects their course of disease.

Different NLR thresholds

Even though increased preoperative NLR is correlated with shorter OS and DFS in general, the NLR cut-off values varied between individual studies. The most commonly used threshold was 5. However, the NLR threshold ranged from 1.94 to 7.26[19,23]. That wide distribution could be attributed to the NLR depending on many pro- and anti-inflammatory parameters and the extent of the body's inflammatory response to cancer, in other words the cancer's biology being unpredictable[7]. In a study where eight different cut-off values were used (2.2, 2.5, 2.6, 3, 3.5, 4, 5 and 7.26), elevated NLR was consistently associated with decreased OS, even though the results were not statistically significant for every cut-off value[23]. The optimal threshold is based on molecular data analyzed by computer applications, such as Cutoff Finder[38]. The cut-off value is calculated with various models, such as ROC curve analysis or Kaplan-Meier curves and proportional hazards regression[39].

Impact on clinical practice

NLR is an easily calculated tool with a possible prognostic significance. High NLR could inform the clinicians about the worse OS and DFS that would be expected. Since worse DFS would be expected, patients with high NLR could be submitted to earlier and more frequent diagnostic imaging examinations, in order to diagnose disease recurrence. Moreover, better prognosis would be anticipated in patients with low NLR since they present better OS and DFS.

Moreover, some patients are initially diagnosed with unresectable or potentially resectable CRLM. Many studies have shown that inoperable CRLM can be down-staged to resectable CRLM after chemotherapy, but this happens in less than 35% of patients with inoperable CRLM[40]. Therefore, more than 65% of patients with unresectable CRLM will not benefit from chemotherapy and it would be important to identify biomarkers that could identify chemosensitive patients. Later, those patients would be submitted to secondary CRLM curative resection. Mao *et al*[20] and Wu *et al*[31] demonstrated in their studies that the normalization of NLR after chemotherapy is correlated to chemosensitivity. Consequently, NLR could be used as an assisting tool in stratifying patients as chemosensitive or chemoresistant. Chemoresistant patients would possibly benefit more from interventions such as RFA or RE rather than chemotherapy. More studies are needed to assess whether NLR can be used as an indicator of chemosensitivity or if NLR could be combined with other biomarkers to increase accuracy.

Our results clearly demonstrate that elevated NLR is associated with adverse OS and DFS. These results are significant and they are the same across heterogeneous studies that included different populations, age groups, cancer stages, chemotherapy regimens and medical interventions, which shows that NLR could be an important prognostic factor that can be used in CRLM patients. High pretreatment NLR is associated with worse outcomes independently of the treatment received by the patients.

Prospective studies are needed in order to examine whether NLR could be used as part of an algorithm for the treatment of CRLM. It could also be potentially used in combination with other biomarkers or parameters such as CEA, CA19-9, primary tumor location and primary tumor TNM stage, which have been used in other studies in order to create a novel scoring system that would improve the predictive accuracy of recurrence and survival[19,41].

Limitations

One limitation of our study is that the cut-off values were different among the studies. That prevents the utilization of NLR as a tool for the management of patients in clinical practice. The timing of blood sampling was also not consistent among the studies. Regarding neoadjuvant chemotherapy, even though it appears to improve outcomes, there is a need for larger studies that distinguish different chemotherapy types and regimens to reach a certain conclusion. Finally, the heterogeneity of patient demographics and clinicopathological characteristics (*e.g.*, primary tumor location and treatment, size or extent of the metastases) prevented the conduction of a meta-analysis.

It is obvious that more research is needed in order to enhance the role of NLR as an inexpensive, independent, crucial prognostic marker. More prospective randomized trials should be designed and executed as all the articles that were available to us were retrospective except one. In upcoming studies the authors should clearly state the clinicopathological details of every patient, the dates of blood sampling, the primary tumor and liver metastasis characteristics and how they were treated. Ideally, all patients should have their primary colorectal tumor resected and not have extrahepatic metastasis as these raise the tumor burden of patients with CRLM and therefore affect NLR. Moreover, all of these patients should be treated with similar chemotherapy sessions and with interventions by surgeons with similar levels of experience and training.

CONCLUSION

Neutrophil to lymphocyte ratio calculation could potentially be an assisting tool in identifying patients with CRLM who have a higher probability of poor prognosis after treatment, so that the periprocedural management could be adjusted to benefit the patient. Overall, high pretreatment NLR was significantly associated with worse OS and DFS. Larger studies could help identify a standard, widely accepted cut-off value and therefore make the NLR's prognostic significance applicable in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Patients with CRLM can be treated surgically or non-surgically, but regardless of the medical intervention they have low overall survival and disease-free survival.

Research motivation

It is important to develop prognostic biomarkers that could predict survival, tumor recurrence and response to treatment in order for patients to benefit most from medical interventions and receive personalized treatment.

Research objectives

To identify all possible articles related to our topic and examine the use of NLR as a prognostic factor in CRLM patients in clinical practice. We aimed to demonstrate that NLR is a possible significant biomarker that could assist in the management of CRLM patients by predicting survival, tumor recurrence or response to treatment.

Research methods

We performed an extensive search of PubMed, the Cochrane Library and also searched for unpublished articles in "clinicaltrials.gov". We used combinations of the words "Neutrophil to Lymphocyte ratio", "NLR", "survival", "prognostic factor", "metastasis", "metastases", "liver metastasis", "liver metastases". The results were screened by two independent researchers and any potential differences were resolved between them and a third researcher through discussion. The aim was to identify studies

that investigated the correlation between NLR and survival or tumor recurrence in CRLM patients.

Research results

We included 19 studies that included CRLM patients who were treated with different medical approaches, surgically or non-surgically. All the studies demonstrated that high NLR was associated with poor survival, disease-free survival and response to chemotherapy.

Research conclusions

The NLR could potentially be used as a predictor of survival, tumor recurrence and chemosensitivity in CRLM patients.

Research perspectives

Prospective, well-structured studies are needed in order to examine the role of the neutrophil to lymphocyte ratio (NLR) as a prognostic factor and establish it as part of the decision-making tools of clinicians in the management of colorectal liver metastasis (CRLM) patients.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Menelaos Papakonstantinou 0000-0001-5030-7009; Stylianos Fiflis 0000-0003-0427-6859; Gregory Christodoulidis 0000-0003-3413-0666; Mariano Cesare Giglio 0000-0002-9222-5885; Eleni Louri 0000-0003-4790-419X; Savvas Mavromatidis 0000-0002-6435-8349; Dimitrios Giakoustidis 0000-0002-6023-4744; Vasileios N Papadopoulos 0000-0002-1009-1685; Alexandros Giakoustidis 0000-0002-3786-4609.

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SCIENTOMETRICS

Current global research landscape on COVID-19 and cancer: Bibliometric and visualization analysis

Sa'ed H Zyoud, Amer Koni, Samah W Al-Jabi, Riad Amer, Muna Shakhshir, Rand Al Subu, Husam Salameh, Razan Odeh, Sultan Musleh, Faris Abushamma, Adham Abu Taha

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Sa'ed H Zyoud, Amer Koni, Samah W Al-Jabi, Department of Clinical and Community Pharmacy, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine

Sa'ed H Zyoud, Clinical Research Centre, An-Najah National University Hospital, Nablus 44839, Palestine

Amer Koni, Riad Amer, Husam Salameh, Razan Odeh, Sultan Musleh, Hematology and Oncology Department, An-Najah National University Hospital, Nablus 44839, Palestine

Riad Amer, Rand Al Subu, Husam Salameh, Sultan Musleh, Faris Abushamma, Department of Medicine, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine

Muna Shakhshir, Department of Nutrition, An-Najah National University Hospital, Nablus 44839, Palestine

Faris Abushamma, Department of Urology, An-Najah National University Hospital, Nablus 44839, Palestine

Adham Abu Taha, Department of Pathology, An-Najah National University Hospital, Nablus 44839, Palestine

Adham Abu Taha, Department of Biomedical Sciences, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine

Corresponding author: Sa'ed H Zyoud, PhD, Associate Professor, Department of Clinical and Community Pharmacy, College of Medicine and Health Sciences, An-Najah National University, Academic Street, Nablus 44839, Palestine. saedzyoud@yahoo.com

Abstract

BACKGROUND

Cancer is a severe public health issue that seriously jeopardizes global health. In individuals with coronavirus disease 2019 (COVID-19), cancer is considered an independent risk factor for severe illness and increased mortality.

AIM

To identify research hotspots and prospects, we used bibliometrics to examine the global production of COVID-19 literature published in the field of oncology.

METHODS
Data on publication output were identified based on the Scopus database between January 1, 2020, and June 21, 2022. This study used VOSviewer to analyze collaboration networks among countries and assess the terms most often used in the titles and abstracts of retrieved publications to determine research hotspots linked to cancer and COVID-19. The *Impact Index Per Article* for the top 10 high-cited papers collected from Reference Citation Analysis (RCA) are presented.

RESULTS
A total of 7015 publications were retrieved from the database. The United States published the greatest number of articles (2025; 28.87%), followed by Italy (964; 13.74%), the United Kingdom (839; 11.96%), and China (538; 7.67%). The *University of Texas MD Anderson Cancer Center* (n = 205, 2.92%) ranked first, followed by the *Memorial Sloan-Kettering Cancer Center* (n = 176, 2.51%). The *European Journal of Cancer* (n = 106, 1.51%) ranked first, followed by the *Frontiers in Oncology* (n = 104, 1.48%), *Cancers* (n = 102, 1.45%), and *Pediatric Blood and Cancer* (n = 95; 1.35%). The hot topics were stratified into "cancer care management during the COVID-19 pandemic"; and "COVID-19 vaccines in cancer patients".

CONCLUSION
This is the first bibliometric analysis to determine the present state and upcoming hot themes related to cancer and COVID-19 and vice versa using VOSviewer during the early stages of the pandemic. The emergence of hot themes related to cancer and COVID-19 may aid researchers in identifying new research areas in this field.

Key Words: Bibliometric; Scopus; COVID-19; Cancer; Coronavirus disease; VOSviewer; Reference Citation Analysis

Core Tip: Many systematic reviews and meta-analyses found that the number of papers investigating the impact of coronavirus disease 2019 (COVID-19) on cancer in various countries increased during the pandemic. The existing literature on COVID-19, focusing on cancer research, has not been provided by any bibliometric analysis. The hot topics were stratified into "cancer care management during the COVID-19 pandemic"; and "COVID-19 vaccines in cancer patients". Cancer and COVID-19 have emerged as hot topics, which may help researchers uncover new research opportunities in this area.

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INTRODUCTION

The first confirmed case of coronavirus disease 2019 (COVID-19) was recorded in Wuhan, China, on December 31, 2019[1]. Since that time, COVID-19 has been spreading rapidly throughout the world. Although some individuals diagnosed with COVID-19 have no symptoms, patients who become symptomatic exhibit a wide range of severity, ranging from mild respiratory symptoms to critical lung disease, sepsis, multiple organ failure, or even death[2,3]. As of June 22, 2022, a total of 538321874 cases of COVID-19 have been confirmed worldwide, including 6320599 deaths[4]. According to the Sustainable Development Goals (SDGs) Report 2020, COVID-19 halts the progress of SDG 3, which seeks to guarantee well-being and a healthy life for everyone. During the crisis, health services for cancer screening have been disrupted or ignored in many places[5].

Cancer patients represent a district group in the population with a weakened immune system due to anticancer treatments and disease activity[6,7]. In pandemics like COVID-19, cancer patients may be deprived of receiving appropriate health care as many health institutes announced shortages of their resources, along with the inadequate information available in the literature to manage them properly [8]. Therefore, health care practitioners have to decide whether to initiate or defer anticancer treatments, considering the risks and benefits of such action. Notably, patients with active cancer are highly susceptible to COVID-19. They are suspected of having serious consequences, such as admission to the

intensive care unit, a requirement for mechanical ventilation, or death[9]. These unfavorable outcomes could sometimes be related to types of cancer, particularly hematologic malignancies and lung cancer [9].

Some studies reported a death rate of 28% among COVID-19 patients with cancer, which was far higher than the rate in the general population[10,11]. It was also found that certain demographics and disease-related factors, including male gender, smoking, old age, having ≥ two medical conditions, cancer status, and performance situation, were strongly associated with the mortality rate among COVID-19 cancer patients[12,13]. However, receiving antitumor therapy within four weeks of diagnosis with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was not associated with the death rate[10].

According to several systematic reviews and meta-analyses, the number of publications analyzing the impact of COVID-19 on cancer in various nations increased during the pandemic[14-18]. Although various bibliometric studies have been undertaken to evaluate COVID-19 research worldwide[19-23], limited studies have been identified that have presented the current literature on COVID-19, focusing on cancer research. The bibliometric methodology was utilized to measure and categorize research output, allowing for mapping the subject area based on the most involved authors, institutions, nations, citations, journals, and hot topics[24-28]. Therefore, this study sought to comprehensively analyze the current status of publications on COVID-19 in the oncology field through visual and bibliometric analysis. This study intends to be a valuable resource and guide for oncologists, clinicians, virologists, and epidemiologists conducting research on the emerging human coronavirus in the field of cancer in order to generate novel ideas for effective control measures and to outline COVID-19 vaccine guidance for cancer patients as soon as possible.

MATERIALS AND METHODS

Data source

The present study, which includes the analysis, was performed in June 2022. The authors utilized the Scopus database to find relevant publications as: (1) It is available to the author through the "Research4 Life" library; (2) it is the largest database available, and it has a greater number of indexed journals than other databases (*e.g.*, PubMed or Web of Science) and is completely inclusive of all journals in Medline [29-31]; and (3) it indexes journals in the disciplines of health, social sciences, life sciences, and physical sciences[32,33]. In addition, Scopus has previously been used to analyze and visualize research publications on various health-related topics[34-38].

Search strategies

In order to obtain all publications pertaining to COVID-19 and cancer published between January 1, 2020, and June 21, 2022, we employed the 'Advanced search' feature of the Scopus online database. The retrieval and export of data took place within one day to avoid the risk of bias induced by ongoing database changes (June 21, 2022). The following strategy was used to retrieve data for this study (Figure 1):

Step 1: The phrases associated with COVID-19 were entered into the Scopus engine to accomplish the study's objectives. They were drawn from previous bibliometric researches on COVID-19[20,21,39-41]. All selected "terms" were included in the "Article Title/Abstract/Keywords" section.

Step 2: The documents identified in step 1 were then limited to those having the phrases "cancer and related terms" in their titles. Cancer-related terms were taken from PubMed's Medical Subject Headings (MeSH), and from a previous systematic and meta-analysis on COVID-19 in the oncology field[14-17,42] and placed into the Scopus engine. Some documents (*i.e.*, erratum, and retracted) were excluded (Figure 1).

Bibliometric analysis

The following bibliometric indicators were compiled using an Excel spreadsheet: total number of publications, type of publication, prolific countries, prolific institutions, prolific journals, and top-cited publications. Reference Citation Analysis (RCA) data were used to calculate the *Impact Index Per Article* for the top ten most cited papers. Baishideng Publishing Group Inc. owns the RCA, an open transdisciplinary citation analysis database (Pleasanton, CA 94566, United States)[43].

Visualization analysis

The network visualization maps were created using the VOSviewer (version 1.6.16) software program [44,45]. VOSviewer was used in our study as it is well-known as a software tool for visualizing quantitative data. VOSviewer is widely used for mapping, networking, and visualization to emphasize international collaboration and create a co-occurrence matrix to identify research hotspots based on published evidence. A node represents a certain element, such as a country or term. Stronger

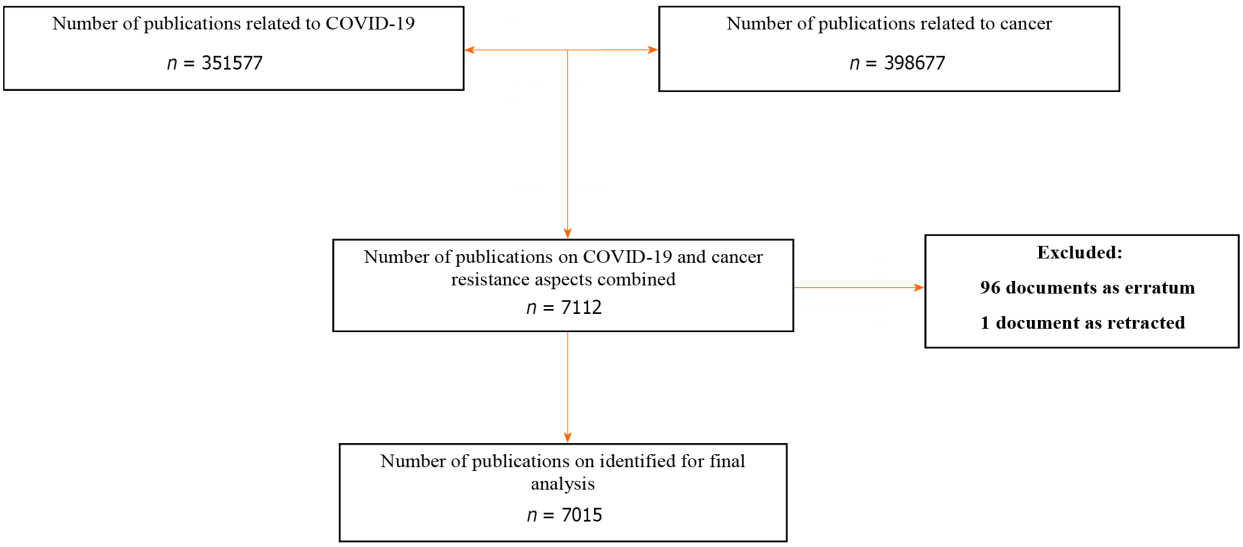

Figure 1 Flowchart for including and excluding literature studies.

cooperation is shown by wider links between nodes, whereas a bigger node size suggests a large number of publications[44,45]. The study themes in the collected literature were determined by mapping the most common terms in titles/abstracts. Using VOSviewer, it is possible to create an overlay visualization in which the most recently used author terms are shown in yellow. Terms overlay visualization was based on the occurrences and average publication per year scores.

RESULTS

Volume and types of publications

At the time of data collection (June 21, 2022), Scopus has published 351577 documents on COVID-19 throughout all research fields. During the study period (January 1, 2020, to June 21, 2022), Scopus identified 7015 papers on cancer and COVID-19 which were categorized into ten types. Among them, "Article" accounted for 57.59% of the total publications (4040 articles) and was the most frequent type, followed by letters to the editor (n = 1061; 15.12%), and reviews (n = 936; 13.34%). The remaining publication types were 978 documents (13.94%).

Contributions of countries to global publications

We ranked ten high-output countries according to the number of publications (Table 1). The United States published the greatest number of articles (2025; 28.87%), followed by Italy (964; 13.74%), the United Kingdom (839; 11.96%), and China (538; 7.67%). Figure 2 depicts a network map of the major participating countries' international research collaborations on cancer and COVID-19-related literature.

Active institutions/organizations

Table 2 shows the top ten active institutions. The *University of Texas MD Anderson Cancer Center* (n = 205, 2.92%) ranked first, followed by the *Memorial Sloan-Kettering Cancer Center* (n = 176, 2.51%) and the *Harvard Medical School* (n = 155; 2.21%). The majority of active institutions were from the United States (n = 4), followed by Italy (n = 3), Canada (n = 1), France (n = 1), and India (n = 1).

Active journals

For cancer and COVID-19-related literature, Table 3 shows the top ten active journals. The *European Journal of Cancer* (n = 106, 1.51%) ranked first, followed by the *Frontiers in Oncology* (n = 104, 1.48%), *Cancers* (n = 102, 1.45%), and *Pediatric Blood and Cancer* (n = 95; 1.35%).

Top cited publications

Table 4 lists the top ten most cited works in the field of COVID-19 and cancer, ranked by total citations. The citations in the top ten ranged from 2498 to 340[9-12,46-51]. Among the top 10 papers by total citation frequency, Liang *et al*[46], published in *The Lancet Oncology* in 2020, had the greatest overall citation frequency (number of citations = 2498). The *impact index per article* of the ten most cited articles ranged from 118.5 to 1017.0 (Table 4).

Table 1 Publication contributions of the top 10 productive countries

Ranking	Country	Number of documents	%
1st	United States	2025	28.87
2nd	Italy	964	13.74
3rd	United Kingdom	839	11.96
4th	China	538	7.67
5th	India	489	6.97
6th	France	403	5.74
7th	Canada	363	5.17
8th	Germany	349	4.98
9th	Spain	327	4.66
10th	Australia	237	3.38

Table 2 Top ten active institutions/organizations on research related to coronavirus disease 2019 and cancer

Ranking	Institution	Country	*n*	%
1st	University of Texas MD Anderson Cancer Center	USA	205	2.92
2nd	Memorial Sloan-Kettering Cancer Center	USA	176	2.51
3rd	Harvard Medical School	USA	155	2.21
4th	Dana-Farber Cancer Institute	USA	152	2.17
5th	University of Toronto	Canada	132	1.88
5th	Università degli Studi di Milano	Italy	127	1.81
7th	Istituto Europeo di Oncologia	Italy	121	1.72
8th	INSERM	France	120	1.71
9th	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan	Italy	119	1.70
10th	Tata Memorial Hospital	India	116	1.65

Research themes in cancer and COVID-19-related literature

Mapping the most frequent appearing terms in the title/abstract fields of publications in cancer and COVID-19 with a minimum occurrence of 100 resulted in 253 terms being distributed into two clusters corresponding to the two primary study topics (Figure 3). The clusters are "cancer care management during the COVID-19 pandemic" (cluster 1, red), and "COVID-19 vaccines in cancer patients" (cluster 2, green); (Figure 3). The guideline, emergency, procedure, safety, process, recommendation, guidance, approach, and care are the most often used terms in cluster 2. The most often used terms in cluster 2 are vaccine, vaccination, immunotherapy, and development.

The evolution of color from dark blue to yellow represents the variation of the hot topic over time. As shown in Figure 4, researchers focused on topics related to COVID-19 vaccines in cancer patients during the last year and have become the hot research topics, attracting increasing attention.

DISCUSSION

This is the first bibliometric study in the field of cancer to assess and visualize COVID-19 research. We reviewed a total of 7015 publications from the Scopus database, and we present a detailed analysis of worldwide contributions and hotspots in COVID-19 and cancer research during the early stages of the pandemic. According to our study, the growing number of publications in cancer and COVID-19-related literature indicates that this topic is receiving considerable attention. During the COVID-19 pandemic, the popularity of sustainable development research has increased. The number of publications indicates that as the pandemic expanded internationally, more countries were impacted, which has led to an increase in researchers paying attention to the pandemic's influence on sustainable development[52].

Table 3 Top ten active journals on research related to coronavirus disease 2019 and cancer

Ranking	Journal	*n*	%	IF
1st	*European Journal of Cancer*	106	1.51	9.162
2nd	*Frontiers in Oncology*	104	1.48	6.244
3rd	*Cancers*	102	1.45	6.639
4th	*Pediatric Blood and Cancer*	95	1.35	3.167
5th	*Lancet Oncology*	90	1.28	41.316
6th	*Supportive Care in Cancer*	86	1.23	3.603
7th	*Cancer*	81	1.15	6.860
8th	*JAMA Oncology*	75	1.07	31.777
9th	*JCO Oncology Practice*	73	1.04	NA
10th	*Advances in Radiation Oncology*	60	0.86	NA

IF: Impact factor; NA: Not available.

Table 4 List of the top 10 cited articles for coronavirus disease 2019 studies related to cancer between January 1, 2020, and June 21, 2022

Ranking	Ref.	Title	Year	Source title	Cited by	Impact Index Per Article[1]
1st	Liang *et al* [46]	"Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China"	2020	The Lancet Oncology	2498	1017.0
2nd	Zhang *et al* [47]	"Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China"	2020	Annals of Oncology	859	296.0
3rd	Tian *et al*[49]	"Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer"	2020	Journal of Thoracic Oncology	835	315.5
4th	Kuderer *et al* [12]	"Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study"	2020	The Lancet	825	292.5
5th	Dai *et al*[9]	"Patients with cancer appear more vulnerable to SARS-CoV-2: A multicenter study during the COVID-19 outbreak	2020	Cancer Discovery	774	118.5
6th	Yu *et al*[50]	SARS-CoV-2" "Transmission in Patients with Cancer at a Tertiary Care Hospital in Wuhan, China"	2020	JAMA Oncology	659	236.0
7th	Maringe *et al* [48]	"The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study"	2020	The Lancet Oncology	579	189.0
8th	Lee *et al*[10]	"COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: A prospective cohort study"	2020	The Lancet	574	210.5
9th	Mehta *et al* [11]	"Case fatality rate of cancer patients with COVID-19 in a New York Hospital system"	2020	Cancer Discovery	426	158.5
10th	Feldmann *et al*[51]	"Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed"	2020	The Lancet	340	140.0

[1]The Impact Index Per Article is presented based on Reference Citation Analysis.

One of the key hot issues in the current study was "Cancer care management during the COVID-19 pandemic". According to several studies, the probability of developing COVID-19 in cancer patients is considered twofold higher than in the normal population. Therefore, oncologists should employ appropriate therapeutic methods in the event of a pandemic, weighing the risks of mortality from COVID-19 against the risks and benefits of continuing anticancer therapy[53-55]. Additionally, managing patients efficiently during pandemics or big crises should be a key component of the cancer care continuum. Common immunosuppressive treatments are likely to make cancer patients more vulnerable to COVID-19-related severe outcomes. Although recent studies of immunocompromised people suggest that outcomes may be less severe, several malignancy studies show a link between

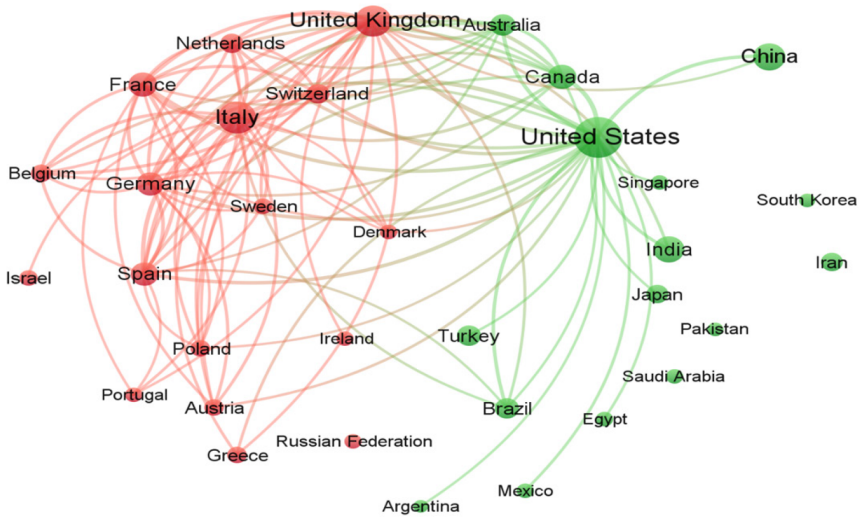

Figure 2 International collaboration in cancer and coronavirus disease 2019-related literature is visualized as a network map among the most active countries. This graphical collaboration map was created after a minimum of 50 publications were placed in each country. Of 143 countries working in this field, 33 met this threshold. The node size denotes the number of publications for that country.

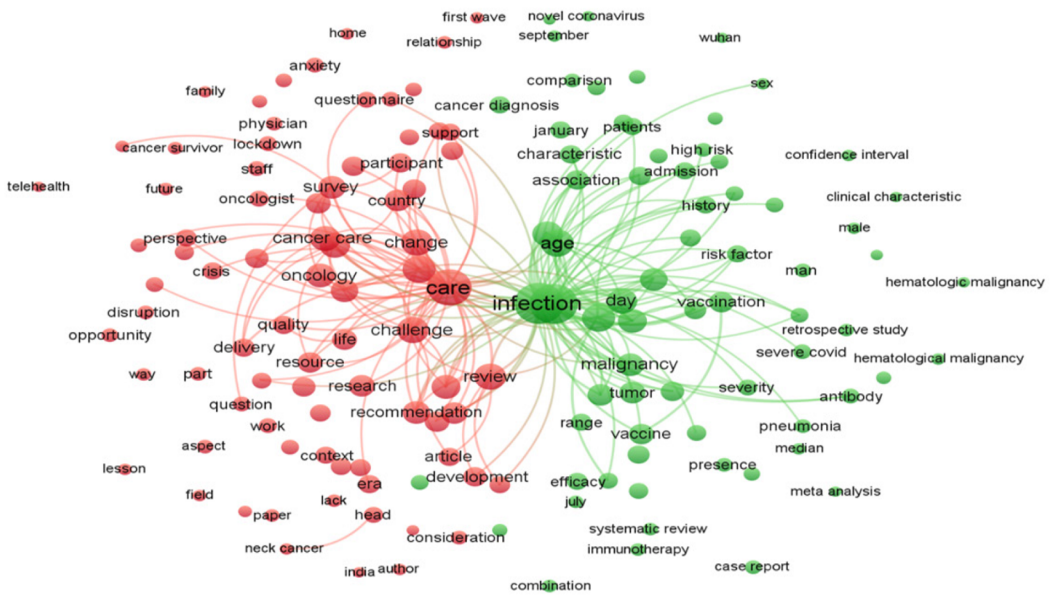

Figure 3 Map of terms in the title/abstract fields of papers relating to cancer and coronavirus disease 2019 as a network visualization. This graphical map of terms was created by placing the minimum number of term occurrences at least 100 times. Out of 75191 terms in this field, 253 terms met this criterion, grouped into three clusters and colored differently. The node size denotes the number of articles that contain that term.

increased fatality rates[12,56]. These risks are likely to differ depending on the type of cancer treatment and type of cancer[46,50,57]. According to the findings from a large systematic review and meta-analysis[58], it was shown that cancer is a comorbidity in between 1% and 2% of COVID-19 patients who are hospitalized in China, and in 5% to 7% of patients in Western nations. Based on these findings, it appears that the subjects clinically appear the same as normal individuals, and early research has shown that patients with cancer and COVID-19 have a greater in-hospital mortality risk.

Thus, this also minimizes harm in the event of a future pandemic, but it also empowers the gains generated by the current pandemic to improve overall health care delivery for all cancer patients and, by leveraging the efforts of many organizations across the cancer care stakeholders, helps all patients receive the highest-quality care while simultaneously fostering cooperation on a global scale[59,60].

Another hot subject is the COVID-19 vaccine in cancer patients. Since the early stages of the pandemic, patients with cancer have been designated as a high-risk group for COVID-19[61,62]. Therefore, the safety and effectiveness of COVID-19 vaccination in immunosuppressed persons must be better understood urgently, as excluding them and other susceptible groups from continuing trials of COVID-19 vaccines would result in inaccurate prognostic health models, which will impact subsequent

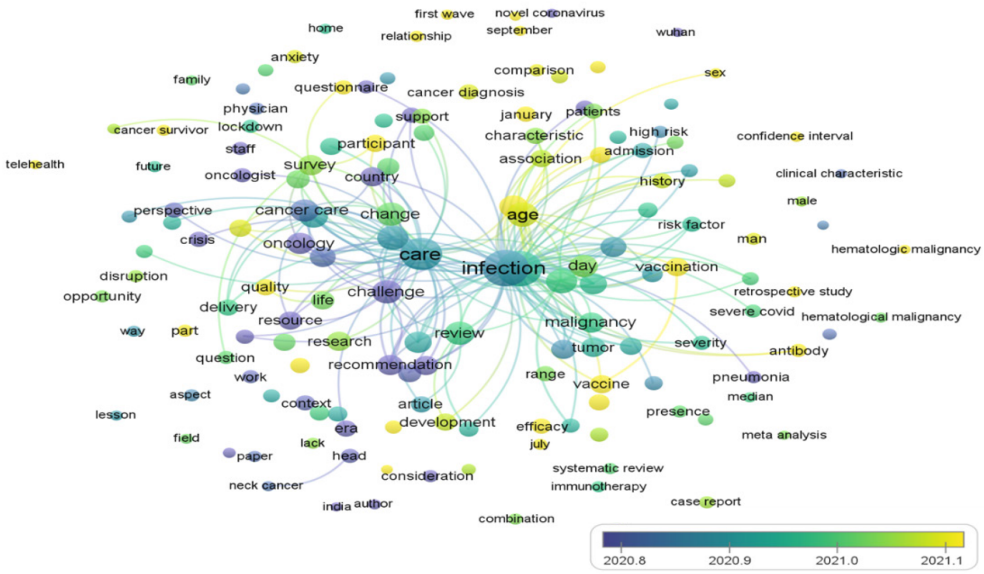

Figure 4 Overlay visualization of terms co-occurrence cluster analysis. The color of the nodes, which denotes the average publication year, changes from dark blue to yellow, representing the average publication year of the keyword from 2000 to 2022.

pandemic waves[63,64]. Given the significant risk of morbidity and death from COVID-19 in cancer patients, current information on the safety and efficacy of the approved COVID-19 vaccinations in these patients is limited. However, the benefits likely outweigh the risks of vaccine-related adverse effects[65].

Published documents that are often cited have a large academic influence. Table 4 lists the ten cancer and COVID-19-related documents with the highest citation frequency. The most frequently cited paper on the subject is "Cancer patients with SARS-CoV-2 infection: a nationwide analysis in China," published in *The Lancet Oncology* and cited 2498 times. This prospective observational study found that cancer patients were more likely to develop SARS-Cov-2 infection, require mechanical ventilation, and have an increased mortality risk[46]. It also showed that the clinical conditions of cancer patients got worse more rapidly than that of the other populations[46]. The paper by Zhang *et al*[47], which was published in *Annals of Oncology*, was the second most cited article. This study aimed to describe the clinical characteristics of COVID-19 patients who had cancer. The results revealed that more than 80% of patients had a dry cough, low lymphocyte count, high body temperature, low protein levels, and high value of inflammatory markers (C-reactive protein). In addition, patients who received anticancer therapy during the last two weeks were more likely to have serious consequences.

The third highest cited paper, published in *Journal of Thoracic Oncology*[49], analyzed two lung cancer tissue specimens of patients with COVID-19 and showed multinucleated giant cells, exudate-containing proteins, and central reactive hyperplasia of pneumocytes, along with infiltrated patches of inflammatory cells. The paper by Kuderer *et al*[12], which was published in the *Lancet*, was the fourth most cited article. This cohort analysis of 928 cancer patients diagnosed with COVID-19 noted that male gender, smoking, old age, having ≥ two medical conditions, use of chloroquine and azithromycin, cancer status, and performance situation were the determinants of death during one month. However, the types of malignancy or antitumor treatments used did not predict the death rate.

The paper by Dai *et al*[9], which was published in *Cancer Discovery*, was the fifth most cited article. The study was carried out to compare COVID-19 cancer patients *vs* non-cancer patients and their susceptibility to COVID-19. The risk of serious outcomes, including admission to the intensive care unit, developing serious symptoms, invasive ventilation, or death, was higher in cancer patients than in non-cancer cases. Hematologic malignancies, lung cancer, and metastatic tumors were the most frequent types of cancer to have such events.

The paper by Yu *et al*[50], which was published in *JAMA Oncology*, was the sixth most cited article. According to this study, which was conducted in one center in China, the risk of contracting COVID-19 among oncology patients was found to be 0.79%. In addition, the subgroup analysis revealed a greater rate of SARS-CoV-2 infection in non-small cell lung cancer patients over 60 years old compared to those under 60 years.

The seventh most cited article was by Maringe *et al*[48] and published in the *Lancet Oncology*. According to this study, the COVID-19 pandemic in the UK is predicted to significantly increase the number of preventable cancer deaths in England. The COVID-19 pandemic is predicted to impact cancer patients significantly, and urgent policy initiatives are needed to address the backlog in regular diagnostic services. The paper by Lee *et al*[10], which was published in the *Lancet*, was the eighth-most cited article. The outcomes of this study revealed a high mortality rate among COVID-19 patients with

active malignancy (28%). The mortality rate was significantly associated with old age, male gender, and other diseases. However, receiving anticancer treatment within four weeks of being diagnosed with SARS-CoV-2 infection was not related to the mortality rate.

The paper by Mehta *et al*[11], which was published in *Cancer Discovery*, was the ninth most cited article. This study reported a mortality rate of 28% (61/218) among COVID-19 cancer patients, which were distributed as 20 deaths of blood cancer (37%) and 41 of solid cancer (25%). The predictors of mortality were advanced age, presence of other medical conditions, a high level of inflammatory markers, and admission to the intensive care unit.

The tenth most cited article was by Feldmann *et al*[51] and published in the *Lancet*. This study revealed that tumor necrosis factor (TNF) is considered one of the main targeted therapies for certain inflammatory diseases, such as rheumatoid arthritis. Importantly, COVID-19 involves an inflammatory process with a role for TNF, indicating a possible benefit of using anti-TNF agents in COVID-19 patients. Moreover, no adverse outcome was found in COVID-19 patients who used anti-TNF therapy. Thus, there is an urgent need for clinical trials of anti-TNF treatment targeting COVID-19 patients.

Strengths and limitations

Publications in cancer and COVID-19-related literature were assessed and analyzed comprehensively and objectively using the largest abstract and citation database containing peer-reviewed research. Although this is the first bibliometric investigation of COVID-19 in the field of oncology, there are certain limitations: (1) The search was conducted on June 21, 2022, and included all documents from January 1, 2020, up to June 21, 2022, but the Scopus database would have been open for new documents from 2022, so this part was omitted; (2) Only publications containing the terms related to cancer in the title were retrieved; and (3) As the search was limited to Scopus indexed journals, a few publications not included in the Scopus database were missed. Other bibliometric studies have also noted some limitations[35,66,67].

CONCLUSION

In conclusion, this is the first bibliometric analysis to determine the present state and upcoming hot themes related to cancer and COVID-19 and vice versa using VOSviewer during the early stages of the pandemic. The top five most productive countries reporting high research on cancer and COVID-19-related literature are the United States, Italy, the United Kingdom, China, and India. In terms of publications in this discipline, the *University of Texas MD Anderson Cancer Center* and *the Memorial Sloan-Kettering Cancer Center* are the most prolific institutions. The results of the present bibliometric analysis revealed that most hot research topics have evaluated "cancer care management during the COVID-19 pandemic", and "COVID-19 vaccines in cancer patients". The emergence of hot themes related to cancer and COVID-19 may aid researchers in identifying new research areas in this field.

ARTICLE HIGHLIGHTS

Research background

In comparison to the general population, cancer patients with coronavirus disease 2019 (COVID-19) have a mortality rate that is two times higher.

Research motivation

Despite the fact that numerous bibliometric studies have been carried out to assess COVID-19 research across the globe, there are few studies that have focused on COVID-19 literature and cancer research.

Research objectives

Through visual and bibliometric analysis, this study aimed to thoroughly examine the current state of publications on COVID-19 in the field of cancer.

Research methods

The Scopus database was searched to identify publishing output data. To identify research hotspots related to cancer and COVID-19, this study used VOSviewer to analyze international collaboration networks and evaluate the terms most frequently used in the titles and abstracts of the articles retrieved. The *Impact Index Per Article* is shown for the top 10 highly cited publications gathered *via* Reference Citation Analysis (RCA).

Research results

The results of the present bibliometric analysis revealed that most hot research topics have evaluated

"cancer care management during the COVID-19 pandemic", and "COVID-19 vaccines in cancer patients".

Research conclusions

Based on a current review of hot topics and research patterns, the findings of this study may help researchers uncover new research areas in the field of cancer and COVID-19.

Research perspectives

For oncologists, clinicians and virologists, this study aims to be a valuable resource and guide for research on emerging COVID-19 in the field of cancer to generate novel ideas for effective control measures and to outline COVID-19 vaccine guidance for cancer patients in the most timely manner.

FOOTNOTES

Author contributions: Zyoud SH designed the study, collected the data, analyzed the data, made major contributions to the manuscript's existing literature search and interpretation, and drafted the manuscript; Koni A, Al-Jabi S, Amer R, Shakhshir M, Al subu R, Salameh H, Odeh R, Musleh S, Abushamma F, and Abu Taha A were involved in interpretation of the data, and made revisions to the initial draft; all authors provided a critical review and approved the final manuscript before submission.

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Country/Territory of origin: Palestine

ORCID number: Sa'ed H Zyoud 0000-0002-7369-2058; Amer Koni 0000-0002-0514-9352; Samah W Al-Jabi 0000-0002-4414-9427; Riad Amer 0000-0001-8806-0304; Muna Shakhshir 0000-0002-6213-8457; Faris Abushamma 0000-0002-0530-5466; Adham Abu Taha 0000-0002-2889-1138.

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CASE REPORT

Ascending colon cancer and situs inversus totalis – altered surgeon position for successful laparoscopic hemicolectomy: A case report

Ji-Long Hu, Qi-Yun Li, Kun Wu

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Ji-Long Hu, Qi-Yun Li, Kun Wu, Department of Abdominal Tumor Surgery, Jiangxi Cancer Hospital, Nanchang 330000, Jiangxi Province, China

Corresponding author: Qi-Yun Li, MD, Chief Physician and Surgeon, Department of Abdominal Tumor Surgery, Jiangxi Cancer Hospital, No. 519 Beijing East Road, Qingshan Lake District, Nanchang 330000, Jiangxi Province, China. liqiyun878@sina.com

Abstract

BACKGROUND

Situs inversus totalis (SIT) is a rare congenital condition in which the structure of the abdominal and thoracic cavities is the mirror image of normal. This anatomic reversal makes laparoscopic surgery difficult when treating colorectal cancer.

CASE SUMMARY

We describe the successful laparoscopic hemicolectomy of a 68-year-old Chinese woman with SIT and ascending colon cancer. Based on preoperative imaging and careful consideration of the patient's anatomy, the position of the surgeon was modified such that the surgeon stood between her legs, while the surgical assistant and endoscopist stood to the surgeon's left. Trocar position was also adjusted appropriately. The surgery lasted 178 min, during which the patient lost 50 mL of blood. Pathology analysis of the resected tumor confirmed an adenocarcinoma in clinical stage pT3N0M0, without lymph node involvement. The patient experienced no postoperative complications and was discharged 10 d after surgery.

CONCLUSION

This case illustrates that careful positioning of the surgeon can facilitate laparoscopic surgery of SIT patients.

Key Words: Colon cancer; Situs inversus totalis; Laparoscopic surgery; Case report

Core Tip: Situs inversus totalis (SIT) is a rare congenital anomaly in which the organs in the chest and abdomen are located in a mirror image reversal of their normal positions. We present a rare case of SIT accompanied by colon cancer. After careful consideration of the patient's anatomy, we modified the position of the surgeon to enable successful laparoscopic hemicolectomy. This case highlights that careful positioning of the surgeon can make laparoscopic surgery feasible and safe for SIT patients.

Citation: Hu JL, Li QY, Wu K. Ascending colon cancer and situs inversus totalis – altered surgeon position for successful laparoscopic hemicolectomy: A case report. *World J Clin Oncol* 2022; 13(10): 848-852
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INTRODUCTION

Situs inversus totalis (SIT) is a rare congenital anomaly in which organs in the chest and abdomen are positioned in the mirror image of normal. Incidence in the general population ranges from 1 per 8000 to 1 per 25000[1], and SIT patients with colon cancer are even rarer. Surgery in SIT patients, particularly laparoscopic procedures, are considered more difficult because of the anatomical abnormality[2,3].

Here, we report the case of a 68-year-old patient with SIT and ascending colon cancer who successfully underwent laparoscopic hemicolectomy with radical lymph node dissection. The success of the procedure was due to careful consideration of the patient's anatomy and optimization of the surgical team's position.

CASE PRESENTATION

Chief complaints

A 68-year-old Chinese woman visited our hospital in December 2020 due to gradual enlargement of a mass in the left lower abdomen.

History of present illness

The patient had experienced intermittent bloody stool for nearly 1 year.

History of past illness

The patient did not have any history of past illnesses.

Personal and family history

The patient had no remarkable personal or family history.

Physical examination

The patient was 142 cm tall and weighed 35 kg, corresponding to a body mass index of 17.4 kg/m^2. Physical examination revealed a mass measuring 4 cm × 5 cm in the left lower abdomen.

Laboratory examinations

Laboratory tests indicated no anemia, normal electrolytes, and no dysfunction of the liver or kidneys. The level of carcinoembryonic antigen in serum was slightly elevated (8.37 ng/mL; normal, < 2.5 ng/mL), while levels of carbohydrate antigen (CA) 12-5 and CA 19-9 were normal.

Imaging examinations

Chest and abdominal computed tomography (CT) revealed that the structure of the thoracic cavity and all abdominal organs were inverted from the normal position, leading to a diagnosis of SIT (Figure 1A). A mass in the ascending colon was confirmed (Figure 1A), and no evidence of distant metastasis was found. CT angiography showed that the superior mesenteric artery was located on the left side (Figure 1B). Colonoscopy revealed a mass in the ascending colon that occupied the complete diameter of the lumen, which together with intestinal stenosis prevented the passage of the colonoscope.

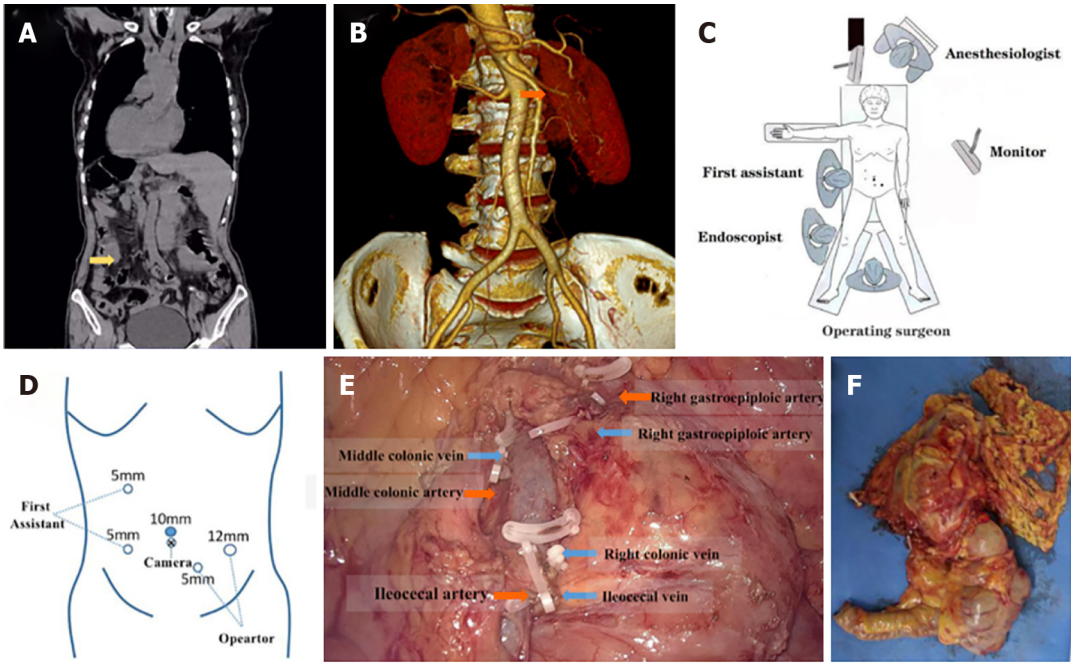

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Figure 1 Images of computed tomography and the surgery. A: Computed tomography (CT) showed complete transposition of the thoracic and abdominal viscera. The ascending colon tumor is marked with a orange arrow; B: Three-dimensional CT angiography of the superior mesenteric artery on the left side; C: Schematic of the surgical procedure; D: Positioning of the trocars; E: Exposure of blood vessels during operation; F: The excised tumor mass.

FINAL DIAGNOSIS

The patient was diagnosed with colon cancer and SIT.

TREATMENT

Laparoscopic hemicolectomy with radical lymphadenectomy was performed under general anesthesia. The patient was placed in a modified lithotomy position, with her head down and legs apart. The surgeon stood between her legs, and the first assistant and endoscopist stood on the surgeon's left, which is the opposite of the usual position for surgery (Figure 1C). The trocar placement was adjusted in order to facilitate surgical procedures (Figure 1D). The ileocolic vessels were carefully dissected, then the colon was dissected and reconstructed uneventfully (Figure 1E).

Pathology of resected tumor tissue revealed it to be moderately differentiated adenocarcinoma in stage pT3N0M0 involving invasion of the serosa (Figure 1F). All 22 resected regional lymph nodes were negative.

OUTCOME AND FOLLOW-UP

The entire surgery lasted 178 min, during which total blood loss was 50 mL. After surgery, the patient received six courses of chemotherapy with oxaliplatin and capecitabine, which proceeded uneventfully. At 12-mo follow-up, the patient reported being in good condition, and no symptoms or recurrence were noted.

DISCUSSION

SIT may arise from inherited or spontaneous genetic mutations that affect embryonic development[4]. Organ function is normal in most patients with SIT, and there are no obvious clinical symptoms, so most are diagnosed with the condition on the basis of X-ray imaging, ultrasonography, magnetic resonance imaging, or CT as in the present case. SIT can lead to misdiagnosis of colon cancer because the cancer manifests as the mirror opposite of the typical manifestations of obstruction, constipation, and diarrhea in the case of left colon cancer, or of anemia, weight loss, and fatigue in the case of right colon cancer.

Gastroscopy, colonoscopy, and CT are recommended to avoid misdiagnosis of cancer patients with SIT. As reported for other SIT patients[5], colonoscopy was successful in our patient, who was in the right decubitus position.

The success of treatment in the present case was due to the clinical team's experience and a clear understanding of the patient's anatomy, leading the team to adjust their normal positions for surgery. The team also remained flexible during the procedure in order to adapt to last-minute discoveries of vascular anomalies. Both CT angiography and CT colonography are useful for investigating anatomy and planning laparoscopic procedures[3,6,7]. Laparoscopic surgery, which is increasingly applied to a broad range of patients[8], can be a good option for SIT patients, following appropriate planning based on careful imaging[6,9-12]. While laparoscopic procedures on SIT patients can be more challenging for right-handed surgeons than for left-handed ones[13], adjusting the surgeon's position can help compensate for this[6].

Several adjustments to the laparoscopic procedures were made to compensate for our patient's SIT. The position of the surgical team was reversed from normal, and the trocar positions were correspondingly different, similar to those used to treat colorectal cancer on the left side. The surgeon in our case was right-handed, so he ligated the ileocolic vessels and mobilized the ascending colon using the right hand through a 12-mm trocar in the right lower quadrant. In this way, the surgeon compensated for the normal requirement to use the left hand during laparoscopic right hemicolectomy. In fact, the surgeon and his associates were able to complete the procedures smoothly despite the limited operating space due to the patient's small stature.

Our case report highlights that with careful preoperative imaging and planning, the surgical team can adjust their positions around the patient and the placement of trocars accordingly, allowing a safe and effective procedure. In this way, SIT patients with cancer can benefit from the minimal invasiveness of laparoscopic surgery like patients with normal anatomy.

CONCLUSION

Our case describes the successful laparoscopic hemicolectomy and radical lymphadenectomy of a SIT patient with ascending colon cancer. It highlights the importance of careful imaging assessment and preoperative planning, with the corresponding optimization of the surgical team's positioning around the patient. Laparoscopic surgery of SIT patients can be challenging but it remains a safe and effective minimally invasive option if appropriate steps are taken.

FOOTNOTES

Author contributions: Hu J, Wu K, and Li Q treated the patient, reviewed the literature, and contributed to manuscript drafting; All authors approved the final version.

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ORCID number: Ji-Long Hu 0000-0003-4199-0779; Qi-Yun Li 0000-0001-9436-1154.

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CASE REPORT

Mucinous adenocarcinoma arising from a tailgut cyst: A case report

Petra Malliou, Antonia Syrnioti, Triantafyllia Koletsa, Eleni Karlafti, Anestis Karakatsanis, Georgia Raptou, Stylianos Apostolidis, Antonios Michalopoulos, Daniel Paramythiotis

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Petra Malliou, Anestis Karakatsanis, Stylianos Apostolidis, Antonios Michalopoulos, Daniel Paramythiotis, The First Propaedeutic Surgery Department, AHEPA University General Hospital of Thessaloniki, Thessaloniki 54636, Greece

Antonia Syrnioti, Triantafyllia Koletsa, Georgia Raptou, Department of Pathology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54636, Greece

Eleni Karlafti, Department of Emergency, AHEPA University Hospital, Thessaloniki 54636, Greece

Corresponding author: Petra Malliou, MD, Doctor, The First Propaedeutic Surgery Department, AHEPA University General Hospital of Thessaloniki, Stilponos Kyriakidi 1, Thessaloniki 54636, Greece. malliou_petra@yahoo.gr

Abstract

BACKGROUND

Retrorectal hamartomas or tailgut cysts (TCs) are rare. In most cases, they are asymptomatic and benign; however, rarely, they undergo malignant transformation, mainly in the form of adenocarcinoma.

CASE SUMMARY

A 55-year-old woman presented to our hospital with lower back pain. On magnetic resonance imaging, a large pelvic mass was found, which was located on the right of the ischiorectal fossa, extending to the minor pelvis. The patient underwent extensive surgical resection of the lesion through the right buttock. Histological examination confirmed the diagnosis of a retrorectal mucinous adenocarcinoma originating from a TC. Surgical resection of the tumour was complete, and the patient recovered without complications. The pilonidal sinus was then excised. One year later, semi-annual positron emission tomography-computed tomography and magnetic resonance imaging scans did not reveal any evidence of local recurrence or metastatic disease.

CONCLUSION

Preoperative recognition, histological diagnosis, and treatment of TCs pose significant challenges. In addition, the possibility of developing invasive mucinous adenocarcinoma, although rare, should be considered.

Key Words: Retrorectal tumour; Mucinous adenocarcinoma; Tailgut cyst; Mucosal tumour; Pilonidal cyst; Case report

Core Tip: Retrorectal hamartomas or tailgut cysts are extremely rare. In certain cases, they undergo malignant transformation, predominantly in the form of adenocarcinomas. Mucinous adenocarcinomas are rare forms of carcinoma arising from tailgut cysts, with only 18 cases reported in the literature from 1988 to 2021. Furthermore, to our knowledge, coexistence of a pilonidal tract and mucinous adenocarcinoma is extremely rare; this being the second reported case in the literature. We present the case of a 55-year-old woman with a large pelvic mass on the right of the ischiorectal fossa and a pilonidal cyst. Surgical resection of the tumour and cyst was completed and the patient recovered well.

Citation: Malliou P, Syrnioti A, Koletsa T, Karlafti E, Karakatsanis A, Raptou G, Apostolidis S, Michalopoulos A, Paramythiotis D. Mucinous adenocarcinoma arising from a tailgut cyst: A case report. *World J Clin Oncol* 2022; 13(10): 853-860
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INTRODUCTION

Retrorectal hamartomas or tailgut cysts (TCs) are very rare, with an incidence rate of approximately 1/40000[1]. TCs are believed to be embryologically derived from a remnant of the posterior intestine[2]. Alternative terminologies such as 'cyst of postanal intestine', 'retrorectal cystic hamartoma', 'tailgut vestiges', 'myoepithelial hamartoma of the rectum', and 'rectal cyst' have been used in the literature to describe these lesions[3]. These tumours are thin-walled, multi-layered structures lined by various glandular or transitional epithelia[4].

TCs occur more often in middle-aged women, whereas they are rare in children[5]. Forty percent of TCs occurring in children and new-borns are teratomas. Moreover, 10% of teratomas coexist with developmental disorders of the midline such as encephalocele[2,5]. In this age group, tumours could be benign, whereas malignant tumours are more common in older children[5]. Most TCs in adults are benign; however, malignant transformation has been reported in the literature, particularly in symptomatic cases[6].

TCs are mostly asymptomatic prior to clinical recognition. Symptoms are often associated either with a growing tumour mass and may include lower abdominal pain, rectal tenesmus and constipation or with infectious complications, even including fistulas[5].

Considering the rarity of this developmental anomaly, we present an interesting case of invasive mucinous adenocarcinoma originating from a TC associated with a pilonidal cyst that was managed in the Emergency Surgical Department of University Hospital.

CASE PRESENTATION

Chief complaints

A 55-year-old woman presented to the Emergency Surgical Department of the University Hospital with lower back pain.

History of present illness

The patient complained of pain in the previous 6 mo.

History of past illness

The patient had a history of ductal breast cancer, which was diagnosed 10 years ago and treated with lobectomy and adjuvant therapy. She also underwent hip arthroplasty 1.5 years ago and was under no medication and in good physical condition with good nutrition, according to her age.

Personal and family history

No pathological conditions were found.

Physical examination

The arterial blood pressure was 130/85 mmHg, temperature was 36.7 °C, and oxygen saturation level was 98%. Physical examination revealed a large, palpable gluteal mass.

Laboratory examinations

On her admission to our department, the routine laboratory test and carcinoembryonic antigen (CEA) results were within normal limits.

Imaging examinations

Magnetic resonance imaging (MRI) of the pelvis (Figure 1) revealed a pelvic mass that was located to the right of the rectus fossa, in contact with the uterus and rectum, which seemed to apply pressure on the adjacent structures and possibly on the sciatic nerve, and extended to the minor pelvis. The dimensions of the mass were 11 cm × 10 cm and 6 cm × 16.2 cm, and neural derivation was initially suspected.

Chest X-ray and computed tomography (CT) scans showed no abnormal findings. The abdominal CT scan revealed a large multifaceted formation located on the right side of the rectum, between the urinary bladder and coccyx and up to the fatty tissue of the buttocks, with enriched diaphragms. The appendix and ovaries were normal.

FINAL DIAGNOSIS

The CT findings raised the suspicion of a TC or cystic teratoma (Figure 1B and D).

TREATMENT

The patient underwent extensive surgical resection of the lesion through the right buttock (Figure 2).

An incision approximately 20 cm long was made, and sharp dissection was performed to carry the incision down directly into the midline until the presacral fascia was found. The medial gluteal fibres were then divided bilaterally to expose the attached mass which pushed the rectum and uterus away without infiltrating these structures. During dissection, it was crucial to avoid injury to the rectal wall, vagina, sciatic nerve, and urethra. This was facilitated by the use of rectoscopy during surgery, along with preoperative bowel preparation. A Foley catheter was used as a guide for the urethra. The lesion was resected, and the gluteal muscles were returned to the midline. The remaining layers of the incision were reapproximated and closed. Simultaneously, a pilonidal sinus was found and removed.

Preoperative planning concerned proper positioning of the patient. Lithotomy positioning was preferred because of the direct approach to the mass, rectum, and vagina and the potential need for a combined transabdominal incision.

Concerns were also raised about the contingent need for other specialists such as gynaecologists and urologists if the lesion was found to infiltrate the vagina or urinary tract. On that ground, these specialists stood by during the surgery.

The recuperation of the patient was uneventful, and she was discharged from the hospital on the seventh post-operative day because of delayed bowel movement.

Wound care was performed as usual, and the skin sutures were removed 2 wk later, without any complications.

Both the mass and the pilonidal sinus were sent separately for histopathological examination. Upon grossing, a large mass was found to be cystic and filled with mucohaemorrhagic material. In a peripheral location, two smaller cystic spaces were identified, which were also filled with mucus and an amorphous material. Microscopic examination confirmed the presence of a cystic mass comprising thick fibrous bands that divided it into three cystic spaces, the largest of which corresponded to mucinous adenocarcinoma (Figure 3A). The neoplastic cells were medium to large in size, with roundish or irregular hyperchromatic atypical nuclei surrounded by an eosinophilic or pale cytoplasm (Figure 3B). Few "signet ring" cells were also observed. Tumour cells were arranged in glandular or cribriform structures, trabeculae, variably sized solid groups, and within large "lakes" of mucin. Rarely, isolated neoplastic cells floating in the mucin were identified. A large number of mitoses was observed. Regions of tumour necrosis and calcification were also observed. On immunohistochemical evaluation, the neoplastic cells exhibited the following immunophenotypes: CK20+ (Figure 3C), CDX2+, CK7+, GATA3-, ER-, PR-, and calretinin-.

Most current and similar published cases reported positivity, even partially, of TC or adenocarcinoma arising on the cyst to CK7 antibody.

Embryologically, the rectum is the last part of the tailgut, and both normal rectal mucosa and rectal adenocarcinomas present CK7 positivity in almost one-fifth of cases[7].

HER2 immunostaining showed faint, segmental, and membranous positivity in a small number of tumour cells (HER2 1+). The two other cystic spaces were lined with keratinising squamous or pseudostratified ciliated columnar or metaplastic squamous epithelia (Figure 3E). The mass was circumscribed with bundles of connective tissue at the periphery, and the surgical margins were tumour-free. Based on these findings, the diagnosis of an invasive mucinous adenocarcinoma, possibly on the grounds of the presence of a posterior rectal cyst sinus (TC), was established.

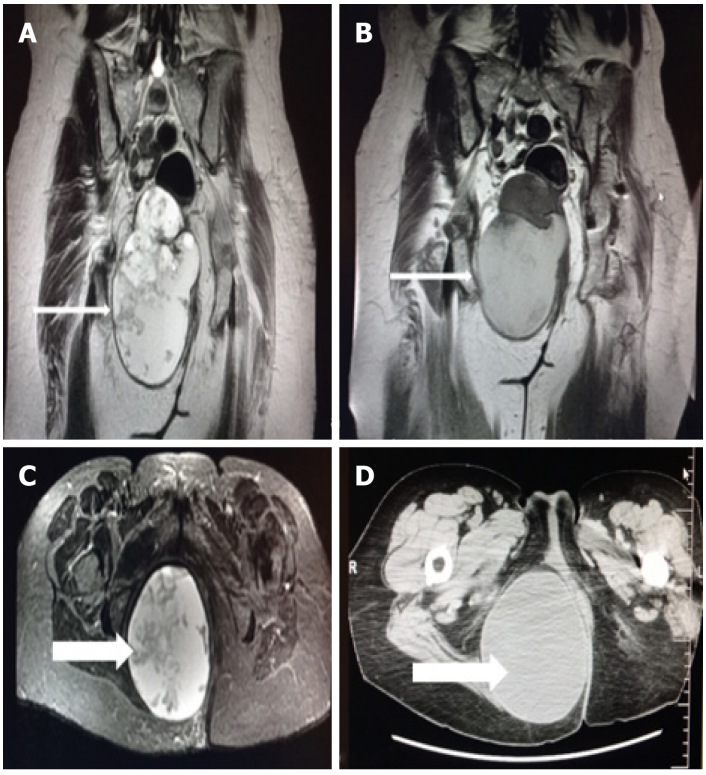

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Figure 1 Magnetic resonance imaging. A and C: Coronal and axial planes of the mass with smooth borders, lobed on the upper side with a beak sign. Cystic and solid elements, septa, and haemorrhagic and protein elements. It absorbs paramagnetic substance; B and D: Computed tomography scan - Coronal and axial planes of the mass. Differential diagnosis of tail gut cyst or cystic teratoma (arrows).

Gross examination of the sacrococcygeal pilonidal cyst revealed an elliptical skin-excision specimen. On the skin's surface, a hole measuring 0.1 cm in the greatest diameter was identified, which upon parallel sectioning was found to be continuous with a sinus tract that terminated in a brownish grey-coloured area. Microscopic examination revealed that the sinus tract was lined mainly by stratified squamous epithelium and partially by granulation tissue. Hair shafts were also focally identified around the sinus tract (Figure 3F). The latter extended to the deep tissue resection margin. No communication between the sinus tract and TC was found, albeit multiple sections.

OUTCOME AND FOLLOW-UP

The recuperation of the patient was uneventful, and she was discharged from the hospital on seventh post-operative day. According to the histopathology report, the oncology council recommended 22 sessions of radiotherapy while the patient completed the treatment. After 1 year, follow-up of the patient with semi-annual positron emission tomography-CT and MRI, did not show any evidence of local or metastatic recurrent disease.

DISCUSSION

Herein, we present an interesting case of mucinous adenocarcinoma arising on a TC. Mucinous adenocarcinoma is a rare type of carcinoma occurring on TCs, with only 18 cases reported in the English literature from 1988 to 2021. Furthermore, to our knowledge, coexistence of a pilonidal tract is extremely rare, this being the second reported case in the literature. A connection between the pilonidal sinus and TC was not established using imaging, intraoperatively, or on pathological examination.

Primary retrorectal tumours include congenital (55%-65% of all tumours in this region), neurogenic (10%-12%), osteogenic (5%-11%), inflammatory (5%), and other tumour types (5%-11%). According to their embryonic origin, cysts are classified into epidermal, dermal, neural, teratoma, enteric, rectal duplication, mucous-secreting, enterogenous, simplex, gland anal, rectal, hamartoma, and TCs[5,8]. TCs are found in the presacral space and are typically thin-walled cysts that may be single or multiloculated, branched, and may contain green opalescent colloid fluid[2].

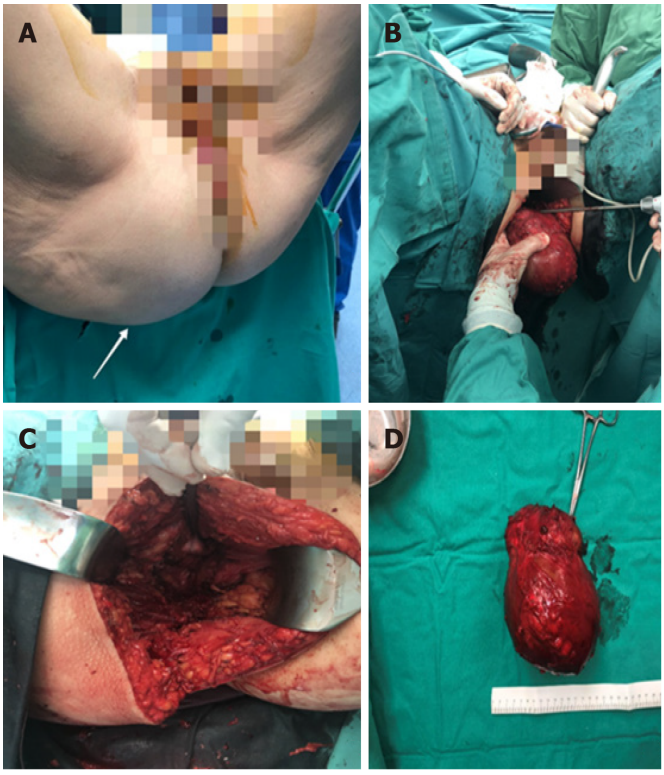

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Figure 2 Patient underwent extensive surgical resection of the lesion through the right buttock. A: Preoperative view of the mass (arrow); B and C: Extensive surgical resection of the lesion through the right buttock; D: Removed mass.

In 1885, Middeldorpf *et al*[9] reported the first case of a cystic mass in the retrorectal space in a 1-year-old girl, which was most likely a rectal duplication cyst. Hjermstad and Helwig reported the largest case series of TCs, which included 53 patients with an age range of 4 days to 73 years and average age of 36 years[10]. Based on the current literature, TCs may be asymptomatic or present with non-specific symptoms owing to the large size of the pelvic mass[2,5,8]. They can also lead to several complications including a neurogenic bladder, haemorrhage, faecal incontinence, faecal fistula, intestinal obstruction, infections, or malignant transformation as observed in the present case[11,12].

The diagnosis of TCs may be delayed because of the absence of typical symptoms[6]. Often, TCs are discovered incidentally through imaging tests during the investigation of other entities[5]. A CT scan typically shows a well-defined homogeneous retrorectal mass of water to soft-tissue density)[12]. A more solid appearance could also be described because of the keratinous or inflammatory debris within a cyst[3,5]. Higher-resolution scans may identify most TCs as multiloculated cysts[3]. On T1-weighted images, MRI scans reveal a hypointense lesion, whereas lesions are homogeneously hyperintense on T2-weighted images. However, MRI is not the gold standard for discriminating benign and malignant lesions[3].

A definitive diagnosis is established by histopathological examination[14]. TCs are congenital lesions that develop from the residual posterior remnant of the intestine, which retains its structure and architecture regarding the mature ectodermal, endodermal, and mesodermal tissue elements. The lining epithelia may vary, including squamous, ciliated columnar, pseudostratified, columnar, transitional, goblet columnar, and cuboidal epithelia[8,14]. Additionally, it is characterised by the presence of a smooth muscle layer and connective tissue, which may be disarrayed and do not encompass the nerve plexus or differentiated neuronal cells[14]. The immunophenotype of the mucinous adenocarcinoma in this case was that described in similar previously reported cases and is characterised by CK7, CK20, and CDX-2 positivity[15].

Most TCs are benign; nevertheless, rare cases of malignancies have been reported, including the present case[6]. Apart from adenocarcinomas, neuroendocrine, endometrioid, adenosquamous, and squamous cell carcinomas and sarcomas have also been described[13]. Although the option of needle biopsy seems attractive, it is not broadly recommended because of the possibility of false-negative results and the risk of tumour seeding[16].

Once a presacral tumour is diagnosed, the treatment of choice is extensive surgical removal due to the possibility of malignant transformation. The surgical approach depends on tumour location. Complete excision could be achieved with a posterior approach for tumours extending below the sacral spinal nerve 4 (S4), which is effective at a rate of 95%. For tumours that extend above S4, the abdominal or

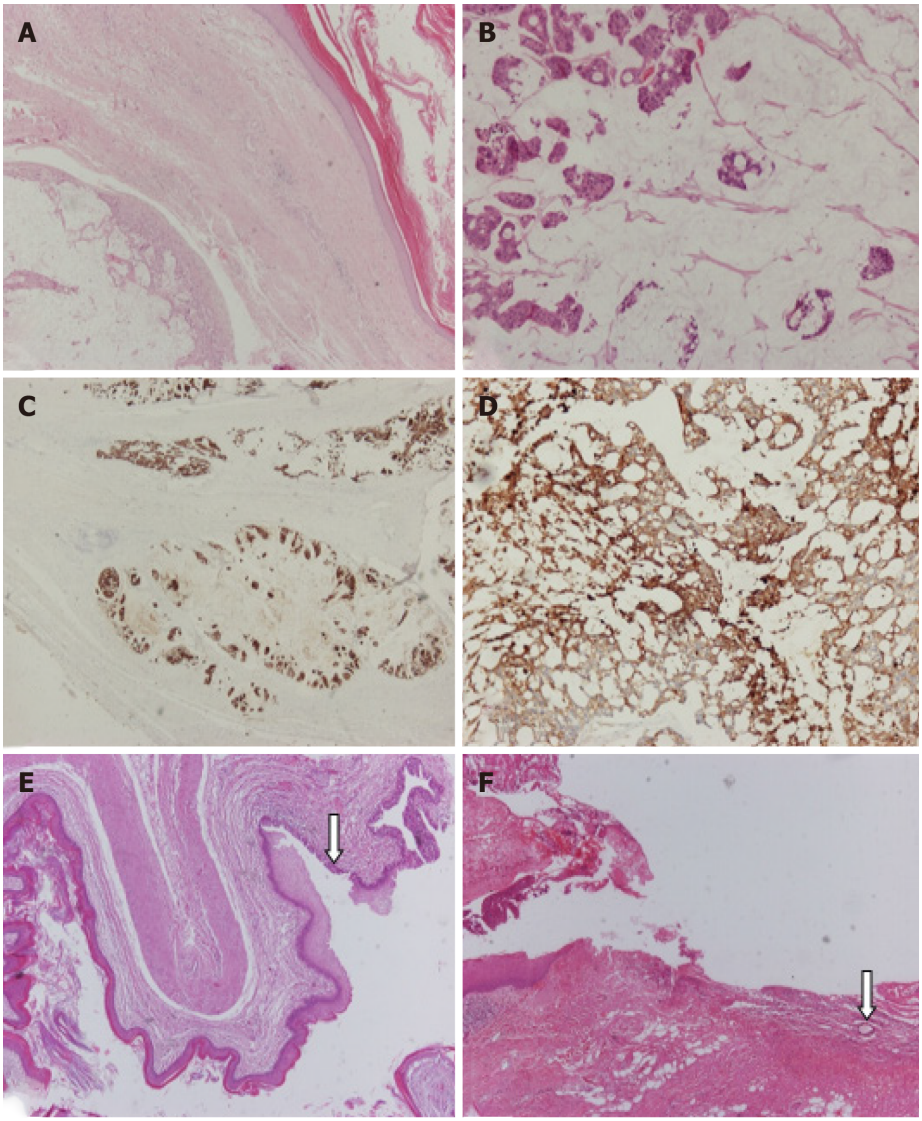

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Figure 3 Microscopic examination confirmed the presence of a cystic mass that comprised thick fibrous bands that divided it into three cystic spaces, the largest of which corresponded to mucinous adenocarcinoma. A: Fibrous tissue separates two cystic spaces, one benign lined by keratinized squamous cell epithelium and the other corresponding to mucinous adenocarcinoma; B-D: Higher magnification of mucinous adenocarcinoma that is immunohistochemically positive (IHC-positive) for antibodies CK20 and CK7; E and F: A smaller cystic space with fibromuscular wall lined by keratinized squamous epithelium and partially by pseudostratified ciliated columnar epithelium (arrow) is observed. Section of the pilonidal cyst (arrow: Hair shaft). [A: Hematoxylin-eosin staining (HE), magnification × 40; B: HE × 100; C: IHC × 20; D: IHC × 100; E and F: HE × 40].

abdominal-perineal approach is suggested[16]. When TC is malignant, many studies suggest that treatment should include adjuvant radiation therapy alone or in combination with chemotherapy[6,17-19]. Martins *et al*[20] suggest both radiation therapy and chemotherapy. Liang *et al*[6] argue that the mainstream treatment method for TCs with adenocarcinoma is surgical resection followed by chemotherapy. Baverez *et al*[21] suggest that neoadjuvant chemoradiotherapy, similar to locally advanced rectal adenocarcinoma, decreases the risk of post-operative recurrence. Supplemental treatment can be administered as it is believed to contribute to the prevention of tumour recurrence. However, there is no clear evidence that it would improve the prognosis as there is no general consensus on treatment standards for TC-associated adenocarcinoma owing to its very low incidence rate[22]. Factors that determine prognosis include the stage during diagnosis, tumour histology and grade, and completeness of resection[3]. Compared with neuroendocrine tumours, adenocarcinomas arising from TCs have a poorer prognosis and carry a risk of local recurrence and metastasis[8]. Follow-up of the patient is also recommended, including monitoring for signs of recurrence with periodic positron emission tomography-CT and MRI scans in addition to serum CEA levels that serve as an indicator of the tumour's response to treatment and development of recurrence[19]. According to Chhabra *et al*[3], once a TC malignancy has been diagnosed and is associated with an elevated CEA level, CEA levels may be used as a simple measure to assess the tumour's response to treatment or development of recurrence. In our case, the patient did not have elevated CEA levels; therefore, this

measure was not monitored after surgery. Di Nuzzo *et al*[23] reported the use of combined MRI and endoscopy for post-operative follow-up.

CONCLUSION

TCs are rare clinical and pathological entities. The novelties of this case include the presence of a mucinous adenocarcinoma arising from a TC and that it is the second reported case of an association between TC and pilonidal cyst. Generally, TCs constitute both diagnostic and treatment challenges. Imaging tests may be helpful; however, a definitive diagnosis is usually established after complete surgical excision and histopathological examination. Guidelines for appropriate therapeutic management are required for TC-associated adenocarcinomas, although timely and extensive surgical resection along with adjuvant radiation therapy with or without chemotherapy have been used with good outcomes.

FOOTNOTES

Author contributions: Malliou P, Apostolidis S, Michalopoulos A, and Paramythiotis D were the patient's surgeons, and reviewed the literature and contributed to manuscript drafting; Karlafti E reviewed the literature and contributed to manuscript drafting; Syrnioti A, Koletsa, and Raptou G performed the microscopic examination and contributed to manuscript drafting; all authors were responsible for the manuscript's revision for important intellectual content and issued final approval for this version to be submitted.

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ORCID number: Petra Malliou 0000-0003-4567-1425; Antonia Syrnioti 0000-0002-9232-6715; Triantafyllia Koletsa 0000-0002-4435-3532; Eleni Karlafti 0000-0001-7094-0338; Anestis Karakatsanis 0000-0002-5509-8645; Georgia Raptou 0000-0002-9499-0740; Stylianos Apostolidis 0000-0002-7733-8988; Antonios Michalopoulos 0000-0002-0580-2585; Daniel Paramythiotis 0000-0002-5844-1867.

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LETTER TO THE EDITOR

Diagnostic biopsy of cutaneous melanoma, sentinel lymph node biopsy and indications for lymphadenectomy

Efstathios T Pavlidis, Theodoros E Pavlidis

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Efstathios T Pavlidis, Theodoros E Pavlidis, 2nd Prodedeutic Department of Surgery, Hippocration Hospital, Aristotle University of Thessaloniki, School of Medicine, Thessaloniki 54642, Greece

Corresponding author: Theodoros E Pavlidis, Doctor, PhD, Chief Doctor, Director, Full Professor, Surgeon, 2nd Propedeutic Department of Surgery, Hippocration Hospital, Aristotle University of Thessaloniki, School of Medicine, 49 Konstantinoupoleos, Thessaloniki 54642, Greece. pavlidth@auth.gr

Abstract

The incidence of cutaneous melanoma appears to be increasing worldwide and this is attributed to solar radiation exposure. Early diagnosis is a challenging task. Any clinically suspected lesion must be assessed by complete diagnostic excision biopsy (margins 1-2 mm); however, there are other biopsy techniques that are less commonly used. Melanomas are characterized by Breslow thickness as thin (< 1 mm), intermediate (1-4 mm) and thick (> 4 mm). This thickness determines their biological behavior, therapy, prognosis and survival. If the biopsy is positive, a wide local excision (margins 1-2 cm) is finally performed. However, metastasis to regional lymph nodes is the most accurate prognostic determinant. Therefore, sentinel lymph node biopsy (SLNB) for diagnosed melanoma plays a pivotal role in the management strategy. Complete lymph node clearance has undoubted advantages and is recommended in all cases of positive SLN biopsy. A PET-CT (positron emission tomography-computed tomography) scan is necessary for staging and follow-up after treatment. Novel targeted therapies and immunotherapies have shown improved outcomes in advanced cases.

Key Words: Surgical oncology; Malignant melanoma; Skin cancer; Cutaneous melanoma; Sentinel lymph node biopsy; Complete lymph node dissection

Core Tip: The value of excision biopsy for the initial diagnosis of melanoma in every suspected cutaneous lesion is important. In positive cases, the roles of sentinel node biopsy and subsequent complete lymph node dissection, along with adequate margin excision of the primary lesion site are evaluated to improve the prognosis. Novel biological agents and molecular factors will open new horizons for future management policy.

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TO THE EDITOR

We read with great interest the recent paper by Koumaki *et al*[1] and we would like to congratulate the authors for their excellent trial on melanoma and atypical mole syndrome, which impressed us. This study is meticulous and arduous work that describes, for the first time, many details about the demographic and clinical characteristics of 121 patients. We absolutely agree with the authors that photoprotection education is required to prevent skin cancer development. Taking this opportunity, this paper presents some thoughts and observations from a surgical point of view on the latest developments in biopsy for the diagnosis of suspected primary lesions and the role of sentinel lymph node biopsy and the subsequent prophylactic or therapeutic lymphadenectomy.

The incidence of cutaneous melanoma has steadily increased over the past years. It has been estimated that this increase in the United States has reached up to 3% per year. However, most cases with early-stage disease (I and II) usually have a favorable prognosis[2]. The eighth edition of the American Joint Committee on Cancer (AJCC) staging system is the most widely used standard for the staging and classification of melanoma[2-4]. Cutaneous lesions with macroscopic features that raise the suspicion of melanoma can be used as an alternative for changes in color, outline, bleeding, rapid increase in size, nodular growth and ulceration.

Biopsy and histological examination will initially confirm the diagnosis and determine the stage of the disease, the extent of surgical resection and the management of the sentinel lymph node (SLN). The types of biopsy might be excisional, incisional, shave biopsy (superficial or deep scallop) or punch biopsies[5]. The most preferred excisional biopsy is reliable for defining the T stage in TNM staging. It resects the lesion beyond its margins to an extent of 1-3 mm according to NCCN (National Comprehensive Cancer Network) guidelines or 1-2 mm according to AJCC guidelines. This limit is crucial, given that avoiding lymphatic destruction ensures feasible detection of sentinel lymph nodes[6-8]. The other types of biopsy can potentially lead to misdiagnosis and inaccurate staging. The incisional biopsy removes a small part of the lesion for cosmetic reasons. It is indicated for large lesions of more than 2 cm in diameter that are mainly located on the face.

In a positive biopsy of the initial evaluation of the suspected skin lesion, sentinel lymph node biopsy (SLNB) follows. This is because the involvement of regional lymph nodes is considered an important prognostic factor for survival. SLNB is indicated by the current data and 15% to 20% of patients have regional node metastasis[9]. In addition, the presence or absence of nodal micrometastases is the most important prognostic factor in early-stage melanoma, particularly in intermediate thickness melanoma [10]. Thus, SLNB is considered the standard of care and has high diagnostic value. It is a minimally invasive procedure with a low complication rate[9,11]. The detection of sentinel lymph nodes is performed either 24 h preoperatively by Tc-99 administration and the use of a gamma probe or intraoperatively by methylene blue administration. Moreover, their combination can be used. A positive SLNB results in a complete lymph node dissection (CLND). This process provides adequate regional disease control and has an indication for adjuvant chemotherapy[11]. A negative SLNB has a minimal likelihood of metastasis. The final CLND biopsy ensures accurate staging and prognosis. Furthermore, CT (computed tomography) and PET (positron emission tomography) scans contribute to staging by defining the M (distant metastasis)[12]. However, the prognosis is influenced by disease progression [13].

The incidence of nodal metastases clearly depends on the thickness of the primary melanoma. Lesions more than 1 mm in thickness are more likely to have metastases in the sentinel node, and lesions between 1 mm and 2 mm only have metastases in the sentinel node. However, lesions more than 2 mm in thickness have metastases in additional lymph nodes and distant metastases[9]. According to the excision biopsy, when the depth of invasion (Breslow thickness) is less than 1 mm, or from others, less than 0.75 mm, then the positive SLNB will be less than 5%. An exception to this rule is the mitotic index (≥ 1 mitoses/mm^2), especially in cases with a Breslow thickness between 0.75 mm and 0.99 mm. The rate of false-negative SLNB reached 1.5% to 4.1%[11].

In the case of early-stage (pT1b, pT2a) melanoma with sentinel node micrometastases, when the deposits are less than 0.3 mm in maximum diameter, no adjuvant treatment will be necessary. Otherwise, when they are equal to or more than 0.3 mm, adjuvant systemic therapy could be beneficial [14].

The final differential diagnosis between melanoma and dysplastic nevus is made by histopathology. A molecular assay would be of value for early-stage lesions, but thus far, there is no such test[15].

PET-CT has the greatest diagnostic accuracy both for staging and follow-up. However, for the latter, the currently used immunotherapy can create various organ side effects; thus, radiologists should be aware of this[12].

The dataset of dermoscopic images is a useful tool for the early detection of skin cancer[16]. Ultrasound-guided fine needle aspiration cytology (FNAC) and core needle biopsy (CNB) can be used for the detection of subcutaneous or lymph node metastases[17]. Melanomas can be diagnosed in early stages (50%). They are more commonly located on the extremities in women and on the back in men. On the lower limbs, they can be more invasive and are without sex differences[18].

Current recommendations indicate complete excision biopsy to avoid residual disease in the complementary resection after partial excision biopsy. However, this treatment does not influence survival[19]. A recent large, retrospective study found that SLNB was more likely to be indicated for a Breslow depth >1 mm or mitotic rate ≥ 1/mm^2. It was less likely to be indicated in patients of older age (> 75-years-old) and those without an extremity location[20].

The prognostic value of complete lymph node dissection (CLND) after positive SNDB *vs* observation and therapeutic lymph node dissection (TLND) has been evaluated[21], despite the initial aspect of a nonsignificant difference between them[22]. A large, retrospective study from Italy including 2086 patients after CLND for lymph node involvement found improved survival. The 3-year survival was 79%, the 5-year survival was 70%, and the 10-year survival was 54%[23]. The preliminary results indicated that the clinicopathologic information (thickness, mitoses, age, and Breslow thickness 2 mm) and gene expression profiling (CP-GEP) were independent predictive factors for lymphatic metastases [24]. Similarly, 31-gene expression profiling (i31-GEP-SLNB) has become commercially available[25]. A vitamin D level < 9.25 ng/mL is another negative independent prognostic factor for survival. It is associated with ulceration formation in melanoma[26].

A stage-based follow-up scheme has recently been proposed by the European consensus for melanoma[27].

Tilmanocept, a CD206 receptor-targeted novel radiotracer, has recently been introduced for lymphoscintigraphy to assess nodal mapping[28].

Adequate margin excision (1-2 cm, depending on the invasion depth) has been the standard therapy, despite the de-escalation of its extent, together with SLNB[10,29]. Targeted therapy and immunotherapy have further improved the prognosis[30].

In conclusion, SLNB is indicated for melanoma stage IB (T1b ≤ 1 mm, ulceration, and mitoses >1 mm^2) and stage II. In positive cases, CLND is required instead of TLND. SLNB offers staging accuracy and has indications for adjuvant therapy. Thus, it can improve prognosis and survival. New diagnostic modalities and immunotherapies will contribute further to improved outcomes.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Efstathios T Pavlidis 0000-0002-7282-8101; Theodoros E Pavlidis 0000-0002-8141-1412.

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