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Original Article

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Small Intestinal Tumours: Histopathological Findings in Enterectomy Specimens. A Ten-Year Experience from a Tertiary Surgical Center in Greece and Review of the Literature

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ABSTRACT

Introduction: Small intestine tumours represent ~3% of gastrointestinal neoplasms and 0.6% of all cancers, despite the extensive intestinal surface. Diagnosis is often delayed (up to two years for malignant tumours) due to non-specific symptoms, necessitating heightened clinical awareness and improved diagnostics.

Purpose: This study investigated the prevalence, characteristics, and clinical presentation of small intestine tumours in patients undergoing enterectomy.

Methodology: A retrospective study was conducted at the Surgical Department of a tertiary center in Athens, including patients who underwent primarily emergency enterectomy during the period 2014–2024. All relevant medical records and pathology reports were evaluated, and statistical analysis was performed using IBM SPSS Statistics Version 26. A literature review (2000–2025) was also conducted.

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Results: Among the participants (N=62), 37.1% underwent enterectomy for obstruction and 29% for incidental tumor detection. The mean resection length and mean tumour size were 30.1 and 5.7 cm, respectively. Malignancy was detected in 79% of cases, with lymph node metastases in 25% and pT4 staging in 42.9%. Histological types included gastrointestinal stromal tumours (21%), metastatic tumours (17.7%), neuroendocrine tumours (14.5%), lymphomas (9.7%), and adenocarcinomas (9.7%). R0 resection was achieved in 88.1% of cases. Procedures were mostly emergency-based in patients with advanced disease at diagnosis.

Conclusions: Small intestine tumours are rare but clinically significant, often presenting late. Our findings align with the current literature, confirming the predominance of malignancy and emergency presentations. Geographic and histological variations may reflect genetic and environmental influences. Early diagnosis and tailored surgical management could improve outcomes.

Key Words: *Small intestine; neoplasm; tumour; enterectomy; histopathology*

INTRODUCTION

Small bowel neoplasms are thought to account for as few as 4 to 13 hospital admissions per 100,000 patients [1]. They represent approximately 0.6% of all new cancer cases and 3% of all gastrointestinal tumours in the United States [2], with a rising incidence, particularly for neuroendocrine tumours. Although the small intestine comprises over 90% of the gastrointestinal surface [3], diagnosing small bowel tumours (SBTs) is challenging mainly due to their non-specific symptoms.

While most patients - especially in cases of malignancy- are asymptomatic, SBTs often present with intermittent abdominal pain, nausea, vomiting, anaemia, and weight loss [4]. Complications may include gastrointestinal bleeding, bowel obstruction, perforation, and jaundice, with larger tumours more likely to cause obstructive symptoms. Due to the small bowel's ability to compensate, even advanced lesions may present subtly, as incomplete ileus involving two-thirds of the lumen [5].

Histological types also vary according to tumour location: adenocarcinomas are more frequently found in the duodenum and jejunum, whereas neuroendocrine tumours are predominantly located in the ileum [3].

Regarding the molecular pathogenesis of SBTs, data remain scarce. However, KRAS mutations—commonly observed in colorectal cancer—are frequently detected in small bowel adenocarcinomas [6,7]. Allelic losses involving tumour suppressor genes have been reported, particularly at 5q (APC gene), 17q (p53), and 18q (DCC and SMAD4) chromosomal sites [8]. Approximately 15% of small bowel adenocarcinomas are also microsatellite instability-high (MSI-H) cancers, typically due to inactivation of DNA mismatch repair genes [9]. MSI-H status is often seen in coeliac disease-associated tumours, resulting from abnormal methylation of CpG (cytosine-guanine) islands [10]. Furthermore, gene expression studies suggest that common mediators of oncogenic pathways such as the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) correlate with a significant proportion of small intestinal tumours [11].

Although literature reports regarding small bowel neoplasms are expanding, published data on broader, postoperative cohorts from Greece remain limited. The aim of this study was to present a ten-year retrospective case series of patients who underwent enterectomy for small bowel tumours at a tertiary university hospital and to review current literature on their epidemiology, pathology, and clinical behaviour. In addition, the study aimed to evaluate the stage of the tumour at the time of diagnosis.

MATERIALS AND METHODS

Study Design and Setting

This is a single-centre, retrospective, observational study conducted at the Surgical Department of a tertiary university hospital in Athens, Greece. The study covered a ten-year period, from January 2014 to August 2024, and aimed to investigate the prevalence, histopathological characteristics, and clinical features of patients undergoing enterectomy for small bowel tumours. In addition, a systematic review of the literature was conducted following PRISMA guidelines in order to assess our findings.

Inclusion and Exclusion Criteria of the Study

Patients of any gender or age who underwent segmental small bowel resection (enterectomy) for a histologically confirmed primary or metastatic neoplastic lesion of the small intestine during the study period were included. Only complete enterectomies either performed electively or, more commonly, on an emergency basis were included in our analysis.

Patients who underwent small bowel resection combined with resection of another organ for a different primary pathology or patients whose enterectomy did not involve a tumour or tumourous lesion of the small intestine, including operations for ischaemic or inflammatory bowel conditions were excluded from the cohort. The latter included cases such as ischaemic necrosis, Crohn's disease, non-neoplastic perforation, adhesions, mesh erosion, or local extension of extraintestinal malignancies.

Patient Sample and Data Collection

During the study period, a total of 192 enterectomies were performed by twelve different general surgeons at the Surgical Department. Of these, 130 cases were excluded for not meeting the inclusion criteria, resulting in a final sample of 62 patients with histologically confirmed small bowel tumours or tumourous lesions.

A structured review of medical records, operative reports, and pathology files was conducted to extract the following variables:

- Patient demographics (age, gender)
- Clinical presentation and indication for surgery (e.g., obstruction, bleeding, incidental discovery)
- Type and length of bowel resection
- Tumour size (measured macroscopically)
- Histopathological diagnosis and classification
- Resection margin status (R0: negative margins, R1: microscopically positive margins)
- Tumour, Node, Metastasis (TNM) staging and histological grade of differentiation

All histological data were obtained from official pathology reports issued by the hospital's Department of Pathology. Tumours were classified based on the World Health Organization (WHO) criteria, and tumour staging was assigned according to the American Joint Committee on Cancer (AJCC) TNM staging system, where applicable.

However, although pathology reports were generally comprehensive, variability in documentation was observed across cases, particularly in older reports or those prepared during emergency interventions. Missing data were treated accordingly, and all available information was included in the statistical analysis.

Histopathological Classification

Histological classification was performed using standard WHO diagnostic categories for small bowel neoplasms, including adenocarcinomas, neuroendocrine tumours (NETs), gastrointestinal stromal tumours (GISTs), lymphomas, and metastatic lesions from extraintestinal primary tumours. SBTs from all small bowel parts were included along with duodenal, ampullary and periampullary lesions.In addition, when immunohistochemical or molecular testing (e.g., CD117, DOG1 for GISTs; chromogranin, synaptophysin for NETs) was available, these findings were used to support the final diagnosis.

Statistical Analysis

Descriptive statistical analysis was performed using IBM SPSS Statistics software, version 26. Quantitative variables (e.g., age, tumour size, length of resection) were summarised using the mean, standard deviation (SD), range, minimum and maximum values, and categorical variables (e.g., gender, tumour type, stage, resection margin status) were expressed as absolute frequencies and percentages.

Due to the retrospective nature of the study and the relatively small sample size, no inferential statistical tests were performed to compare subgroups or assess predictors. Instead, the statistical analysis focused on descriptive epidemiology and the presentation of trends observed within the cohort.

Due to incomplete data in some pathology reports—particularly regarding tumour grade, TN stage, resected bowel length, mass size, and resection margins—analyses were performed using a complete-case approach. Therefore, missing values were clearly identified and the corresponding cases were excluded from specific calculations where the relevant information was unavailable. Absolute counts and percentages for the data regarding these parameters are detailed in the tables included in the Supplementary Index (Tables S1-S5). In addition, all study findings were compared to the current literature following a systematic review of relevant sources.

Ethics Statement

Ethical approval was obtained from the Ethics Committee of the study hospital and all study procedures were conducted in accordance with the Declaration of Helsinki. The study also adhered to national and institutional standards for biomedical research involving human subjects.

Data were collected anonymously, and recorded using a structured Excel form. Personal data were processed in compliance with the General Data Protection Regulation (GDPR) 2016/679 of the European Union. Access to medical records and pathology reports was restricted to authorised personnel involved in the study, and data was used exclusively for research purposes.

RESULTS

Demographics

The study included 62 patients who underwent enterectomy for small bowel tumours, with a predominance of males (58.1%). Patient ages ranged from 25 to 90 years,

with the majority over 50 years old. The mean age was approximately 63 years (SD ± 16.68), reflecting a predominantly older adult population.

Clinical Presentation and Indications for Surgery

Clinical indications for enterectomy varied. The predominant symptom was obstructive ileus, accounting for 37.1% of cases. Incidental detection of an intra-abdominal mass, either during imaging/operation for other reasons or imaging as follow-up to previously known malignancy, was the second most frequent indication, observed in 29% of patients. Other clinical presentations included small bowel perforation (8.1%), gastrointestinal bleeding presenting as mesenteric haemorrhage or anaemia (4.8%), and abdominal pain (4.8%). Less frequent indications included incidental finding of small bowel lesions within a hernia sac (3.2%) and jaundice due to obstruction of Vater's ampulla (1.6%). A notable proportion (11.3%) underwent surgery for miscellaneous reasons, such as fistula formation or the presence of a tumour adjacent to other intra-abdominal pathology (Table 1).

Tumour Characteristics: Size, Location, and Histopathology

The length of the small bowel resected varied significantly, reflecting differences in surgical indication and intraoperative findings, with a mean resection length of 30.1 cm. Tumour size ranged from 0.4 cm to 18.5 cm, with an average diameter of 5.7 cm. However, due to incomplete data in several histopathology reports regarding tumour size or the length of the resected intestine, these measurements should be interpreted cautiously.

TABLE 1. Presenting clinical condition (Data from our institution).

Clinical Condition - Indication for surgery		
	Frequency	**Percent**
Bowel Obstruction	23	37,1
Abdominal Mass	18	29,0
Other (incidental finding, fistula, adhesions)	7	11,3
Bowel Perforation	5	8,1
Hemorrhage	3	4,8
Abdominal Pain	3	4,8
Abdominal Hernia	2	3,2
Jaundice	1	1,6
Total	62	100,0

The location of the excised tumour in patients who underwent enterectomy could not be evaluated also due to several incomplete histopathology reports, which in 61.3% of cases (38/62) labelled the tumour origin as "undefined part of the small bowel". Among the adequately documented SBT cases, 8% (5/62) were located in the duodenum, 9.7% (6/62) in the ileum and 11.3% (7/62) in the distal jejunum. Finally, six of the excised tumours corresponded to obtained from Whipple procedures.

Histopathological analysis revealed that 79% of the small bowel lesions were malignant, with a predominance of advanced disease. Specifically, 42.9% of the detected small bowel malignancies were classified as pT4, 21.4% as pT3, 17.9% as pT2 and 10.7% as pT1 (Figure 1). In 25% of all malignant cases, lymph node metastases (N1 or N2) were detected, whereas in 46.4% of cases, lymph node status was unknown, limiting the assessment of nodal involvement. Tumour differentiation varied, with 38.5% of tumours classified as well-differentiated (Grade 1), 34.6% moderately differentiated (Grade 2), and 26.9% poorly differentiated (Grade 3).

Resection margins were negative (R0) in 88.1% of patients, indicating complete tumour excision in the majority of cases, while 11.9% had microscopically positive margins (R1).

Detailed analysis of the histological findings revealed that gastrointestinal stromal tumours (GISTs) were the most common tumour type, comprising 21% of cases (N=13/62). In 11 patients with GISTs, the TNM staging was reported as T2Nx in one case, T2N0 in two cases, T3Nx in two cases, T3N0 in one case, T4Nx in four cases and T1Nx in one more case. The grading of the GISTs was only reported in three cases (one as G1 and two as G3). Metastatic tumours accounted for 17.7% (11/62) of patients who underwent enterectomy for small bowel tumours in the study period, reflecting secondary involvement of the small bowel from other primary sites (e.g., gastric GIST= 1, gastric neoplasms=2, gastric adenocarcinoma=1, large-bowel adenocarcinomas=4, pancreatic adenocarcinomas=1, leiomyosarcoma=1, lung adenocarcinoma=1) (Supplementary Table S6). Regarding NETs, they represented 14.5% of the total cohort (N=9/62), while lymphomas and adenocarcinomas each accounted for 9.7% of the tumours. Out of nine NETs, TNM staging was available in seven of them; one case was T1Nx, two were T2N1, one was T3N0, one was T4N1, one was T4N0 and one more case was T4N1M1. In addition, three NETs were reported as G1, five as G2 and one as G3. Regarding adenocarcinomas (N=6/62), two patients were staged as G3, two as G2 and two as G1. Only one adenocarcinoma case missed the TNM classification in our population. The rest adenocarcinoma cases (N=5/6) included one participant with T4N1M1,

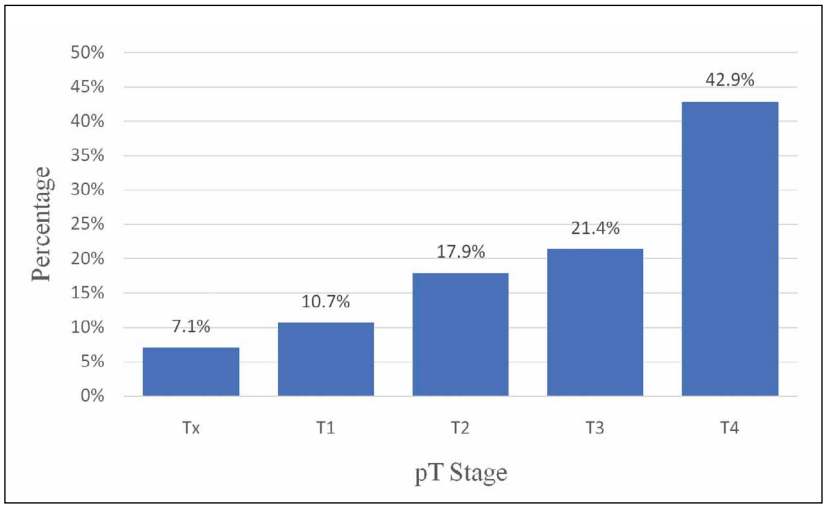

FIGURE 1. Staging by T stage, small bowel tumours (Data from our institution).

two with T4N0, and other two with T4N2. Benign neoplasms including lipomas, adenomas, desmoid tumours, Meckel's diverticulum and small bowel diverticula were identified in 21% of the participants. In addition, several rare tumour types were observed: one case of duodenal paraganglioma, two cases of small bowel sarcoma, one case of primary small bowel melanoma, and one case of PJS with an associated hamartomatous polyp (Figure 2).

Operative Data and Outcomes

The majority of enterectomies were performed as emergency procedures due to obstruction or perforation, indicative of advanced disease at the time of diagnosis. Data on postoperative morbidity, mortality, and long-term follow-up evaluations of the participants were limited, and therefore not included in this analysis.

DISCUSSION AND COMPARISON WITH LITERATURE

Early diagnosis of SBTs remains challenging due to non-specific symptoms, which do not easily raise high clinical suspicion. Therefore, the majority of SBTs remain clinically silent for long periods, being misdiagnosed and untreated until emergency surgical intervention is required. The median time between the onset of symptoms and diagnosis is estimated at around three years

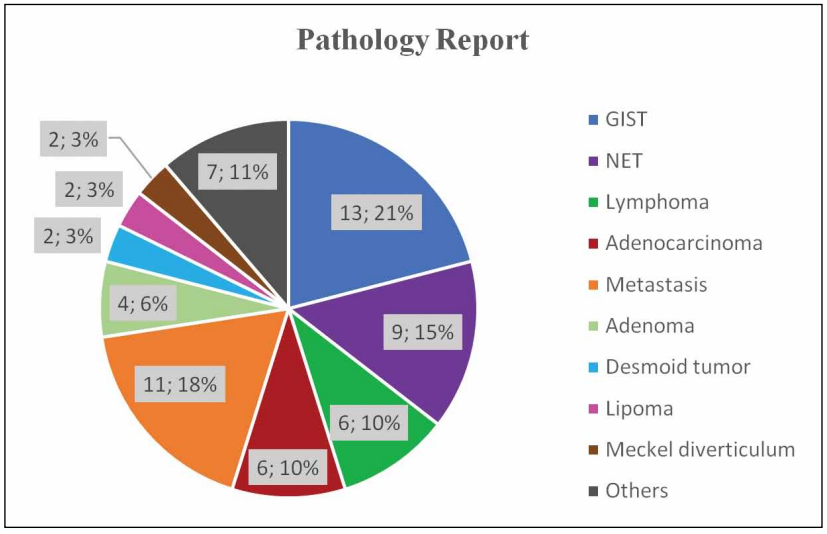

FIGURE 2. Histological distribution of small bowel tumours. Pathology reports from our institution (numbers on the pie chart representing: frequency; percentage).

for benign and up to two years for malignant tumours, contributing to poorer prognosis [3]. This study provides valuable insight into the clinical and histopathological characteristics of SBTs over a ten-year period in a single tertiary centre in Greece. The findings of our retrospective study, along with a narrative review, are consistent with current literature, highlighting both consistencies and divergences regarding the epidemiology, histopathology and clinical presentation of SBTs.

A narrative review of the literature was conducted following PRISMA guidelines in order to assess the findings of our study. A total of 56 studies [3,7,12,13,14-65] published between January 2000 and January 2025 were included, identified through searches on PubMed and ScienceDirect using the terms ("Small intestine tumours" OR "small intestine neoplasms"). Only studies meeting predefined inclusion criteria (e.g., more than 20 patients, English language, full-text availability, human subjects, and reporting on histological subtype, incidence, and surgical findings) were considered (Figure 3). Most included studies were retrospective cohorts from North America, Europe, and Asia, with additional contributions from South America and Africa (Figure 4). However, significant heterogeneity in study design limited the feasibility of a reliable meta-analysis, allowing primarily descriptive comparisons among patients with SBTs.

Our demographic findings align partially with international data, though the clinical presentation differs markedly. In particular, the mean age of patients in our cohort was approximately 63 years, slightly younger than the mean age reported in Western studies (approximately 66 years) [35], but consistent with the known epidemiology indicating that SBTs typically arise after the fifth decade of life. A male predominance (58.1%) was observed in our co-

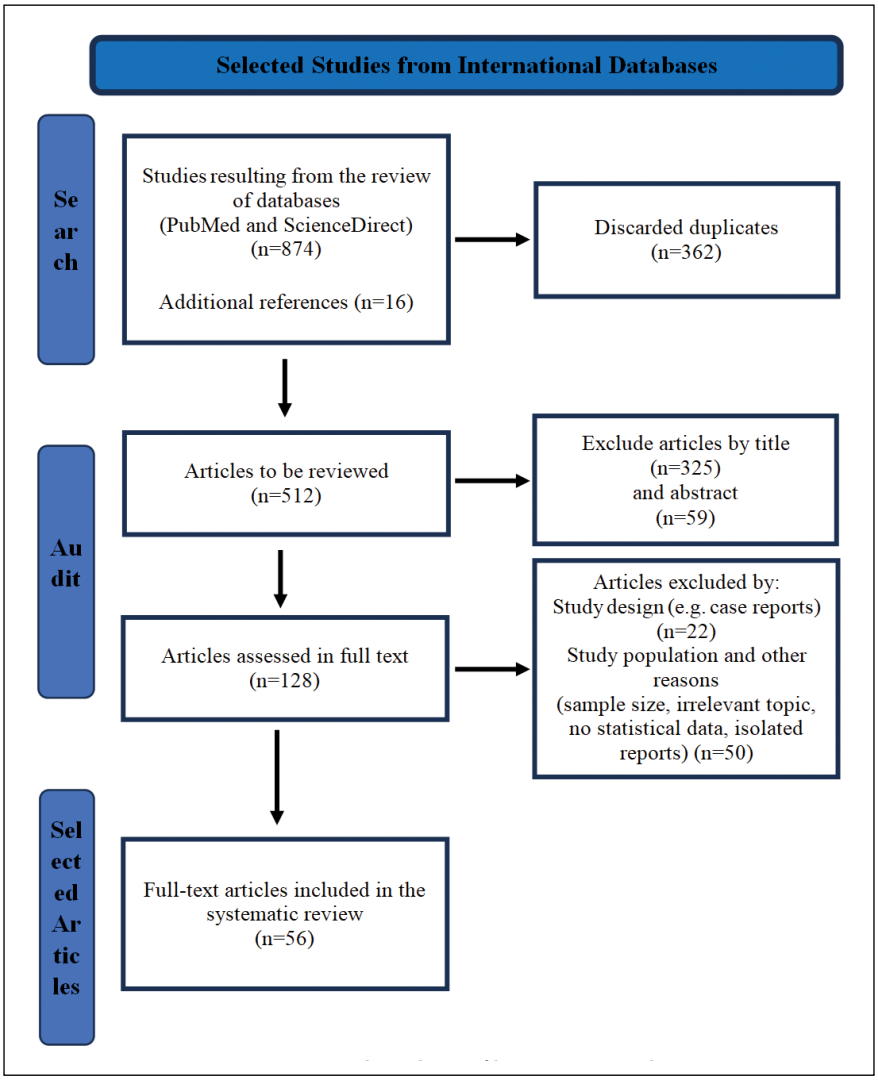

FIGURE 3. Flow chart of literature search.

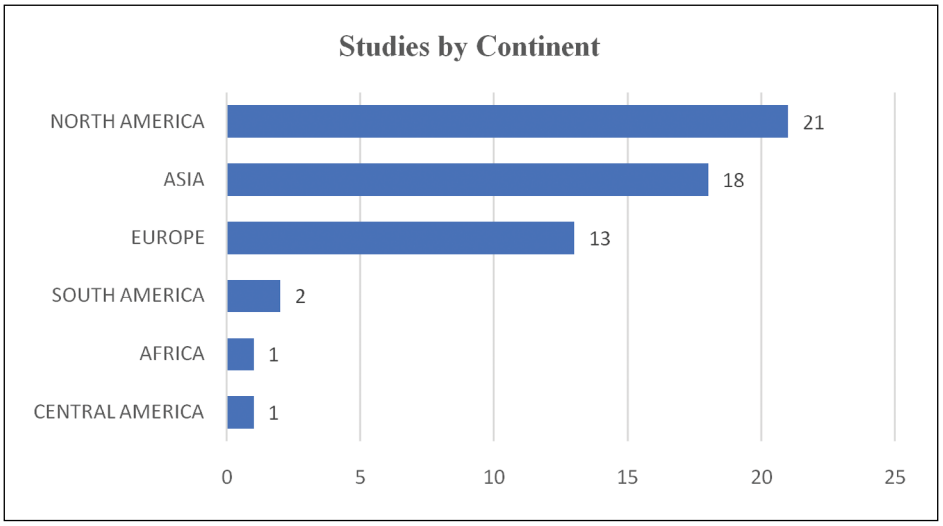

FIGURE 4. Distribution of studies by continent.

hort, in line with global trends (53-62% male patients) [2].

Regarding clinical presentation of SBTs, our study indicated obstructive ileus as the most frequent clinical indication for surgical intervention (37.1%), followed by the incidental detection of intra-abdominal masses (29%). In contrast, according to literature [1,19] gastrointestinal bleeding occurs in 30% to 50% of cases in most Western and Asian series, whereas in our cohort it accounted for only 4.8% (Figure 5). For example, Taiwanese studies report gastrointestinal bleeding in up to 39.2% of patients [19]. However, these divergences could be biased due to the nature of our study population, which mainly consisted of patients requiring urgent surgical intervention due to obstruction, rather than patients with SBTs. In the latter, diagnostic workup often follows subtle or non-specific symptoms such as gastrointestinal bleeding, prior to surgery.

The histological profile of our cases also diverges notably in comparison to other geographic regions. While NETs and adenocarcinomas are predominant in Western cohorts [16], our data showed a higher incidence of GISTs (21%) and metastatic lesions (17.7%). In our study, NETs, adenocarcinomas, and lymphomas accounted for only 14.5%, 9.7% and 9.7% of the participants, respectively. However, in Japan and parts of Asia, lymphomas and GISTs are more prevalent (16,66, Figure 6). The high frequency of GISTs in our findings could reflect both environmental and genetic factors, as well as the geographic positioning

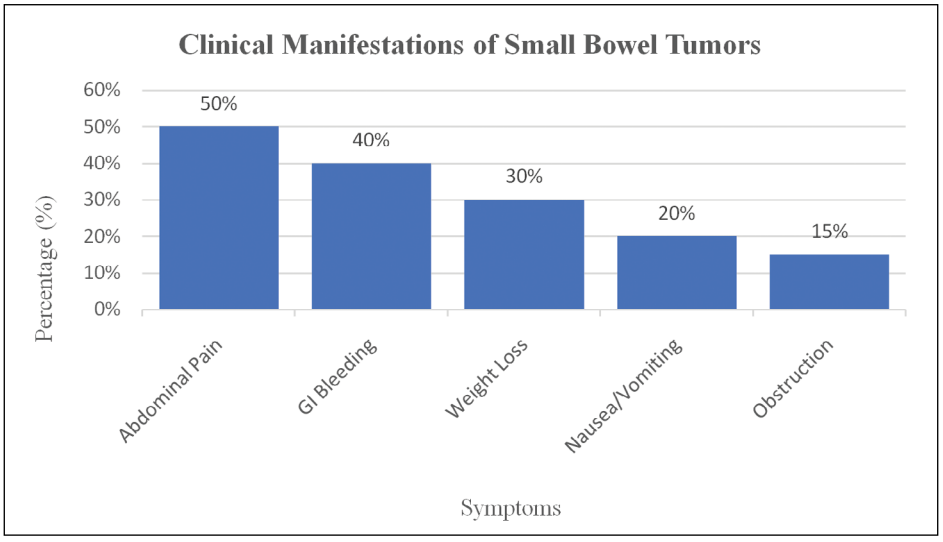

FIGURE 5. Bar chart showing the prevalence of clinical manifestations of small bowel tumours based on literature data.

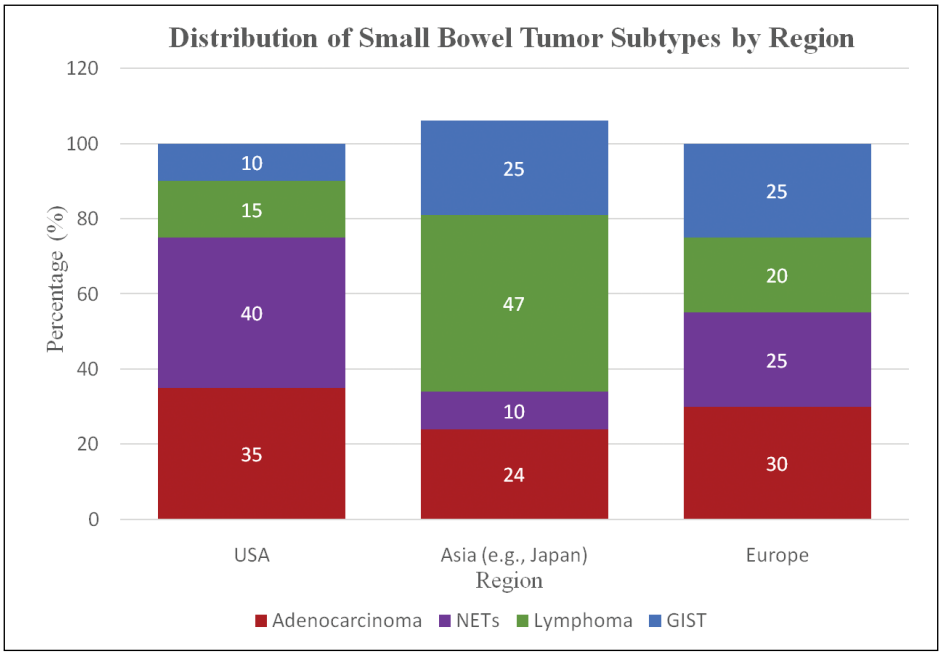

FIGURE 6. A stacked bar chart illustrating the regional distribution of small bowel tumour subtypes across the USA, Asia, and Europe.

of Greece between Western Europe and Asia. Furthermore, the higher incidence of metastatic lesions may reflect secondary involvement of the small bowel by other primary tumours, indicative of patients with advanced histopathological stage such as the majority of our patients.

According to the literature review, the frequency of SBTs decreases from proximal to distal segments—affecting mostly the duodenum, the jejunum, and least often the ileum [3]. The histological types also vary based on the tumour location with adenocarcinomas representing the predominant malignancies in the duodenum and jejunum, whereas neuroendocrine tumours occur most commonly in the ileum [3]. However, anatomical tumour location could not be consistently assessed in our study due to incomplete histopathology data recording. In addition, based on the available reports in our study centre, ileum and distal jejunum appeared to be frequently involved in patients who underwent enterectomy, in alignment with obstruction-related manifestations. However, this is a hypothesis-generating finding that contrasts with global data, which indicate that most SBTs occur in the duodenum (55%), followed by the jejunum (30%) and ileum (15%) [67].

Concerning the tumour size, the mean value for patients who underwent enterectomy for SBTs in our study centre was 5.7 cm, in line with the literature [4,14,20,30,39,65,66] indicating that SBTs are often large at the time of diagnosis due to diagnostic delays. The average length of bowel resected in our study population was 30.1 cm; however, we did not find relevant data on this parameter in our review.

Survival outcomes were not assessed in our cohort due to lack of long-term follow-up assessments. Nonetheless, literature data indicate that prognosis is closely linked to histological subtype and tumour stage, parameters which were not accurately documented in all our cases. NETs are generally associated with a more favorable prognosis, with median survival exceeding 8 years [68], whereas adenocarcinomas and sarcomas are linked to significantly worse outcomes. According to large registry data, five-year survival rates can reach 84% in cases of localised disease, but decline to 42% in metastatic cases [69]. Given that nearly half of our tumours (42.9%) were staged as pT4 and a significant proportion had nodal involvement (25%) or unknown status (46.4%), overall survival outcomes are likely to be poorer in this cohort. However, the high R0 resection rate (88.1%) even in emergency procedures such as those in our study, may partially mitigate this, enhancing an improved overall outcome in case of malignancy.

Finally, several risk factors are associated with small bowel malignancies. Chronic inflammatory conditions including Crohn's disease and celiac disease, dietary habits (e.g., high intake of alcohol, red meat, smoked or processed foods), tobacco use, HIV infection, and genetic syndromes including Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Familial Adenomatous Polyposis (FAP), Peutz-Jeghers Syndrome (PJS), and Multiple Endocrine Neoplasia type 1 (MEN1) are the most common [3,67]. However, due to limited access to our patients' medical reports, a review of potential risk factors for SBTs was not feasible.

Strengths and limitations

The strengths of this study include detailed clinical presentations and histological types on SBTs over a ten-year period at one of the largest hospitals in our country, as well as an extensive literature review of 56 studies published over the past 25 years. To our knowledge, this is the first observational study to document the histopathological subtypes and clinical presentation of SBTs in a Greek patient population. The real-world nature of our data, particularly regarding emergency presentations, offers a valuable perspective on the management of SBTs in the Greek population.

However, this is a retrospective, single-centre study involving patients who underwent enterectomy primarily due to emergency symptoms and were subsequently found to have a SBT, which limits the generalizability of our findings to all SBTs cases. The predominance of emergency procedures in our cases may have biased the cohort towards more aggressive and advanced-stage tumours, while similar tumours presenting with vague symptoms and not requiring surgical management may have been missed. Specifically, slow-growing SBTs presenting with non-typical symptoms (e.g., unexplained abdominal pain, anaemia, subtle gastrointestinal haemorrhage, weight loss) may also have been detected in elective or outpatient settings such as gastroenterology departments, although the small intestine is not always accessible by conventional endoscopic techniques. This delay in diagnosis frequently results in the need for emergency surgical management due to acute obstruction or perforation such as in our cohort.

Furthermore, the absence of documented data on tumour size, nodal status, and precise anatomical location in some pathology reports impairs the interpretation of certain findings. We surely acknowledge this as a limitation of our study, but also as an opportunity to improve our documentation practices as medical providers, when assessing biopsy specimens. Finally, regarding the long-term outcomes of SBTs, conclusions could not be drawn, as no follow-up evaluations or survival data were available for the participants.

Future directions

Our findings on SBTs may provide a basis for future multicentre, prospective research including patients with a broader spectrum of clinical manifestations. In addition, establishing national or regional tumour registries standardised for tumour details (e.g., dimensions, location, histopathology), would enhance data completeness and quality, thereby optimizing the generalizability of the results. Moreover, the integration of molecular and genomic profiling may strengthen our understanding of tumour biology and enable personalised treatment approaches on SBTs. Finally, future research should focus on recurrence, survival rates, and quality of life following surgery through long-term studies, in order to refine clinical management and improve prognostic counselling. In light of this, integrating advanced diagnostic methods such as capsule endoscopy, CT enterography, or magnetic resonance enterography into standard clinical practice for patients with unexplained abdominal symptoms could support the timely diagnosis of STBs at earlier tumour stages, where curative resection is more likely and prognostic outcomes more favourable.

CONCLUSION

SBTs are rare tumours with diverse histopathological profiles which significantly influence their clinical presentation and surgical management. Our retrospective, single-centre study highlights notable variations regarding the clinical presentation and histopathology of SBTs, particularly the higher incidence of emergency presentations and advanced-stage tumours compared to international literature. These findings may serve as a pilot for future quality improvement initiatives focused on heightened clinical suspicion in patients with non-typical symptoms, tailored diagnostic strategies and timely surgical intervention in order to improve outcomes in patients with SBTs. In view of this, further large-scale, prospective, multicentre studies in broader cohorts are needed to enhance epidemiological knowledge, refine treatment strategies, and improve prognosis in patients with SBTs.

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Supplementary Index

TABLE S 1. Resected bowel length and mass size (Data from our institution).

Statistics			
		Resected Bowel Length (cm)	Mass Size (cm)
N	Valid	43	18
	Missing	19	44
Mean		30,1419	5,7111
Median		20,0000	3,7500
Std. Deviation		31,93421	5,06451
Variance		1019,794	25,649
Range		176,50	18,10
Minimum		3,50	,40
Maximum		180,00	18,50
Percentiles	25	10,0000	2,3000
	50	20,0000	3,7500
	75	39,0000	7,2500

TABLE S 2. pT stage (Data from our institution).

pT Stage					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Tx	2	3,2	7,1	7,1
	T1	3	4,8	10,7	17,9
	T2	5	8,1	17,9	35,7
	T3	6	9,7	21,4	57,1
	T4	12	19,4	42,9	100,0
	Total	28	45,2	100,0	
Missing	System	34	54,8		
Total		62	100,0		

TABLE S 3. pN stage (Data from our institution).

pN Stage					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Nx	13	21,0	46,4	46,4
	N0	8	12,9	28,6	75,0
	N1	5	8,1	17,9	92,9
	N2	2	3,2	7,1	100,0
	Total	28	45,2	100,0	
Missing	System	34	54,8		
Total		62	100,0		

TABLE S 4. Grade (Data from our institution).

Grade					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	G1	10	16,1	38,5	38,5
	G2	9	14,5	34,6	73,1
	G3	7	11,3	26,9	100,0
	Total	26	41,9	100,0	
Missing	System	36	58,1		
	Total	62	100,0		

TABLE S 5. Resection margins (Data from our institution).

Resection Margins					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	R0	37	59,7	88,1	88,1
	R1	5	8,1	11,9	100,0
	Total	42	67,7	100,0	
Missing	System	20	32,3		
	Total	62	100,0		

TABLE S 6. Histologic types of metastatic small bowel tumours (Data from our institution).

Small Bowel Metastasis		
Primary tumour site	Frequency	Percentage
Colon adenocarcinoma	4	36.4
Gastric adenocarcinoma	3	27.3
Gastric GIST	1	9.1
Pancreatic adenocarcinoma	1	9.1
Lung adenocarcinoma	1	9.1
Leiomyosarcoma	1	9.1
Total	11	100

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Immunotherapy in microsatellite stable colorectal cancer. Current evidence and surgical perspectives

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ABSTRACT

Background: Colorectal cancer (CRC) represents one of the most frequent malignancies worldwide and one of the leading causes of cancer-related mortality. Over the years the treatment options include radiotherapy, chemotherapy and surgery. Immune checkpoint inhibitors (ICIs) show favorable efficacy in microsatellite instability (MSI-H) CRC, however there is no clear benefit in microsatellite-stable tumors (MSS). Since only around 15% of colorectal cancers are MSI-H and the remaining 85% are MSS, the limited efficacy of ICIs in MSS tumors remains a therapeutic challenge. This narrative review aims to examine the mechanisms of therapeutic resistance to ICIs in MSS CRC overall, to summarize the available clinical evidence, and to discuss possible strategies to enhance immunotherapy efficacy. Attention is also given to the evolving role of surgery within modern multifactor management including the potential interaction of immunotherapy across resectable, borderline resectable and metastatic disease settings.

Methods: A narrative review was conducted using Pubmed, Scopus and Web of Science databases. The literature search included articles published up to May 2026. The following keywords were used: "microsatellite stable", "colorectal cancer", "immune checkpoint inhibitors", "immunotherapy" and "colectomy". Narrative reviews, retrospective studies, and systematic reviews in English were considered eligible for inclusion.

Results: MSS CRC is characterized by chromosomal instability involving large-scale genomic alterations and is associated with a low tumor mutational burden (TMB) and limited neoantigen formation, contributing to the limited efficacy of ICIs. Many molecular pathways are responsible for this condition such as Wnt/β-catenin pathway, Mitogen-Activated Protein Kinase (MAPK) pathway and the transforming growth factor-β (TGF-β) pathway. Some trials (IMblaze370, KEYNOTE-016) highlight the limited efficacy of ICIs as monotherapy in MSS CRC and investigate the combined treatments to overcome the resistance. Surgery remains the cornerstone of CRC treatment; however, a non-operative (watch-and-wait) approach may be safe alternative to surgery in selected patients with MSS CRC.

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Conclusions: ICIs have changed the management of MSI-H CRC but remain ineffective as monotherapy in MSS CRC. Combination treatments targeting the tumor microenvironment, angiogenesis and oncogenic signaling pathways represent promising direction for improving immunotherapy efficacy. In this context, surgery continues to play a central role in the management of colorectal cancer. Patients with resectable disease, locally advanced and selected cases of metastatic diseases may benefit from this multidisciplinary approach. Beyond its established cytoreductive effect, surgical intervention may help modify the tumor microenvironment and reduce systemic immunosuppressive signaling. Surgery may also improve the responsiveness to immunotherapy. Future studies are needed to better define patient selection, optimal treatment choice and the role of multidisciplinary teams in the decision between systemic and locoregional therapies.

Key words: *Colorectal cancer, microsatellite stable, immune checkpoint inhibitors, immunotherapy, colectomy*

INTRODUCTION

Colorectal cancer (CRC) represents one of the most frequent malignancies worldwide and one of the leading causes of cancer-related mortality [1]. Early diagnosis of the disease, followed by proper treatment, offers better disease outcomes. However, once metastasis develops, overall survival decreases significantly, with reported rates of approximately 13.1%. Over the years, the treatment options include radiotherapy, chemotherapy and surgery. Immunotherapy plays a significant role in the management of CRC modifying both innate and adaptive immunity enhancing the immune system against cancer cells. Immune checkpoint inhibitors, chimeric antigen receptor (CAR)-T cells, tumor-infiltrating lymphocytes (TILs), and oncolytic viral therapy (OVT) are the main tools of immunotherapy [2]. ICIs, such as monoclonal antibodies targeting programmed cell death-1 (PD-1) and its ligand-1 (PD-L1), restore antitumor T-cell function with inhibition of signaling pathways while cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) has an immunosuppressive role. This mechanism shows favorable efficacy in microsatellite instability (MSI-H) CRC, however, there is no clear benefit in microsatellite-stable tumors (MSS). Since only around 15% of colorectal cancers are MSI-H and the remaining 85% are microsatellite stable, the limited efficacy of ICIs in MSS tumors remains a therapeutic challenge [2]. This narrative review aims to examine the mechanisms of therapeutic resistance to ICIs in MSS CRC overall, rather than focusing on a specific disease setting (resectable, locally advanced, and metastatic disease). It also summarizes the current clinical evidence and explores possible strategies to enhance immunotherapy efficacy. The combination of ICIs with chemotherapy, anti-angiogenic agents and targeted therapies have shown some promising outcomes. Attention is also given to the evolving role of surgery within modern multifactor management including the potential interaction of immunotherapy across resectable, borderline resectable and metastatic disease settings.

METHODS

A narrative review was conducted using Pubmed, Scopus and Web of Science databases. The literature search included articles published up to May 2026. The following keywords were used: "microsatellite stable", "colorectal cancer", "immune checkpoint inhibitors", "immunotherapy" and "colectomy". Narrative reviews, retrospective studies, and systematic reviews in English were considered eligible for inclusion.

RESULTS

Mechanisms Underlying the Limited Efficacy of ICIs in MSS CRC *(Figure 1)*

MSS CRC is characterized by chromosomal instability involving large-scale genomic alterations and is associated with a low tumor mutational burden (TMB) and limited neoantigen formation. Consequently, these tumors develop an immunologically "cold" tumor microenvironment that differs substantially from MSI-high CRC and contributes to the limited efficacy of ICIs. One of the mechanisms that explain this phenomenon is "immune exclusion" or "T-cell exclusion", in which T-cells fail to effectively infiltrate the tumor microenvironment. This process has been linked to increased activity of the Wnt/β-catenin pathway, which appears to reduce the efficacy of ICIs. MSS tumors are often enriched with macrophages, which can further suppress adaptive antitumor immune responses. Overall, these observations suggest that abnormal activation of Wnt/β-catenin pathway seems to develop an immune-excluded microenvironment and works as a biologic barrier to successful immunotherapy into multimodal

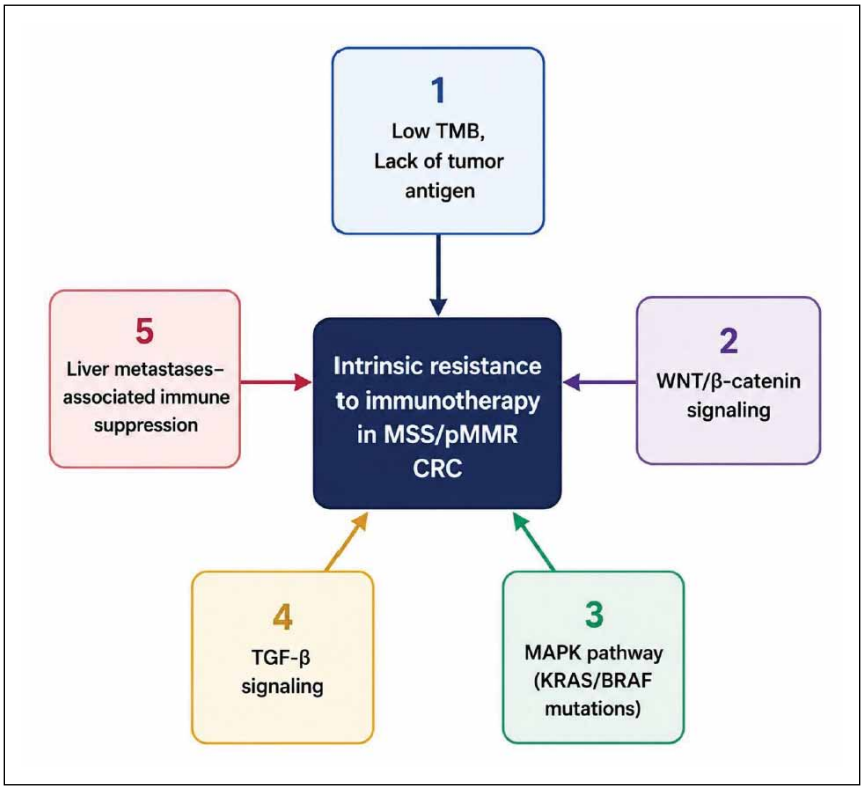

FIGURE 1. Mechanisms Underlying the Limited Efficacy of ICIs in MSS CRC.

treatment approaches [3]. Beyond this, frequent KRAS and BRAF mutations in MSS CRC lead to activation of the MAPK pathway. This pathway has been associated with impaired antigen presentation and reduced T-cell infiltration, negatively affecting the responsiveness to ICIs [3]. Another important pathway involved in 40–50% of CRC cases is the TGF-β pathway [4]. The increase of TGF-β signaling has been linked to downregulation of T cells activity, suppression of antitumor immunity and inhibition of natural killer cells' function. According to preclinical studies, it is described the hypothesis that activation of TGF-β pathway contributes to immune escape and reduced response to immunotherapy in colorectal cancer, especially in patients with liver metastases. Increased TGF-β signaling may create an immunosuppressive tumor microenvironment by promoting regulatory T cells, while reducing the activity of natural killer cells and CD4+/CD8+ T cells, weakening the antitumor immune response. Since liver metastases are often resistant to immune checkpoint inhibitors, TGF-β–mediated immune suppression may represent an important mechanism underlying this resistance. Therefore, targeting the TGF-β pathway could improve antitumor immunity, limit metastatic spread, and enhance the effectiveness of immunotherapy in metastatic colorectal cancer [3].

Clinical Evidence of ICIs in MSS CRC

Several studies have evaluated the efficacy of immunotherapy in MSS colorectal cancer (Table 1). The phase III randomized controlled trial IMblaze370 enrolled 363 patients with locally advanced or metastatic colorectal cancer (mCRC) receiving atezolizumab plus cobimetinib, atezolizumab monotherapy, or regorafenib. The majority of patients (95%) had MSS disease. The trial demonstrated that atezolizumab monotherapy did not have a survival benefit in patients with MSS CRC, highlighting the limited efficacy of ICIs as a single-agent strategy in this setting [5]. In a phase 2 clinical trial (KEYNOTE-016) D. T. Le and colleagues evaluated PD-1 blockade with pembrolizumab in mCRC. The objective responses were 40% in patients with mismatch repair–deficient tumors (dMMR), while patients with proficient mismatch repair (pMMR) CRC did not receive any clinical benefit. These findings identified the mismatch repair status as the main factor of responsiveness to ICIs in colorectal cancer [6]. A systematic review by Leping Kong et al. showed that ICIs demonstrated effectiveness in patients with dMMR/MSI-H metastatic colorectal cancer. In contrast, evidence for benefit in MSS/pMMR colorectal cancer was still limited. It was mentioned that some combination strategies involving ICIs with chemotherapy or tyrosine kinase inhibitors showed potential

TABLE 1. Clinical studies evaluating immunotherapy in MSS CRC.

Study	Phase	Setting	Treatment	Results
IMblaze 370	III	Locally advanced or mCRC	Atezolizumab +- cobimetinib versus regorafenib.	No survival benefit with atezolizumab in patients with MSS CRC
KEYNOTE-016	II	mCRC	Pembrolizumab	No clinical benefit in patients with MSS CRC
CO.26	II	mCRC	Durvalumab + Tremelimumab	Improved survival benefit in patients with MSS CRC
REGONIVO	Ib	Locally advanced or mCRC	Regorafenib + Nivolumab	Promising results in patients with MSS CRC
NICHE	II	Neoadjuvant setting- early stage MSS CRC	Nivolumab + Ipilimumab	Major pathological response in 26% of patients with MSS CRC
NEST-1	II	Neoadjuvant setting- resectable CRC	Botensilimab+ Balstilimab	Promising results in patients with MSS CRC
FFCD 1703-POCHI trial	II	unresectable pMMR/MSS mCRC	Pembrolizumab+ capecitabine plus oxaliplatin (CAPOX)+ bevacizumab	Promising results in patients with MSS CRC

activity, even though the reviewed studies were mostly small retrospective cohorts with heterogeneous results. The authors concluded that for validation of combination immunotherapy, larger prospective multicenter studies are needed, especially for MSS/pMMR colorectal cancer [7]. The Canadian Cancer Trials Group (CO.26 Study) suggest the combination of PD-L1 and CTLA-4 for patients with MSS mCRC. In this trial, 119 patients with CRC received durvalumab plus tremelimumab, while 61 received best supportive care. Patients in the treatment group achieved higher rates of stable disease and disease control than those in the other group, demonstrating a potential overall survival benefit in heavily pretreated patients with MSS CRC [8]. A different study, phase II NICHE II trial explored the efficacy of nivolumab+ipilimumab in early stage MSS CRC, as neoadjuvant therapy. The results were encouraging, demonstrating major pathological response around 26%. These findings suggest that combination of ICIs in the neoadjuvant setting may have an impact on MSS CRC [9]. Similarly, the phase II NEST-1 trial examined the safety and efficacy of the combination of the anti–CTLA-4 antibody botensilimab and the anti–PD-1 antibody balstilimab in patients with localized MSS CRC in the neoadjuvant setting. The study demonstrated encouraging pathological response rates, suggesting that dual ICIs may represent a promising therapeutic strategy for selected patients with MSS disease [10]. Encouraging findings have also been reported in the metastatic setting. The ongoing phase II POCHI trial demonstrated promising preliminary activity of pembrolizumab in combination with CAPOX (capecitabine plus oxaliplatin) and bevacizumab in patients with MSS/pMMR mCRC with high immune infiltrate on primary tumor resection specimens. These results suggest that careful patient selection together with combination treatment may improve the efficacy of immunotherapy in MSS CRC [11]. Overall, the above trials indicate that ICIs as monotherapy have limited efficacy in MSS CRC. More recent studies, evaluating the combination of strategies to enhance immunotherapy resistance, have shown encouraging results.

Combination Strategies to Enhance Immunotherapy Response *(Figure 2)*

The limited efficacy of ICIs as monotherapy in MSS CRC led the investigation to focus on developing combinations of treatments. The main objective was the improvement of tumor immunogenicity and the overcoming of immune resistance. Combined treatments include chemotherapy, anti-angiogenic agents, targeted therapies and locoregional treatments.

a. ICIs Combined with Chemotherapy

Microsatellite-stable mCRC generally respond poorly to ICIs monotherapy for several reasons, and combined treatment with chemotherapy may improve their efficacy. First of all, these tumors have a low mutational burden, resulting in fewer neoantigens that can be recognized by the immune system. Furthermore, activation of the WNT/β-catenin pathway represents a common finding in MSS CRC and limits the infiltration of cytotoxic CD8+ T cells into the tumor. The tumor microenvironment is often

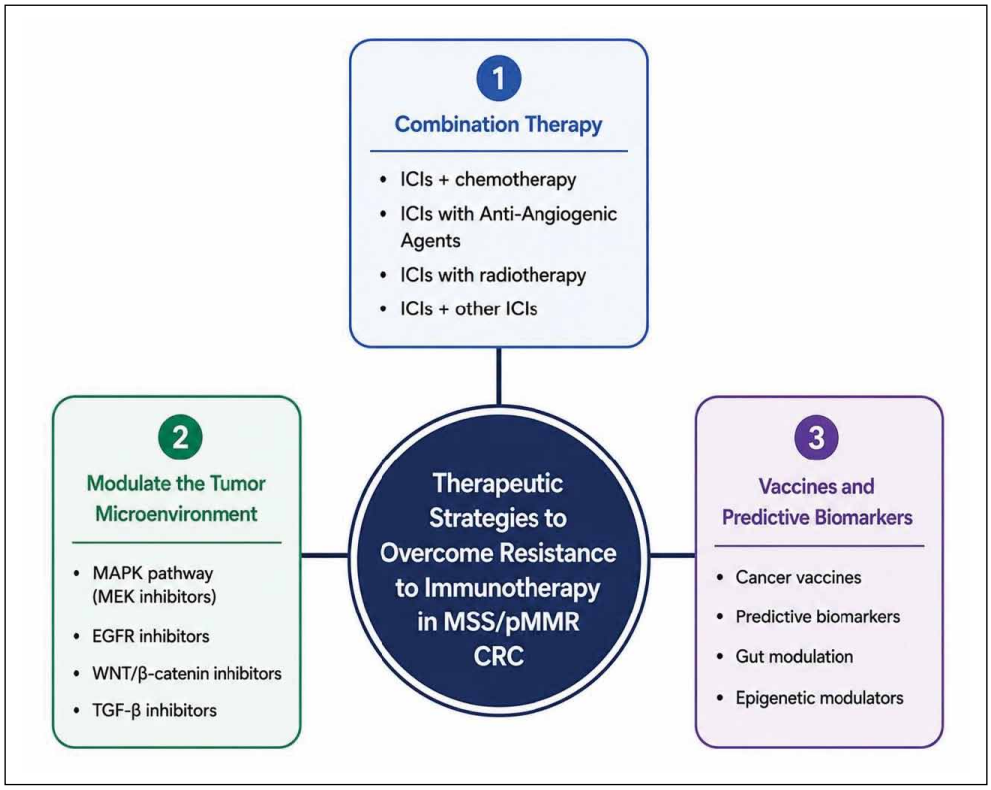

FIGURE 2. Therapeutic strategies to overcome resistance to immunotherapy in MSS CRC.

dominated by immunosuppressive cells, such as regulatory T cells and tumor-associated macrophages, which inhibit effective antitumor immune responses. Finally, the high prevalence of liver metastases in MSS CRC may further reduce the effectiveness of immunotherapy [12]. Previous studies evaluating the efficacy of ICIs on pMMR/MSS tumors have shown limited clinical benefit on patients with mCRC. In the phase II AzetoTRIBE trial, Antoniotti C et al investigated the clinical benefit of atezolizumab an anti-PD-L1 agent combined with chemotherapy (FOLFOXIRI; fluorouracil, leucovorin, oxaliplatin, and irinotecan) and bevacizumab. The results were encouraging, with a median progression-free survival of 13.1 months in the group receiving atezolizumab compared with a median of 11.5 months in the control group. These findings suggest that the addition of immune checkpoint inhibitor into chemotherapy regimens may increase the progression-free survival in some patients with MSS mCRC [13]. Already from 2011 Jurjen Tel and colleagues investigated the role of oxaliplatin in the tumor microenvironment. They found that oxaliplatin increases PD-L1 expression and leads to decreased T-cell levels. They concluded that combining chemotherapy and immunotherapy could improve patients' overall survival [14]. The above combination has also been explored in both preclinical and clinical studies. Certain cytotoxic agents, particularly 5-fluorouracil and oxaliplatin may increase tumor immunogenicity by promoting tumor antigen release, stimulating immunogenic cell death and reducing immunosuppressive immune cells. These actions potentially improve the effectiveness of immunotherapy and based on this fact several clinical trials have investigated chemo-immunotherapy combinations in mCRC. The phase II NIVACOR trial is currently evaluating the combination of Nivolumab with FOLFOXIRI and Bevacizumab (Vascular Endothelial Growth Factor A (VEGF-A)) as first-line treatment in patients with metastatic colorectal cancer. This multicenter study aims to determine whether the combination of ICIs with an intensive chemotherapeutic regimen can boost antitumor immune response and improve clinical outcomes. Patients with mCRC and mutation in RAS or BRAF genes received FOLFOXIRI, Bevacizumab, and Nivolumab. The overall response rate, the safety of the combination and overall survival were the primary and secondary outcomes. Preliminary data suggest that this combination is feasible and generally well tolerated with manageable toxicity profiles. The final efficacy results are awaited [15].

b. ICIs with Anti-Angiogenic Agents

Vascular endothelial growth factor (VEGF) plays a

significant role in tumor angiogenesis and is often overexpressed in colorectal cancer. Thus, it contributes to tumor progression and metastatic disease. VEGF, except its angiogenic effects, also promotes an immunosuppressive tumor microenvironment by inhibiting dendritic cell maturation, impairing T-cell activation and promoting the accumulation of immunosuppressive cell populations such as regulatory T cells (Tregs), tumor-associated macrophages and myeloid-derived suppressor cells. A self-creating immunosuppressive cycle within the tumor microenvironment is developed. Inhibition of VEGF signaling not only suppresses tumor angiogenesis but also restores antitumor immune responses. In conclusion, anti-VEGF improves the efficacy of immune checkpoint inhibitors. The phase Ib REGONIVO study evaluated the combination of regorafenib, a multikinase inhibitor targeting VEGFR2, with nivolumab in patients with advanced colorectal and gastric cancers. In this Japanese cohort, 25 patients with advanced or metastatic CRC (24 with MSS CRC and 1 with MSI-H) were treated with these regimens. The results were promising showing a response rate of about 33% among patients with MSS/pMMR metastatic colorectal cancer. Adverse events matched the previously known safety profiles of the two drugs [16]. However, different results were observed in a single-arm phase II trial from North America (NCT04127333). In this study by Marwan Fakih et al. a cohort of 70 patients with MSS mCRC was analyzed, having received the same treatment. The results were not encouraging with only 5 patients (7.1%) showing partial response and 22 patients (31.4%) having stable disease. This discrepancy may be explained by differences in patient selection. Critical analysis from the North American phase II study revealed that clinical benefit was seen in patients without liver metastases, while those with hepatic involvement showed minimal response. The overall response rate was 21% and 0% respectively. These findings indicate that the efficacy of this combination may be limited to selected patients without metastatic disease in liver and highlight the potential influence of liver metastases on responsiveness to immune checkpoint blockade in mCRC [17]. If confirmed in future studies, this hypothesis could influence the management of patients with MSS tumors and synchronous liver metastases. A possible therapeutic approach may be to prioritize hepatic metastasectomy while administering immunotherapy for the primary tumor, although further evidence is required to support this strategy. Finally, tumor biology and host immune response between Asian and Western populations may explain the different results of the above trials. However, this hypothesis requires further investigation.

c. ICIs with Other Therapies

The MAPK pathway has been involved in regulating major histocompatibility complex class I (MHC-I) expression, thereby influencing antigen presentation during tumor development. In preclinical models of colorectal cancer, inhibition of the MAPK pathway through MEK inhibitors increases MHC-I expression and promotes intratumoral infiltration of CD8 T lymphocytes. The combination of MEK inhibitors with ICIs may represent a promising approach in MSS CRC, considering that MAPK pathway activation is observed in 60% of these tumors [12,18]. Epidermal growth factor receptor (EGFR) inhibitors, such as cetuximab, could benefit patients with refractory MSS CRC when combined with ICIs. In the phase II AVETUXIRI trial, Huyghe et al. evaluated the safety and efficacy of avelumab, cetuximab, and irinotecan regimens in 57 patients with refractory MSS metastatic colorectal cancer. Patients were treated with this triple combination regardless of RAS status. These patients had previously taken standard therapies. Although the study did not meet its primary efficacy endpoints, the treatment was generally well tolerated and showed activity in patients with increased T-cell infiltration. These findings show that this approach may offer benefits in biologically selected subgroups of MSS CRC [19]. Another therapeutic approach has been explored by Fakih et al., 2023. A nonrandomized study involves the following combination of nivolumab, ipilimumab, and regorafenib. Preclinical and clinical evidence confirms that dual checkpoint inhibition with PD-1 and CTLA-4 blockade can enhance effector T-cell activation and improve antitumor immune responses. This strategy has shown activity in several malignancies, including melanoma and MSI-H CRC. Regorafenib which approved for refractory metastatic colorectal cancer, has been shown to modulate the tumor immune microenvironment and may act synergistically with PD-1 inhibition. Consequently, the above combination demonstrates encouraging activity mainly in patients with MSS colorectal cancer without liver metastases, similar to the REGONIVO (regorafenib and nivolumab) study [20]. Despite encouraging preliminary findings, the evidence supporting these immunotherapy-based combination strategies is still limited. Most of the available data comes from early-phase (phase I/II) studies, which are mainly designed to assess safety and initial efficacy. As a result, larger randomized phase III trials are needed to confirm their clinical benefit. Furthermore, several of these studies include relatively small number of patients, which may limit their statistical power and make it difficult to generalize the results to the wider population of patients with MSS colorectal cancer.

d. Predictive Biomarkers

The identification of predictive biomarkers capable of selecting patients with MSS CRC who are most likely to benefit from the above combination strategies remains an important challenge. Immune microenvironment, genomic mutations, and circulating tumor DNA (ctDNA) are some of them. Clinical studies, including the VOLTAGE-A trial, have shown that patients with higher baseline PD-L1 expression, assessed by either tumor proportion score (TPS) or combined positive score (CPS) tend to achieve higher pathological complete response (pCR) rates. In addition, genomic alterations, including mutations in ARID1A, SMAD4, PDGFA, and IL2RG, have been associated with differences in tumor regression suggesting that they may play a role in predicting treatment response. POLE/POLD1 mutations represent another predictive biomarker for immunotherapy response. These mutations, although rare in MSS CRC, are associated with a hypermutated phenotype, increased tumor immunogenicity, and enhanced infiltration of cytotoxic T lymphocytes. Therefore, these tumors may be more sensitivity to ICIs. Moreover, changes in ctDNA levels during neoadjuvant treatment have also shown potential for predicting pathological response and long-term outcomes [21,22].

The Role of Surgery in the Era of Immunotherapy

Surgery remains the cornerstone of CRC treatment offering potential cure, especially when the disease is diagnosed early [23]. Jiahao Zhu et al. consider that surgery may reduce the benefit of adjuvant ICIs because of the destruction of blood vessels and lymph nodes in the surgical area. They suggested that the survival benefit associated with adjuvant ICIs remains limited. This may be due to the reduced availability of tumor-derived antigens following surgical resection, together with disruption of local vasculature and regional lymphatic drainage. These changes may impair antitumor immune responses, diminishing both residual tumor cell eradication and the development of durable tumor-specific immune memory [24]. However, the importance of adjuvant (immuno)therapy is clear for eliminating residual disease and reducing recurrence and metastasis risk [25]. On the other hand, neoadjuvant treatment with the combination strategies described above may achieve significant tumor responses in MSS CRC and in selected cases could allow organ-preserving approaches or even avoidance of surgery [25,26]. After the US Food and Drug Administration (FDA) approved Pembrolizumab and Nivolumab (+/- Ipilimumab) for mCRC, interest grew regarding the possible benefit of ICIs in locally advanced CRC, especially in MSS tumors. This development gives patients the option of "watch and wait" (ww), avoiding surgical morbidity and even the organ loss [26]. This approach (ww) was first examined by Angelita Habr-Gama et al. in a retrospective trial, particularly for patients with rectal cancer, receiving neoadjuvant chemoradiation. Two hundred sixty-five patients with resectable rectal adenocarcinoma received total neoadjuvant chemoradiotherapy. Among them, 71 (26.8%) achieved a complete response and were followed up for an average of 57.3 months. The 5-year overall survival and disease-free survival rates in this subgroup were 100% and 92% respectively, suggesting that a non-operative (watch-and-wait) approach may be a safe alternative to surgery in selected patients. These patients could avoid surgical morbidity, mortality, and stoma formation. Moreover, this strategy has been linked to comparable disease-free and overall survival compared with standard surgical management patients. As expected, the quality of life was also improved [26,27]. Although watch-and-wait was originally developed following chemoradiotherapy and, more recently, total neoadjuvant therapy (TNT), it remains highly relevant from a surgical perspective because organ preservation has become a major treatment goal in rectal cancer. The OPRA trial demonstrated the feasibility of nonoperative management in patients achieving a clinical complete response after TNT [28], while recent immunotherapy studies in dMMR-MSI-H rectal cancer, most notably the dostarlimab trial by Cercek et al., have demonstrated unprecedented complete response rates and renewed interest in organ-preserving strategies [29]. Therefore, watch-and-wait is discussed here not as evidence of immunotherapy efficacy in MSS disease, but as a potential surgical consequence if immunotherapy-based approaches are able to achieve comparable response rates in selected MSS tumors in the future. In such cases, successful tumor downstaging may facilitate less extensive surgical procedures or preservation of lymphatic structures in carefully selected patients, a concept that remains investigational and requires further clinical evaluation [24]. This idea is supported by a recent study by Maha et al., which highlights the role of tumor-draining lymph nodes in generating effective antitumor immune responses. Following immunotherapy, $CD8^+$ T cells can activate within non-involved lymph nodes, enter the systematic circulation, and infiltrate the tumor. This concept suggests that preserving lymphatic structures may enhance treatment efficacy [30]. However, since this study was conducted in head and neck squamous cell carcinoma, further research is needed to determine whether similar findings apply to colorectal cancer. This concept is further supported by another study by Huang et al., showing that early removal of disease-free lymph nodes during surgery

may harm overall survival [31]. Based on these observations, more studies have investigated whether the addition of immunotherapy to TNT could further increase complete response rates and expand the eligibility for a watch-and-wait approach in patients with MSS rectal cancer. Xing Li et al. in his study aimed to evaluate whether the addition of PD-1 blockade to TNT could improve complete response rates and increase the feasibility of a watch-and-wait strategy in patients with pMMR/MSS locally advanced rectal cancer. The study included 141 patients with locally advanced rectal cancer (LARC), who were divided into two groups. In the first one, patients received short-course radiotherapy followed by immunochemotherapy, whereas the second one received immunochemotherapy, followed by short-course radiotherapy and additional immunochemotherapy. The authors concluded that the addition of PD-1 blockade to TNT improved complete response rates in pMMR/MSS locally advanced rectal cancer compared with traditional total neoadjuvant treatment, without compromising tolerability. These findings support further investigation of short-course radiotherapy followed by immunotherapy as a potential organ-preserving treatment strategy [32]. Another review by Farooq et al. highlighted that combining neoadjuvant chemoradiotherapy with immunotherapy in patients with pMMR/MSS locally advanced rectal cancer is evolving toward maximizing tumor regression and facilitating organ preservation. The authors reviewed several clinical trials, comparing conventional neoadjuvant therapy with neoadjuvant chemoradiotherapy combined with immunotherapy (VOLTAGE-A, PANDORA, POLAR STAR). Although most of the trials were phase II, the addition of immunotherapy was associated with higher clinical complete response rates and may be candidates for watch-and-wait strategy. These findings suggest that immunotherapy-based neoadjuvant strategies may increasingly influence surgical decision-making by expanding opportunities for non-operative management in carefully selected patients [21].

Future Perspectives

Despite significant advances in immunotherapy, most patients with MSS CRC continue to derive limited benefit from ICIs monotherapy. Future research is therefore needed to be focused on overcoming primary immune resistance through combination approaches that enhance tumor immunogenicity and promote T-cell infiltration (Figure 2). As discussed above, recent clinical trials have evaluated several promising strategies involving ICIs in combination with chemotherapy, radiotherapy and anti-angiogenic agents. However, their efficacy and safety need to be confirmed in larger randomized clinical trials. In addition, research has focused on developing cancer vaccines which enhance the efficacy of ICIs in MSS tumors. Moreover, modulation of human gut microbiome may influence the development or prevention of CRC and the response to immunotherapy through its interaction with the host immune system. This effect is thought to be mediated by activation of CD8+ T cells induced by immunomodulatory molecules and metabolites produced by intestinal bacteria, but further investigation is needed to be confirmed. At the same time, the identification of reliable predictive biomarkers remains essential to optimize patient selection. Biomarkers such as PD-L1 expression, POLE/POLD1 mutations, circulating tumor DNA, and even the presence of liver metastases may help identify patients who are more likely to benefit from immunotherapy-based approaches [22].

CONCLUSION

Immune checkpoint inhibitors have changed the management of MSI-H CRC but remain ineffective as monotherapy in MSS CRC. Combination treatments targeting the tumor microenvironment, angiogenesis and oncogenic signaling pathways represent a promising direction for improving immunotherapy efficacy. Ongoing research is focused on treatment modalities that aim to enhance tumor immunogenicity and overcome immune resistance. The use of chemotherapy, anti-angiogenic agents, and targeted therapies are some of the main tools. In this context, surgery continues to play a central role in the management of colorectal cancer. Patients with resectable disease, locally advanced and selected cases of metastatic diseases may benefit from this multidisciplinary approach. Beyond its established cytoreductive effect, surgical intervention may help modify the tumor microenvironment and reduce systemic immunosuppressive signaling. Surgery may also improve the responsiveness to immunotherapy. Tumor downstaging after multimodal treatment allows selected patients to undergo elective resection. This offers more tailored and organ-preserving surgical options, thereby reducing the morbidity and mortality of surgical operations. Nevertheless, the integration of immunotherapy into surgical decision-making for MSS CRC remains an area of active research. Future research should focus on identifying reliable predictive biomarkers and exploring emerging approaches such as cancer vaccines and gut microbiome modulation to improve the efficacy of immunotherapy in MSS CRC. Future studies are needed to better define patient selection, optimal treatment choice and the role of multidisciplinary teams in the decision between systemic and locoregional therapies. A deeper understanding of these interactions may ultimately lead to more effective and personalized management of patients with MSS CRC.

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Perioperative outcomes and morbidity following pelvic exenteration surgery: A Single-Center Experience

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ABSTRACT

Background: Pelvic exenteration (PE) is a radical, potentially curative procedure for locally advanced and recurrent pelvic malignancies, associated with significant morbidity. This study presents the perioperative outcomes of PE surgery performed at our center.

Material and Methods: In this retrospective, single-center cohort study, all patients undergoing PE surgery between 1 January 2024 and 1 September 2025 were included.No specific inclusion or exclusion criteria were applied. Data, including operative and reconstruction techniques, perioperative complications and pathology outcomes, were collected and analysed; no inferential statistics were performed.

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Results: The cohort included 18 patients, with a mean age of 62 (range 40-76). Sixteen patients had rectal cancer cancer (recurrent in 8 (44%) and primary in 8 (44%) patients) and two patients had recurrent cervical cancer. The principal procedure was total pelvic exenteration, with or without low sacrectomy (8 (44%) and 6 (33%) patients, respectively). Other procedures included abdominosacral resection, palliative PE, high subcortical sacrectomy, extended lateral pelvic sidewall excision, and extralevator abdominoperineal resection. Urinary reconstruction was primarily via ileal conduit (16 patients (88.9%) and flap reconstruction via bilateral gluteal flap (7 patients (38.9%). Most tumours were staged as T4 (83%- 15 patients) and an R0 resection was achieved in 16 patients (89%). The mean hospital stay was 36 days (range 18-68). All patients experienced complications, graded as Clavien-Dindo II (61%- 11 patients), IIIa (3 patients (17%), or IIIb (4 patients (22%). The most common were bloodstream infections (10 patients (56%) and superficial abdominal wound infections (9 patients (50%). Re-operation was required in four patients (22%) due to the following: anastomotic leak, burst abdomen, flap haematoma with dehiscence, and postoperative intra-abdominal bleeding.

Conclusions: PE, while a highly morbid procedure, can achieve high rates of R0 resection in patients with advanced or recurrent pelvic disease. The high incidence of complications underscores the complexity of these cases and highlights the necessity for their management in specialised, high-volume centers with multidisciplinary support.

Key Words: *Pelvic; exenteration; advanced; recurrent; cancer; rectal; outcomes*

INTRODUCTION

Pelvic exenteration is among the most extensive and technically demanding procedures in oncologic surgery, typically reserved for patients with advanced or recurrent pelvic malignancies. Initially introduced as a palliative operation in the management of gynecologic cancers [1], pelvic exenteration has evolved substantially over the past decades. Advances in preoperative imaging, patient selection, multimodal oncologic therapy, surgical technique, anaesthesia, and reconstructive surgery have expanded its indications and transformed it into a potentially curative option for selected patients with locally advanced or recurrent disease [2-5].

Despite these developments, pelvic exenteration remains associated with considerable morbidity and functional disability [2-5], underscoring the need for careful patient selection and treatment within specialised, high-volume centers supported by multidisciplinary expertise. Achieving clear resection margins is the primary determinant of long-term survival [6-8], often necessitating extended resections involving the sacrum, pelvic sidewall and adjacent pelvic viscera. Simultaneously, advances in the reconstructive techniques—particularly in urinary diversion and in pelvic floor reconstruction—have played a critical role in reducing complications, improving outcomes, and enhancing postoperative quality of life.

The present study reports a single-center experience with pelvic exenteration over a 20-month period, focusing on patient characteristics, operative and reconstructive strategies, perioperative morbidity, and pathological outcomes. By presenting these data, we aim to contribute to the growing body of evidence supporting pelvic exenteration as a viable treatment option for selected patients with advanced pelvic malignancies, even in regions where centralised pelvic exenteration services are limited or lacking, and to highlight the significance of centralisation and multidisciplinary care in enhancing outcomes.

MATERIAL AND METHODS

This retrospective single-center cohort study included all patients undergoing a pelvic exenteration (PE) procedure, between 1 January 2024 and 1 September 2025 at our surgical department.The cohort both referred and in-house cases, with locally advanced or recurrent pelvic diseasePatient selection, for either curative or palliative treatment, required agreement from a multidisciplinary tumour board (MDT) and was based on a comprehensive assessment ofclinical, laboratory, imaging, and endoscopic findings.Our cohort included all those patients, who were discussed at the MDT, and operability with curative or palliative intent was deemed possible. Patients with metastatic disease and those in whom an R0 resection was not feasible were excluded from curative resections.

PE procedures included total pelvic exenteration (TPE), with or without sacrectomy, palliative PE and abdominosacral resections. TPE involved en bloc resection of all pelvic

viscera, including the distal GI and urinary tract (distal colon, rectum, anus, urinary bladder and distal ureter) and the internal reproductive organs (uterus, ovaries, fallopian tubes, vagina, prostate, seminal vesicles). Palliative PE included more limited resections aimed at alleviating cancer-related symptoms. Sacrectomy, if needed, included low sacrectomy, below the S2 vertebra, and high subcortical sacrectomy (HiSS), which involved resecting the infiltrated midportion of the anterior sacral body en bloc with the infiltrated structures, leaving the posterior surface and lateral edges in situ. Abdominosacral resections focused on functional preservation and included a more conservative resection of infiltrated pelvic viscera or bony structures. En bloc resection of the infiltrated pelvic structures combined with either extralevator abdominoperineal excision (ELAP), extended lateral pelvic sidewall excision (ELSiE) or high subcortical sacrectomy (HiSS) were included in this category.

Clinical data were retrieved retrospectively, from the institutional database, capturing patient demographics, prior treatment interventions, operative documentation, final pathology reports and intra- and postoperative progress and complications graded according to Clavien-Dindo classification.

Histopathological assessment defined an R0 resection as a circumferential resection margin (CRM) greater than 1 mm. An R1 resection indicated microscopic residual disease, characterised by a CRM of 1 mm or less, while an R2 resection denoted the presence of macroscopic residual disease.

As the study involved only the analysis of anonymised records and non-identifiable photographic content, with no direct patient interaction, it was exempt from formal ethics committee approval per institutional and national regulations. All patients had previously provided written informed consent for their procedures after preoperative counseling on their diagnosis, surgical plan, risks, and alternatives, ensuring voluntary and autonomous participation. Quantitative data are presented as mean and median values and qualitative data as absolute numbers or percentages. Software Microsoft Excel was utilised for data collection, analysis, and table creation. No inferential statistics were performed.

RESULTS

Baseline characteristics

The cohort included 18 patients, mostly males (12 patients; 66%), with a mean age of 62 (range 40-76). Two patients (11%) had recurrent cervical cancer, while 16 patients had rectal cancer: eight patients (44%) with locally advanced rectal carcinoma (LARC) and eight patients (44%) with locally recurrent rectal cancer (LRRC), two of whom had a second recurrence (Table 1). All patients with LRRC had undergone low anterior resection (LAR) and all patients with cervical cancer had undergone total hysterectomy. One of the patients with secondary recurrence had also undergone abdominoperineal resection (APR) after LAR.

Seven patients with LARC and 7 patients with LRRC had received total neoadjuvant therapy (TNT), while1 patient with LARC and microsatellite instability had also received immunotherapy. Both patients with recurrent cervical cancerhad undergone adjuvant chemoradiation and brachytherapy.

On admission, 17 patients were classified as American Society of Anesthesiologists Physical Status (ASA-PS) II (94%) and one patient as ASA-PS III, while the mean preoperative serum albumin was 3.9 mg/dl (range 2.8-4.6 mg/dl).

Operative details

Of all patients, eight (44%) underwent total pelvic exenteration (TPE) with or without sacrecttomy (8 patients; 44% and 6 patients; 33%, respectively). One patient underwent palliative pelvic exenteration, and three patients (17%) underwent abdominosacral resection, combined with high subcortial sacrectomy (HiSS) (1 patient), HiSS with extended lateral pelvic sidewall excision (ELSiE) (1 patient), or extralevator APR (A patient) (Table 2).

TABLE 1. Type of cancer distribution and the respective percentages in our cohort.

Type of cancer	Number of patients (N= 18)
Recurrent cervical	2 (12%)
Rectal cancer	
Locally advanced rectal cancer	8 (44%)
Locally recurrent rectal cancer	8 (44%)
1st recurrence	6 (36%)
2nd recurrence	2 (12%)

TABLE 2. Types of procedures utilised. TPE, total pelvic exenteration; ASR, abdominosacral resection; HiSS, high subcortical sacrectomy; ELSiE, extended lateral pelvic sidewall excision; ELAPE, extralevator abdominoperineal excision

Type of procedure	Number of patients (N= 18)	Percentage
TPE with low sacrectomy	8	44.4%
TPE	6	33.3%
Palliative TPE	1	5.6%
ASR with HiSS	1	5.6%
ASR with HiSS and ELSi--Ele	1	5.6%
ASR with ELAPE	1	5.6%

Urinary reconstruction was necessary in 17 patients (94%); 16 of them underwent ileal conduit, and one patient was subjected to end-to-side uretero-ureteric anastomosis (Table 3). Plastic reconstruction was required in 12patients (67%), with bilateral gluteal flap being the most frequent option (7 of 12 patients; 58%). Other flaps used were unilateral gluteal flap (2 patients), vertical rectus abdominis (VRAM) flap (1 patient), unilateral gluteal and sartorious flap (1 patient), and bilateral gracilis flap (1 patient) (Table 3).

Postoperative outcomes

The mean and median hospital stay were 36 and 31 days Respectively (range 18-68 days), and 30-day mortality was 0%. Complications were classified according to Clavien-Dindo (C-D) classification, with major complications (grade ≥ III) occurring in 7 cases (39%): Clavien Dindo I (0%); Clavien Dindo II (11 patients; 61%); Clavien Dindo IIIa (3 patients; 17%); Clavien Dindo IIIb (4 patients; 22%); Clavien Dindo IV (0%) (Table 4). Most prevalent complications, as shown in Table 4, were bloodstreami nfections (10 patients; 56%) and surgical site infections (SSIs); SSIs included superficial abdominal would infection (9 patients; 50%) and deep abdominal wound infection (3 patients; 17%) , as well assuperficial(3 patients; 17%) and deep flap infection (5 patients; 28%) . Three patients (17%) developed organ-space infection (pelvic abscess), requiring percutaneous drainage.

Leaks occurred in 2 patients (12%); one from the small-bowel anastomosis and one from the ileal conduit.

TABLE 3. Urinary and plastic reconstruction techniques utilised. VRAM, vertical rectus abdominis myocutaneous flap.

Type of reconstruction	Technique	Number of patients (N= 18)
Urinary Reconstruction	Ileal conduit	16 (88.9%)
	End to side ureteric anastomosis	1 (5.6%)
	Not needed	1 (5.6%)
Plastic reconstruction	Bilateral gluteal flap	7 (38.9%)
	Unilateral gluteal flap	2 (11.1%)
	VRAM flap	1 (5.6%)
	Bilateral gracilis flap	1 (5.6%)
	Unilateral gluteal plus sartorius flap	1 (5.6%)
	Not needed	6 (33.3%)

TABLE 4. Clavien-Dindo classification of perioperative complications. CNS, central nervous system; ICU, intensive care unit.

Clavien-Dindo classification	Definition	Number of patients (N=18)
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	0 (0%)
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	11 (61%)
Grade III	Requiring surgical, endoscopic or radiological intervention	7 (39%)
-IIIa	*Intervention not under general anaesthesia*	3 (17%)
-IIIb	*Intervention under general anaesthesia*	4 (22%)
Grade IV	Life-threatening complication (including CNS complications) requiring ICU management	
- IVa	*single organ dysfunction (including dialysis)*	0 (0%)
- IVb	*multi organ dysfunction*	0 (0%)
Grade V	Death of a patient	0 (0%)

Additional complications were acute respiratory failure (3 patients; 17%), psychiatric disorders (3 patients; 17%), pulmonary embolism (2 patients; 11%), flap haematoma/bleeding (2 patients; 11%), postoperative haemorrhage (1 patient; 6%) and burst abdomen (1 patientl 6%). Re-operation with general anaesthesia was necessary in 4 cases (22%) due to the following: postoperative bleeding from the internal iliac artery (1 patient), ileo-ilealanastomoticleak (1 patient), burst abdomen (1 patient), and severe expanding flap haematoma (1 patient) (Table 5).

Histopathology

The final pathology report showed that an R0 resection was achieved in 16 patients (89%). One patient had an R1 resection (6%), and an R2 resection was noted in another patient (6%), who underwent palliative TPE. Of the 16 patients with rectal cancer, 12 (75%) were staged as T4b, with the tumour invading adjacent structures, and 7 patients (44%) had tumour deposits (pN1c). Both patients with cervical cancer were classified as pT4N0. Additional biopsy data are shown in Table 6.

TABLE 5. Type of perioperative complications occurred. SSIs, surgical site infections.

Type of complication	Number of patients
Bloodstream infection	10 (56%)
SSIs	
Superficial abdominal wound infection	9 (50%)
Deep flap infection/ dehiscence	5 (28%)
Organ Space SSIs (Pelvic collection)	3 (17%)
Superficial flap infection	3 (17%)
Deep abdominal wound infection	3 (17%)
Return to the operation theatre	4 (22%)
Respiratory Failure	3 (17%)
Psychiatric disorders	3 (17%)
Anastomotic leak	2 (12%)
Ileal conduit leak	1 (6%)
Small bowel anastomosis leak	1 (6%)
Flap haematoma/ bleeding	2 (11%)
Pulmonary embolism	2 (11%)
Burst Abdomen	1 (6%)
Post-operative intraabdominal bleeding	1 (6%)

TABLE 6. Pathology report of surgical specimens. TNM stages with no patient representation were omitted. EMVI, Extramural Venous Invasion; LVI, Lymphovascular invasion; TD, tumour deposits; PNI, perineural invasion; 1patients with cervical cancer; 2 patients with rectal cancer.

Pathology report	Number of patients (N= 18)
R status	
R0	16 (89%)
R1	1 (6%)
R2	1 (6%)
EMVI	
EMVI+	2 (11%)
EMVI-	16 (89%)
LVI	
LVI+	5 (28%)
LVI-	13 (72%)
TD	
TD +	8 (44%)
TD-	10 (56%)
PNI	
PNI+	2 (11%)
PNI-	16 (89%)
T status	
pT3	3 (17%)
pT41	2 (11%)
pT4a2	1 (6%)
pT4b2	12 (67%)
N status	
pN0	10 (56%)
pN1a	1 (6%)
pN1c	7 (39%)
M status	
pM0	17 (94%)
pM1c	1 (6%)

DISCUSSION

Pelvic exenteration (PE) has undergone substantial evolution over recent decades, shifting from a primarily palliative operation in gynecologic practice to a potentially curative intervention with excellent outcomes for selected patients with advanced pelvic malignancies [3,4].

Our study examined all patients who underwent a pelvic exenteration procedure in our institution in a 20-month

period, focusing on the operative and reconstructive details and the perioperative morbidity associated with the procedures.

PE, although first described for gynaecologic malignancies, it is now widely and increasingly used for both rectal and non-rectal advanced pelvic malignancies, including urological, gynecological and anal cancers and sarcomas [9]. In our study, apart from patients with recurrent cervical cancer, half the other patients had advanced primary (N=8) and the other half recurrent rectal cancer (N=8).

The most frequently utilised procedure in our patients was a total pelvic exenteration (TPE). Based on preoperative MRI interpretation or intraoperative findings, involved or threatened sacrum and presacral tissues were resected en bloc, below the level of S2 vertebra. In three cases, a more organ-preserving approach—abdominosacral resection (ASR)—was selected. Two adjunctive techniques were utilised: high subcortical sacral resection (HiSS), which preserves pelvic stability and avoids neurological complications associated with dissection along the lateral sacral edges [10] and extended lateral pelvic sidewall excision (ELSiE), which can significantly increase R0 resection rates if the pelvic sidewall is involved [11,12].

In addition to pelvic exenteration performed with curative intent, palliative PE, aimed at relieving intractable cancer-related symptoms, was performed in one patient. It is feasible and regarded safe when practiced in specialised centers, but durable symptom palliation with corresponding improvement or maintenance of quality of life has not been demonstrated, leaving the palliative role of this operation highly controversial in this complex patient population [13].

Reconstruction of the urinary system in our patients primarily involved the creation of a non-continent diversion with an ileal conduit. It involved the creation of an isolated ileal loop with one end being used for ureteric anastomosis and the other being exteriorised as a stoma contralaterally to the colostomy. Other frequent urinary diversion techniques that are being used after a TPE include the colonic conduit, double barrel wet colostomy, and bilateral permanent nephrostomies [14-19]. The ileal conduit, compared with the colonic conduit, has been associated with similar urological and major (Clavien Dindo ≥III) complications rate, and overall 30-day and in-hospital mortality, but with a higher rate of postoperative ileus (~21% versus 7%) and an risk of an ileo-ileal anastomotic leak (~3%), since it involves an additional anastomosis [14]. The colonic conduit, on the other hand, appears to have higher rates of abdominal or perineal surgical-site infections (~31% versus 14%) [14]. Another study found comparable urinary leak rates but fewer total urinary-related complications in the colonic conduit patients (~19% versus 40%) [15].

The double-barrel wet colostomy (DBWC), a modern alternative to the classical wet colostomy described by Brunschwig [1] and largely abandoned due to high morbidity [16], although adding the difficulty for both patients and stoma carers in the postoperative management of combined fecal and urinary discharge, has been shown in comparative studies to have outcomes similar to those of the ileal conduit [16-19].

Plastic reconstruction of the pelvic floor and the perineal defect is often required after a pelvic exenterative procedure. Myocutaneous or fasciocutaneous flaps, biological or synthetic meshes, omentum or combination strategies are being used, although there is no strong evidence to suggest one option over another and the choice is highly individualised and tailored to the patient's needs and expectations [20,21]. Commonly used flaps include the Vertical Rectus Abdominis Myocutaneous (VRAM) flap, gluteal-based flaps, including the Inferior Gluteal Artery Perforator (IGAP), the Inferior Gluteal Artery Myocutaneous (IGAM) and the V-Y advancement flap, and thigh-based flaps, including the gracilis, sartorius and the anterolateral thigh flap [20-25]. The VRAM flap is considered a good option due to its capacity to restore large defects, but this comes at the cost of increased donor area morbidity, while the anterolateral thigh flap is a good option, primarily if two stomas are to be created bilaterally, since it can cover large defects and avoids abdominal wall weakening but at the cost of a high dehiscence rate [20]. In our cohort, we primarily used a modified bilateral gluteal V-Y advancement flap, resembling a "hammock" flap, to provide stable coverage and obliterate pelvic dead space. This flap has been shown to be a reliable and acceptable novel technique, particularly in irradiated fields, which can obliterate dead space with satisfactory functional and aesthetic outcomes and minimise donor-site morbidity [26].

Perioperative morbidity in our study was acceptable and in line with the literature [8,27,28], with most patients (61%) experiencing minor (Clavien-Dindo(C-D)<III)and 39% major (C-D ≥ III) complications, while there were no grade IV or grade V complications. Median and mean hospital stay in our institution were 31 and 36 days respectively, significantly longer than the corresponding values (median~11-16 days; mean 14.5-19.9 days) reported in larger studies [2,8,27,28]. This may be partly explained by the fact that methods and techniques are not standardised and automatised among medical personnel, and delays occur upon inter-specialty collaboration.

Centralisation and the creation of reference centers are of utmost importance for improving outcomes and minimising morbidity among pelvic exenteration patients

[29]. Although such centers exist worldwide, they are scarce or even not existent in many smaller countries, such as Greece, where a recent survey among surgeons who practice pelvic exenteration reveals severe and widening disparities across the country [30].

This study is limited by its retrospective case-series design, small sample size, absence of standardised surgical techniques and postoperative follow-up protocols, and lack of comparative data, which precludes drawing definitive conclusions. Nevertheless, the findings demonstrate that pelvic exenteration is feasible with acceptable morbidity when performed in dedicated high-volume institutions. Establishing such centers as referral hubs, and adding teaching, collaboration, and research opportunities to the "triad" of careful patient selection, appropriate decision-making, and refined surgical technique—the dictum of success for pelvic exenteration surgery as highlighted by Kontovounisios 2024 [29]—would likely lead to improved outcomes and a reduced morbidity profile.

CONCLUSION

Pelvic exenteration represents a complex but increasingly refined surgical strategy that offers a potential curative option for selected patients with advanced and recurrent pelvic malignancies. The findings of this study demonstrate that, despite being technically demanding and necessitating extensive multivisceral resections and complex reconstructions, pelvic exenteration can be performed with acceptable perioperative morbidity and high rates of R0 resection in a specialised, high-volume setting. Although limited by its retrospective structure and small sample size, this study highlights the feasibility and safety of pelvic exenteration when undertaken by experienced multidisciplinary teams. Centralisation of care and the establishment of dedicated reference centers are essential steps toward standardizing practice, reducing morbidity, and improving overall patient outcomes.

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Case Report

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A rare case of Colorectal Cancer in a patient with polyposis and an NTHL1 gene mutation

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ABSTRACT

NTHL1 polyposis syndrome (or FAP-3 syndrome) is a rare familial polyposis syndrome with only 72 reported cases worldwide from 50 different families. A 54-year-old male presented with a change in bowel habits and an incidence of blood in the stools. Colonoscopy demonstrated over 60 polyps and a suspicious cecal lesion with high grade dysplasia on biopsy. Genetic panel testing tested positive for NTHL1 mutation. Subsequently he was operated on with a subtotal colectomy in order to manage the cecal lesion and the polyposis syndrome. A colorectal adenocarcinoma with a squamous feature of the cecum was diagnosed. The patient was the first of his family with a cancer diagnosis. Finally, he was released after 10 days with no major complications. His family was informed about the inheritance characteristics of the syndrome and was advised properly. This is a rare case of familial polyposis syndrome with an NTHL1 gene mutation. APC and MUTYH are the most common gene mutations among patients with FAP. Clinicians should be aware of such mutations and advise patients and families properly.

Key Words: *Case Report; polyposis; NTHL1; colorectal cancer*

INTRODUCTION

The protein encoded by NTHL1, endonuclease III-like protein 1 (NTHL1), is a DNA glycosylase of the base excision repair pathway that removes endogenously damaged nucleotides in DNA [1].Mutations in this gene cause NTHL1 tumour syndrome (or NTHL1 polyposis syndrome, or FAP-3 syndrome) which is an autosomal recessive syndrome characterised by an increased lifetime risk for colorectal cancer (CRC), breast cancer, and colorectal polyposis, as well as endometrial cancer [3], urothelial carcinoma of the bladder, meningiomas [8], unspecified brain tumours, basal cell carcinomas, head and neck squamous cell carcinomas, and haematologic malignancies [5]. Colorectal polyps can be adenomatous, hyperplastic, and/or sessile serrated. Duodenal polyposis has also been reported. NTHL1 tumour syndrome has been described in 50 families with 72 affected individuals.The cumulative lifetime risk of developing extracolonic cancer by age 60 years has been estimated at 35% to 78% [5]. Almost all (93%) homozygous patients have colonic adenomas on colonoscopy, while among heterozygous carriers the percentage is 38% [3]. These patients are at high risk of developing CRC as half of the patients (37 out of 72) developed CRC with a median age of onset at 51 [2]. In most cases it was a right-sided cancer but cancers in the rest of the colon were also found. Heterozygotes do not seem to have an increased risk [4]. To date, diagnostic criteria for NTHL1 tumour syndrome have not been established. Individuals in whom the syndrome should be suspected include those with presence of multiple primary cancers before the age of 50, colorectal cancer (CRC) diagnosed

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before the age of 40, one or more colorectal adenomas in an individual aged ≤40 years, a personal cumulative lifetime history of ten or more colorectal adenomas in an individual aged ≤60 years, a personal cumulative lifetime history of any combination of 20 or more colorectal adenomas, hyperplastic polyps, and/or sessile serrated polyps in an individual of any age or a family history of NTHL1 syndrome [5]. Molecular genetic testing should be performed in these individuals [6].

NARRATIVE

Patient Information

A 54-year-old male individual presented with a reported recent incidence of blood in the stools and a change in his bowel habits. Medical history included hypertension under medication, and he did not report any family history of bowel cancer. He had undergone an appendicectomy at a young age. Endoscopic assessment revealed more than 60 polyps in total from 2mm to 40mm, one of which was located at the cecum and raised a high suspicion of malignant transformation. Biopsies were taken from several polyps.

The biopsies summarised in Table 1 resulted as follows: (A) Cecum lesion biopsies: Parts of a villotubular adenoma with high-grade dysplasia. B-catenin with a pathological expression pattern. (B) Transverse colon polyp: Pedunculated polyp with low grade dysplasia and at some spots high grade dysplasia, excluded within healthy limits. B-catenin with a pathological expression pattern. (C) Rectal polyps: 8 small parts of rectal polyps that originated from a hyperplastic polyp and a sessile serrated lesion with no dysplasia but with a change in the crypt architecture. The above lesions were checked for microsatellite instability and were found to be MSI stable.

The patient had a staging CT of the thorax and the abdomen with IV contrast. The thoracic CT was normal with no findings compatible with metastatic lesions. The CT of the abdomen showed the polyps in the colon, specifically the 35-mm cecum lesion, a 15-mm sessile polyp in the sigmoid colon and a 20-mm pedunculated polyp in the rectum. Some lymph nodes less than 7-mm were found next to the inferior mesenteric artery and on branches of the superior mesenteric artery. No findings of metastatic or peritoneal disease were reported.

TABLE 1. Endoscopic biopsy results.

Type of biopsy	Location	Result
Parts of villotubular adenoma	Cecum	High grade dysplasia
Pedunculated polyp	Transverse colon	Low grade and at some spots high grade dysplasia
8 small parts of rectal polyps	Rectum	Parts of hyperplastic polyps – no dysplasia
Sessile serrated lesion	Rectum	No dysplasia – change in crypt architecture

Finally, the patient had molecular genetic testing from a blood sample as FAP was a probable diagnosis. As the patient had more than 10 polyps on colonoscopy, a multigene panel including genes causing Polyposis or associated with a high risk for CRC was considered necessary [14]. A test including 52 of them was performed, including those suggested by the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer [10]. Twenty-eight of them are mentioned in Table 2. APC, MUTYH, BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2, NTHL1 and several other genes were included in the panel. In the NTHL1 gene the individual was found homozygous for a NM_002528:c.268>T,p.(Gln90*) mutation. This is a mutation in the 268th nucleotide base of the NTHL1 gene that causes an alteration in which glutamine is substituted by a termination codon. The protein produced is an inactive protein [7]. This mutation has been described in individuals with attenuated polyposis and colorectal cancer [8]. He was also found heterozygous for a mutation in the NF1 gene. The mutations in this gene cause Neurofibromatosis type 1 (NF1), an autosomal dominant disorder with several clinical features that include benign and malignant tumours [9]. As mentioned above there was no clinical feature indicative of neurofibromatosis type 1. Furthermore, NF1 is generally not associated with colonic adenocarcinomas.

Multidisciplinary discussion suggested proceeding to surgical intervention taking into consideration the clinical presentation and imaging.The objective was the management of the polyposis syndrome and the excision of the suspicious cecum lesion. Surgical options discussed with the patient were as follows:

1. Right hemicolectomy
2. Subtotal colectomy with IRA (ileorectal anastomosis)
3. Total proctocolectomy with IPAA (ileal-pouch anal anastomosis) with J-Pouch
4. Total proctocolectomy with end ileostomy

Therapeutic Intervention

After a detailed discussion with the patient all the therapeutic choices were reviewed. The patient and his family were also informed about the inheritance pattern of the gene, and they were advised to speak with an expert geneticist. A laparoscopic subtotal colectomy with an ile-

TABLE 2. Sample of genes tested for mutations.

Gene	Reference Sequence	Result	Zygosity	Clinical significance
APC	NM_000038	No Mutation	-	-
ATM	NM_000051	No Mutation	-	-
AXIN2	NM_004655	No Mutation	-	-
BMPR1A	NM_004329	No Mutation	-	-
BRCA1	NM_007294	NoMutation	-	-
BRCA2	NM_000059	NoMutation	-	-
CDH1	NM_004360	NoMutation	-	-
CDK4	NM_000075	NoMutation	-	-
CHEK2	NM_007194	NoMutation	-	-
EPCAM	NM_002354	NoMutation	-	-
MEN1	NM_000244	NoMutation	-	-
MLH1	NM_000249	NoMutation	-	-
MSH2	NM_000251	NoMutation	-	-
MSH3	NM_002439	NoMutation	-	-
MSH6	NM_000179	NoMutation	-	-
MUTYH	NM_001128425	NoMutation	-	-
NF1	NM_000257	NM_000267:c.49992G>A, p.(Trp1664*)	Heterozygous	pathogenic
NTHL1	NM_002528	NM_002528:c268C>T, p.(Gln90*)	Homozygous	pathogenic
PALB2	NM_024675	NoMutation	-	-
PMS2	NM_002528	NoMutation	-	-
PTEN	NM_000314	No Mutation	-	-
RAD50	NM_005732	NoMutation	-	-
RET	NM_020975	NoMutation	-	-
RAD51C	NM_058216	NoMutation	-	-
RAD51D	NM_002878	NoMutation	-	-
SMAD4	NM_005359	No Mutation	-	-
STK11	NM_000455	No Mutation	-	-
TP53	NM_000546	NoMutation	-	-

orectal anastomosis was performed.The rationale behind this decision was that this operation is a safe choice, less radical than other interventions. As no malignancy was detected in the rectum, sparing of the rectum can provide acceptable functional outcomes for a patient of his age. It also achieves excision of all the colon, reducing the risk for a future incidence of CRC and does not include the creation of a stoma, either permanent or temporary. The patient was informed of the need for frequent rectoscopies and the possibility of the need for a more radical intervention in the future.

Outcomes

According to the pathologist's report of the surgical specimen, the cecum tumour was a pT3N1b adenocarcinoma of intermediate differentiation, with a squamous feature in less than 50% of the total mass. The tumour, infiltrating the pericolic fat, was 5 x 4.5 cm, and 2 out of 46 lymph nodes were found positive. Perivascular infiltration was detected. The rest of the colon was found to contain numerous polyps sized from 0 to 18mm (Figures 1 - 2) that were listed according to the distance from the surgical boundaries and the size of the polyp.

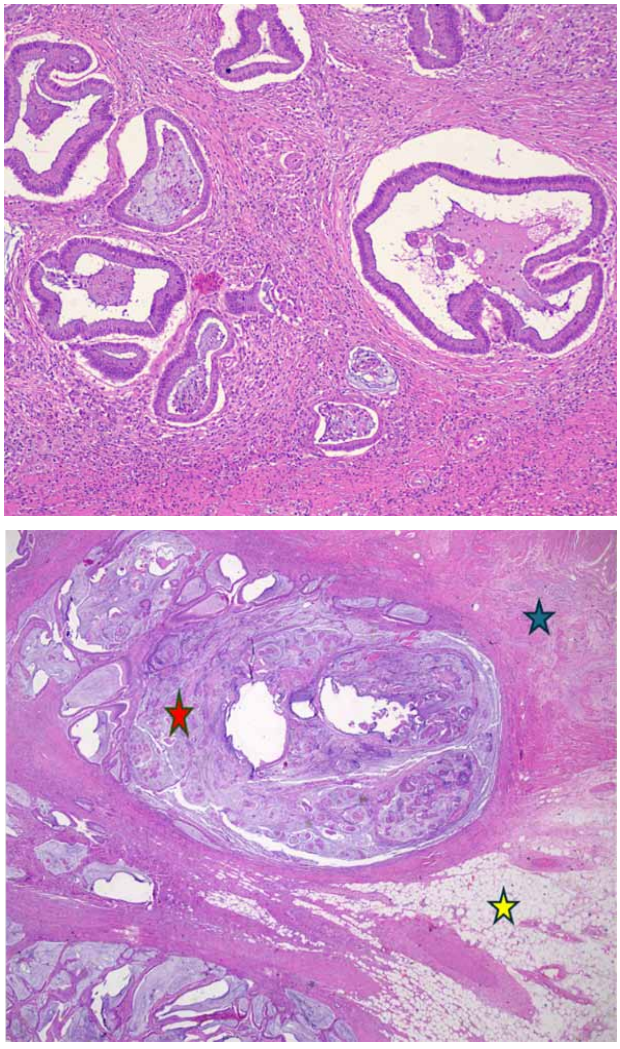

FIGURE 1. Colorectal adenocarcinoma composed of neoplastic gland invading muscular propria ★ and the pericolic fat tissue ☆. Presence of extracelular mucin in <50% of the adenocarcinoma ★.

The pathologist report was discussed in the oncological MDT, and the administration of adjuvant chemotherapy was suggested.

DISCUSSION

This is a case report of a rare case of familial adenomatous polyposis and colorectal cancer in an individual with a homozygous NTHL1 mutation, which is called NTHL1 polyposis syndrome or FAP-3. Our purpose is not to suggest guidelines or diagnostic and therapeutic approaches, but to raise awareness of this syndrome as up to now it is reported to affect only 72 individuals among 50 families [2]. These patients are at high risk of developing colorectal cancer. From our experience patients with more than 10 polyps, or young patients less than 40 years old with polyps on a colonoscopy should

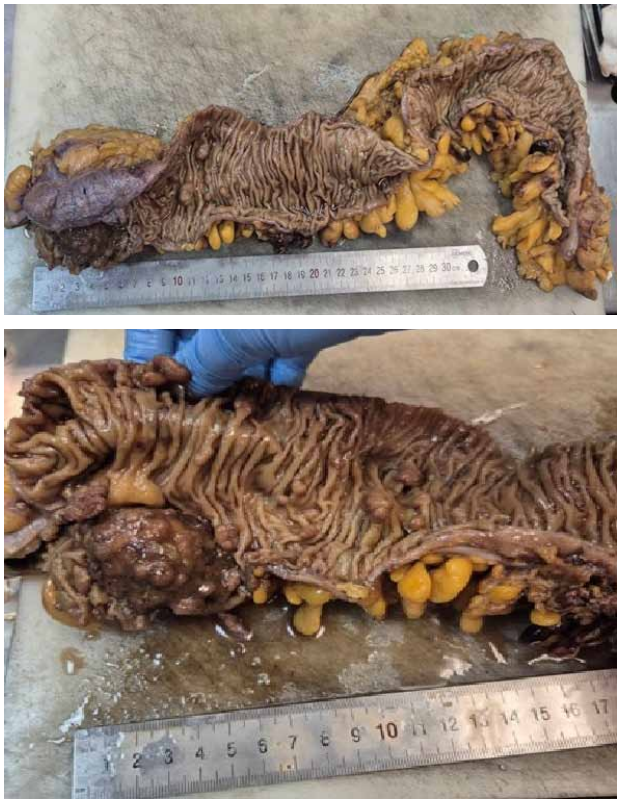

FIGURE 2. Up: Surgical specimen of subtotal colectomy. Numerous polyps can be detected throughout the colon and a cecum lesion on the left of the figure. Down: Ascending colon. The cecum lesion can be seen more closely. Several polyps can also be detected.

be suspected of having a familial polyposis syndrome. Thus, they should be candidates for molecular genetic testing [14). Except for the most common APC and MUTYH gene mutations, there are other less frequent mutations [8) like those of NTHL1, that can cause such syndromes. In such patients it is reasonable to take endoscopic biopsies from several lesions across all parts of the colon and rectum, with more attention to more suspicious lesions. Gene testing should be the next step. A multigene panel is a reliable way of molecular genetic testing with the advantage of the inclusion of several possible mutations that may cause the same phenotype [10). Patient and family consultation is of utmost importance firstly because such syndromes need radical surgical intervention that can affect the quality of life, and secondly because they have a hereditary pattern and they can affect other family members [2). An oncological MDT including surgeons, geneticists, oncologists and pathologists could amplify this process. As far as therapeutic intervention is concerned radical colectomy should be the first option including Right hemicolectomy, subtotal colectomy, total proctocolec-

tomy with IPAA with J-Pouch, and total proctocolectomy with end ileostomy. The patient's characteristics such as age, comorbidities, way of life and preferences should be seriously considered in the decision making and options should be discussed with the patient. Possible dangers, the way quality of life is affected, and the need for future follow-up related to each therapeutic choice should be analysed for the patient. In general, such syndromes are diagnosed in younger patients, with NTHL1 polyposis syndrome affecting patients less than 60 years old in most cases, who have an active way of life [3]. In these cases, subtotal colectomy with ileorectal anastomosis and regular endoscopic evaluation of the rectum afterwards, or total proctocolectomy with J-pouch anastomosis could be reasonable solutions, as they exclude all or most of the colon and provide a good quality of life.

In our case, subtotal colectomy with ileorectal anastomosis was chosen as it was considered safe and with the optimal functional results for the patient. As mentioned above, sparing of the rectum can provide an acceptable functional outcome for a patient of his age.It also achieves excision of all the colon, reducing the risk for a future incidence of CRC, and does not include the creation of a stoma either permanent or temporary. The patient was informed and agreed with a close follow-up with frequent rectoscopies and accepted the possibility of the need for a more radical intervention in the future.

Squamous features in colorectal adenocarcinomas represent a rare subtype of colorectal cancer accounting for 0.06-0.18% of cases. Due to its rarity, immunohistochemical and biological profiles have not been well investigated, anda specific percentage cut-off necessary for each componentto characterise it as adenosquamous has not been established, as with other gastrointestinal adenosquamous malignancies. This feature predisposes to an aggressive clinical course in several case series, often diagnosed at later stages and with lower overall survival than typical adenocarcinomas [13). To our knowledge, there is no other case of NTHL-1 colorectal adenocarcinoma with a squamous feature reported.

Regarding the heterozygous NF1 variant, Neurofibromatosis type 1 is a soft-tissue autosomal dominant condition. Individuals with NF1 are at high risk of several malignancies [9). Some molecular mechanisms may indicate a connection between NF1 gene mutations and sporadic colorectal cancers [12). Yet, there has not been any association described between this condition and colorectal cancer including several cohort studies [11). Consequently, in this case, this mutation was considered incidental.

CONCLUSIONS

Not all familial polyposis syndromes are caused by the most described genes APC and MUTYH. There are more genes, like NTHL1, with such a phenotype. Therefore, molecular genetic testing in proper candidates is important to determine the responsible gene which helps clinicians give proper therapeutic advice as well as appropriate family guidance. NTHL1 polyposis syndrome is a newly described syndrome, so clinicians should be informed about it. Subtotal colectomy and close follow-up due to the risk of other malignancies in the future seem like a reasonable approach. Such cases should be reported as they are uncommon. More data are necessary to better determine its clinical manifestations and therapeutic approach.

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Declaration of interest statement:
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Fluorescence-guided laparoscopic adrenalectomy: A step-by-step technique

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ABSTRACT

Indocyanine green (ICG) fluorescence is emerging as a valuable aid during laparoscopic adrenalectomy (LA), providing intraoperative assistance in the identification of the adrenal vein and the delineation of adrenal anatomy and tumour margins. Herein, we describe our standardised technique of injecting ICG at two different stages of LA, including patient selection and stepwise execution. We also share our experience, having performed over 67 ICG fluorescence-guided LAs, along with practical tips for overcoming initial technical difficulties. We believe that ICG in LA may play a role in the teaching process of junior surgeons, in challenging cases of LA as an assisting adjunct, and in selected cases of cortical-sparing LA.

Key Words: *Laparoscopic adrenalectomy; ICG imaging; fluorescence-guided laparoscopy; cortical-sparing adrenalectomy; minimally invasive adrenalectomy*

INTRODUCTION

Laparoscopic adrenalectomy (LA) has become the standard of care for most benign adrenal lesions since its first description in 1992 [1]. Although the procedure is well-established, the conditions requiring treatment by LA are rare, making it difficult for many young surgeons to gain sufficient operative experience. Fluorescence-guided laparoscopy with the use of indocyanine green (ICG) has emerged as valuable a tool to enhance a surgeon's ability to discern between different types of tissues during minimally invasive surgery [2]. The fluorescent properties of ICG can be utilised during LA, to visualise the margins of the adrenal gland, identify the adrenal vein and even delineate the tumour borders from the normal adrenal gland [3].This article provides our accumulated experience from 67 cases of fluorescence-guided LAs, with a step-by-step description of the technique, along with useful tips and tricks to facilitate adoption of this technique.

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Rationale for the use of ICG in adrenal surgery

The most challenging and time-consuming step of an LA is the identification of the adrenal vein. It is therefore logical that an intraoperative fluorescent angiographywith the use of ICG, which will improve a surgeon's ability to safely and quickly identify the adrenal vein, is a valuable tool. In addition, ICG, when injected intravenously, binds to plasma proteins and therefore its concentration and fluorescence are proportional to a specific organ's blood supply. When taking under consideration that adrenal glands possess the third highest blood flow in the abdomen, early adopters of the technique hypothesised that ICG will prove valuable in adrenal surgery, as most anatomical

landmarks of the procedure can be easily distinguished from their surrounding tissue.

Patient selection and perioperative considerations

After a thorough review of the literature, a protocol was created, in which all patients undergoing LA were considered eligible for ICG administration. ICG has no known metabolites according to the literature, so no adverse effects have been reported [4]. A contraindication to ICG administration is allergy to iodine-containing agents, so it was decided that such patients were to be excluded from the protocol.

SURGICAL TECHNIQUE

Operating room setup and patient positioning

The right equipment is of paramount importance for the completion of this procedure, as a laparoscopic tower with fluorescence imaging capabilities and an infrared (IR) camera are needed. We use a VISERA ELITE II 3D Imaging System (Olympus Medical System Corp., Tokyo, Japan) with an Olympus laparoscopic tower (Olympus Medical System Corp., Tokyo, Japan). The equipment is calibrated, and we make sure that we can switch from the conventional laparoscopic view to ICG imaging by pressing one button on the laparoscopic tower. Successful integration of fluorescence imaging requires close coordination with the anaesthesiology team, so the ICG dye, diluted in water for injection, is prepared prior to the operationand placed near the anesthesiology table and clear instructions are given to the anesthesiologists about ICG injection prior to the procedure. A lateral decubitus position, with the table flexed to around 30° is selected for the operation, as this position enhances the accessibility of the surgical field. In left adrenalectomies three trocars are used, whereas in right adrenalectomies a fourth trocar is needed, to retract the liver (Figure 1). An IR camera, capable of activating and capturing ICG's fluorescent capabilities, is used from the beginning of the operation, to minimize the additional time of the fluorescence imaging component of the operation.

Initial stages

Since right and left LA are two different operations, we will describe the initial steps in each procedure, immediately before the first dose of ICG, to clarify the purpose of ICG administration.

In right LA, the assisting surgeon retracts the liver and the operating surgeon divides the liver's retroperitoneal attachments. The right liver lobe is mobilised laterally to achieve good high subhepatic access in the lateral region.

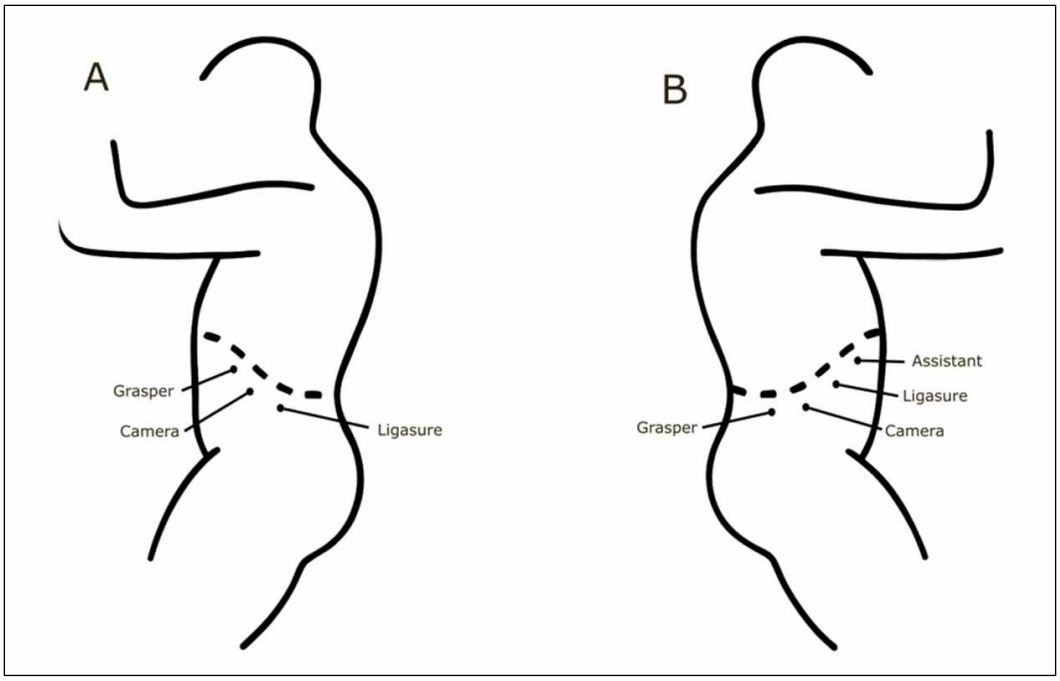

FIGURE 1 A) Trocar placement in left laparoscopic adrenalectomy. A 12 mm camera port in the subcostal area and two 5–10 mm working ports (the midclavicular and anterior axillary lines)were placed. B) Trocar placement in right laparoscopic adrenalectomy. A 12 mm camera port in the subcostal area and two 5–10 mm working ports (the subcostal region near the mid-clavicular line and the posterior axillary line) were placed along with a fourth trocar (at the right of the umbilicus) to retract the liver.

With the adrenal gland being gently pushed caudally with a grasper holding a gauze, we divide the retroperitoneum along the edge of the liver. After identifying the anatomic plane of the adrenal gland and before any further dissection of the gland or any vascular manipulation is performed, the first dose of ICG is administered, as will be described later. The adrenal gland is further dissected, and the adrenal vein is identified. In our series, ICG imaging delineated the course of the adrenal vein prior to visual identification in most cases. The next step is the careful dissection of the adrenal vein. This is the time frame for the administration of the second ICG dose. Then, the adrenal vein is ligated and divided with electrocautery. This is the most crucial step of the procedure, as the adrenal vein drains, after a very short distance, directly into the inferior vena cava. The final steps include the complete dissection of the adrenal gland, which is placed in an endobag and extracted from the abdomen.

In left LA, the splenic flexure of the descending colon is mobilised and retracted medially. The ligaments of the spleen are divided and both the spleen and the pancreas are mobilised anteriorly and retracted medially, until we reach the anatomic plane of the left kidney and adrenal gland. Again, the first dose of ICG is injected before any further dissection of the adrenal gland or vascular manipulation occurs. The adrenal gland is identified and further dissected, while the adrenal vein is visualised in most cases by fluorescence imaging in this study, before visual confirmation. The procedure continues as described for right LA.

ICG preparation and administration

In accordance with the published literature, we reconstitute the ICG by adding 10 cc of sterile water for injection (WFI) to a vial containing 25 mg of ICG, providing a final concentration of 2.5 mg/cc. ICG is administered in two doses at different time points during the surgery, with each serving completely different purposes.

The first dose is administered immediately upon identifying the adrenal gland, intentionally preceding visual identification of the adrenal vein. The aim of this first fluorescence imaging is to quickly and accurately distinguish the adrenal vasculature, as well as the margins of the adrenal gland. This technique can prove particularly useful, reducing operating time and increasing the safety of the operation, as it facilitates timely identification of the principal anatomical landmarks required to safely complete the operation.

The second dose is administered after the adrenal gland and the adrenal vein have been further dissected. The purpose of this is to identify the adrenal tumour, as most of the times the tumour exhibits different fluorescence intensity compared with the normal adrenal gland. If this is the case, the margins of the tumour are delineated, which can serve as the leading point of excision when cortical-sparing adrenalectomy is the choice of operation. In addition, in complicated cases involving huge adrenal tumours, adrenal fluorescence clearly defines its margins and improves the surgeon's ability to perform the operation safely.

DISCUSSION

Right and left LA are two different procedures; therefore, it is only natural to expect different results when ICG imaging is involved. The most profound difference is the presence of the liver, as it exhibits higher fluorescent intensity than its surrounding tissues, adrenal included, so it poses a challenge in the early stages of the ICG experience. We believe that this challenge is overcome with experience. In our study, we recorded each procedure individually, and after every 10 right-sided LAs we performed a structured review to enhance our familiarity with the technique and analyse our observations.

Another important note is that the administration of ICG and the fluorescence imaging do not prolong the procedure, if adequate preparations have taken place preoperatively and there is some experience with the technique. On the contrary, the use of ICG enhanced our ability to quickly identify the adrenal vein, in most of the cases, especially in left-sided LAs, which, in our experience, can lead to decreased operating times. This remains an observation of our team through experience, as it was not an endpoint of our study, and further research is required to confirm this.

Our surgical department places strong emphasis on surgical education and training. Fluorescence-guided laparoscopic adrenalectomy represents a valuable educational tool, particularly for trainees. It facilitates the most technically demanding step of the procedure, the identification of the adrenal vein, thereby enhancing visual guidance. Indocyanine green (ICG) fluorescence allows precise localisation of the vein, enabling safe and effective ligation. Furthermore, the use of ICG supports surgical training by providing a reproducible and standardised approach, thereby enhancing teaching within the department.

The optimal use of ICG imaging in LAs has not yet been established. However, there is a strong focus in the literature on cortical-sparing adrenalectomy. The study by Kahramangil et al., including 100 patients which

is the largest number up to date, reports that 67% of pheochromocytomas appear "hypofluorescent" compared to its surrounding tissues, which means that they exhibit lower fluorescent intensity than them. It is suggested that in 2 cortical-sparing robotic adrenalectomies performed, the technique proved to be useful, as it enhanced the surgeon's ability to delineate the tumour margin, as the adrenal gland was more fluorescent than the pheochromocytoma [5]. This is also suggested by the study of Lerchenbergeret al., involving three partial adrenalectomies, where the modality was useful in the two pheochromocytomas included [6].

Our findings are consistent with the existing literature, as pheochromocytomas in our series also demonstrated relative hypofluorescence compared to the surrounding adrenal cortex. Similar observations have been reported previously, including in our prior study [7], further supporting the reproducibility of this fluorescence pattern.

CONCLUSION

In this study, we presented a novel technique, fluorescence-guided LA. We found that the technique has a relatively short learning curve and is easily reproducible. We believe that even though ICG imaging during LAs should not yet be considered a routine technique, as its optimal use is not yet defined, surgeons should become familiar with it, as it can prove useful in complex cases and in cortical-sparing laparoscopic adrenalectomy.

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Conflict of interest: *Nothing to declare*

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Development of a novel Virtual Reality simulation training curriculum for laparoscopic transabdominal preperitoneal inguinal hernia repair

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ABSTRACT

Background: Advances in modalities such as Virtual Reality (VR) laparoscopic simulators have led to their widespread implementation in surgical training. Various modules exist, spanning across basic tasks and even segmented procedures. For one of the most common surgical procedures performed, laparoscopic transabdominal preperitoneal (TAPP) inguinal hernia repair, a structured training curriculum can be developed for future surgeons, and shorten the learning curve of training. Practicing the associated techniques in a complication-free environment, prior to application in the operating theatre, is a crucial aspect of safe and effective training, which can be achieved through VR simulators.

Material and Methods: The development of the program will include an arm of ten expert general surgeons and an arm of thirty novice general surgery trainees performing a group of three tasks at a single Simulation Center. Analysis of their performance will be used to test face and construct validity of the program. Data acquired will also be assessed based on Messick's framework.

Results: Data from the development will be analysed to formulate the preliminary curriculum proposal. The success baseline will be defined according to experts' performance data and will be adjusted to novices' level (±1 SD). A Delphi consensus will ultimately be conducted to formulate the final curriculum parameters.

Conclusions: In light of technological advances that reshape medical education, VR simulators are transformative in surgical skill acquisition while engaging trainees effectively. In order to utilise their full potential in effective training, evidence-based curricula are necessary. They can contribute to skill acquisition to a predetermined level of proficiency before progression to more challenging cases and can objectively evaluate each trainee. Such validated training curricula will result in more efficient skill acquisition and retention, ultimately contributing to better patient outcomes.

Key Words: *Laparoscopic training curriculum; virtual reality (VR); simulation; laparoscopic inguinal hernia; surgical training*

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The emerging need to train future surgeons and evaluate their acquired skills in a safe and controlled environment led to the development of simulation. Simulation is now an integral part of surgical training with the use of "box trainers", as well as more advanced modalities such as Virtual Reality (VR) simulators. Its ultimate goal is that

skills acquired in VR modalities are transferable to actual operating room performance, especially for laparoscopic procedures. Through VR simulators it is feasible to train on basic skills, as well as on full operations, according to preset objective criteria [1-3].

Worldwide, over 20 million inguinal hernia repairs are performed annually, making it one of the most common surgical procedures [4]. In the context of the rapid development of modern medicine, various surgical modalities for the treatment of inguinal hernia through laparoscopic techniques have arisen. Therefore, it is necessary for trainees to familiarise themselves with the associated techniques in a complication-free environment, to avoid pitfalls that could lead to patient harm. Simulation tools such as box trainers have played a major role in achieving this goal. However, such modalities are ideal for the initial development of fundamental skills. VR simulators using haptic feedback, visual guidance and objective performance criteria, can help provide a more holistic training as well as a more objective assessment, before trainees apply their skills in the operating room.

Through the implementation of established scientific research methods and by recording the performance of experienced surgeons and novice trainees, a structured Virtual Reality simulation training curriculum in laparoscopic transabdominal preperitoneal (TAPP)inguinal hernia repair can be designed. Such curriculum will ultimately contribute to more efficient training in this common surgical procedure.

PROGRAM DEVELOPMENT

Developing the index Virtual Reality simulation training curriculum for laparoscopic TAPP inguinal hernia repair will take place at the AKISA Simulation Lab, Attikon Campus, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece. The equipment used will be the VR simulator LAP Mentor III (Simbionix Corporation, Cleveland, Ohio, USA). The software on which the educational program will be developed is the Inguinal Hernia Module v. 1.0.1.169.

The sample size will involve forty participants with specific selection criteria. One of the two arms will include ten experts, defined as specialised surgeons who perform over 25 laparoscopic inguinal hernia operations yearly and have no previous experience in VR simulation. The second arm will comprise thirty non-experts, defined as novice-general surgery residents, who have already completed the Basic Skills program in the VR simulator but have not practiced at the inguinal hernia module.

The above-mentioned group of forty participants will perform three tasks, each focusing on a crucial phase of the inguinal hernia repair operation. For both groups the frequency of practice will be one attempt per day, lasting 40 minutes. For experts, three attempts will be required for three consecutive days, and for novices, three attempts per week until achievement of performance plateau in the scale metrics.

Task description

Task 1 – Anatomy Identification

The anatomy identification task provides an opportunity to become familiar with the anatomy of the inguinal region and identify the anatomical landmarks essential for the TAPP technique for inguinal hernia repair. Pathology involves a right inguinal hernia. The objective of the task is to inspect the operative field and identify the important anatomical structures.

Task 2 – Incision and Dissection

The incision and dissection task allows for practicing an accurate peritoneal incision, performing a safe dissection and gentle reduction of the hernia sac, and preparing a peritoneal flap for further mesh placement. A variety of complications and emergency situations such as injuries to the vessels, vas deferens, nerves, or bladder, are included.

Task 3 - Mesh Placement and Fixation

The mesh placement and fixation task allows for practicing the accurate positioning of the mesh over the primary hernia defect, performing a safe fixation of the mesh to the anterior abdominal wall and closure of the peritoneum. A variety of complications and emergency situations such as injuries to the vessels, vas deferens, nerves, or bladder, are included.

Recording and storage of data

Each participant's performance data will be extracted directly from the simulator and the manufacturer's existing software and stored in a spreadsheet file (Microsoft Excel, Microsoft, Redmond, Washington, USA). Data will be anonymised using a key/ascending number. Only the Principal Investigator and the Academic Supervisor of the protocol will have access to the matching file. Each participant will complete a written consent form for the purpose of using their performance data in this research project.

Statistical processing

The statistical processing of the data will be performed using the statistical processing package SPSS

v25 (IBM, Chicago, Illinois, USA). Descriptive statistics will consist of the median and interquartile range for numeric variables, and the absolute number and percentage of the total for non-numeric variables. The normality of the data distribution will be examined by visual analysis of frequency histograms, and by applying the Kolmogorov-Smirnov test. For continuous numerical data with a normal distribution, parametric tests (t-test, ANOVA, Spearman correlation) will be applied. For continuous numerical data with a non-normal distribution, non-parametric tests (Mann-Whitney-U test, Independent Samples Median Test) will be applied. For non-numerical data, χ^2 and Fisher's exact test will be used. The learning curves will be analysed using the serial comparison method, or the CUSUM analysis method, or the ROC/AUC method (depending on the characteristics of the data). Where possible, two-tailed tests will be applied. P-values <0.05 will be considered statistically significant, and p-values from 0.05 to 0.1 will be considered statistically suggestive. The level of agreement between two or more measurements of parameters will be investigated using concordance analysis.

Program planning

After the completion of the statistical analysis of the data, the program planning will take place. The estimated duration of the program will be determined by the average time (weeks) during which trainees' learning curve approach the baseline of success, defined by experts' opinion, relevant literature, and experts' performance. The success/pass baseline will be set based on the experts' performance data and adjusted to the trainees' level (±1 SD). The "Construct validity" [5] and "Face validity" [6] parameters of the training program will be tested with two different methods. The validity of the program will be assessed based on "Messick's framework" which is now the most widely accepted method [7].

Additionally, each participant will respond to a questionnaire before the start of the index program, regarding expectations, and after completion of the program regarding evaluation, comments, suggestions and observations about the whole experience. Approval has been granted from the Bioethics committee of the School of Medicine, National and Kapodistrian University of Athens (#1128).

Delphi consensus

A group of expert surgeons will take part in the Delphi consensus which is an iterative process aiming to reach a unified opinion on the proposed completion benchmarks of the module [8]. The involved panelists will be supplied with recorded videos of the performed tasks, raw data captured and learning curve analysis. The process will consist of multiple rounds of anonymous questionnaires, allowing experts to share and revise their views without the bias of direct interaction. Questions will refer to technique steps, selection of appropriate metrics and determination of the successful pass threshold. This process will ultimately lead to a structured consensus on curriculum development, aiming to accurately hone the skills needed for inguinal hernia repair on a real patient. The analysis of the data collected by the Delphi consensus will be performed with descriptive, qualitative methods and final curriculum parameters will be proposed.

Communication of results

The results of the index study and training curriculum will be presented in seminars and domestic or international conferences as well as in international scientific journals. The main areas of discussion will involve potential integration of the VR inguinal hernia repair curriculum in comprehensive training programs, in combination with classic box trainers and live tissue labs. Moreover,future research directions can include external validation and implementation of the curriculum. The concordance of the results among participants from different institutions can be investigated to formulate the final curriculum implementation among independent populations. Finally, its impact on actual clinical practice can be investigated, through translational research, by comparing trainees' actual performance in the operating theatre before and after attending the curriculum.

Conflicts of interest: *None*

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A proposed protocol for personalised prediction of opioid response in oncology patients with chronic pain using machine learning methods combining genetic and clinical factors

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ABSTRACT

Opioids are a cornerstone treatment for chronic pain in oncology patients, yet individual response varies widely due to genetic differences in CYP2D6 enzyme activity, which governs the metabolism of codeine and tramadol. Patients are classified into four metaboliser phenotypes, each associated with distinct efficacy and side-effect profiles. The current study proposes a research protocol integrating genetic and clinical data through machine learning models (WEKA, Omics-CNN) to predict individual opioid response. Patients from the Hippocration Pain Unit will undergo CYP2D6 genotyping and standardized pain assessment. The aim is to develop a predictive tool to support personalised, evidence-based opioid prescribing in cancer pain management.

Key Words: *Opioid response; chronic cancer pain; machine learning; CYP2D6 enzyme*

INTRODUCTION

Opioids play a crucial role in managing chronic pain among cancer patients. Their pain-relieving effects stem from their action on μ-opioid receptors, which are encoded by the OPRM1 gene [1]. The hepatic metabolism via the cytochrome P450 (CYP450) enzyme activates the analgesic action of opioids like codeine and tramadol [4]. However, patients differ in their metabolism of analgesics. Genetic differences in CYP450 enzymes impact how a patient responds to medications, influencing both their effectiveness and the risk of side effects like nausea, constipation, or even respiratory issues [2]. The genetic variations, in combination with clinical factors, result in a wide range of responses to opioid therapy. Based on these genetic variations, patients are classified into four metaboliser phenotypes: ultrarapid, extensive (normal), intermediate, and poor [4,5]. The key characteristics of each group are summarised in Table 1.

The high complexity of genetic variations and their interactions with clinical factors presents challenges in predicting individual responses to opioid therapy. Machine Learning algorithms can integrate large, heterogeneous datasets and analyze both the role of individual variables and their interactions in shaping the outcome.

In current literature it has been examined the genetic effects in opioid response. Although, the CYP2D6 plays a crucial role in opioid metabolisation of tramadol and codeine, does not explain alone the full heterogeneity of opioid response. Polymorphisms in other genes, such as ABCB1, COMT, OPRM1 have been implicated in opioid metabolism in patients.

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TABLE 1. Metaboliser phenotypes groups.

Metaboliser phenotype	Characteristics
Ultrarapid Metaboliser	These individuals express multiple functional copies of the CYP2D6 gene, leading to accelerated drug metabolism. The hypermetabolism may lead to reduced drug efficacy due to rapid metabolism and thus the need for higher doses to achieve therapeutic levels, posing a risk of toxicity.
Extensive (Normal) Metaboliser	Extensive Metabolisers typically have functional alleles that facilitate efficient drug metabolism. However, variability within this group can affect drug response and may require individualised therapeutic approaches.
Intermediate Metaboliser	These metabolisers possess alleles that confer intermediate enzymatic activity, resulting in a metabolic rate between that of Poor Metabolisers and Extensive Metabolisers. Intermediate Metabolisers may require dose adjustments or closer monitoring to ensure optimal therapeutic results.
Poor Metaboliser	Individuals with minimal or no CYP2D6 enzyme function due to homozygous or compound heterozygous inheritance of non-functional alleles. Individuals in this category may exhibit reduced metabolic rates, leading to increased drug exposure and increased risk of adverse reactions.

There is limited research, applying machine learning techniques to the analysis of opioid response specifically in chronic cancer pain populations. Previous studies have either focused solely in the role of demographic and clinical data in opioid response or have drawn insufficient conclusions regarding different genetic factors. There is currently a lack of integration of machine learning approaches into predicting patient response to opioids.

The present study aims to address this gap in the literature by analysing both genetic and clinical data, examining their individual and combined contributions to patients' responses to opioid therapy. This study presents a proposed research protocol. Patient recruitment and data collection are underway.

Protocol and Implementation

This study sets out to build a machine learning model that can predict how individual patients will respond to opioids by analysing both their genetic makeup and clinical data. The study will include patients who are monitored in the Hippocration Pain Unit, suffering from chronic pain of benign or malignant aetiology and requiring treatment with weak opioids (codeine or tramadol). Patients with proven contraindication to the administration of paracetamol, codeine or tramadol, serious psychiatric or neurological disease under treatment, history of epilepsy or craniocerebral injury, serious cardiac-renal-hepatic insufficiency under treatment, severe chronic obstructive pulmonary disease, severe sleep apnoea, history of allergic reaction to the administered substances, history of substance and alcohol abuse, pregnancy/lactation, age <18 years and patient refusal will be excluded.

During the initial visit, a comprehensive medical and pain history will be obtained, including concomitant medications and baseline pain intensity, and a blood sample will be collected. To standardise data collection, a predefined questionnaire has been developed to ensure consistent medical history for all participants. Pain intensity will be evaluated through close follow-up, by using the Numeric Rating Scale (NRS 0-10) as well as the Brief Pain Inventory (Greek version). The reassessment of pain intensity and the patient's response to analgesics will be done after 72 hours, where the percentage of pain relief and all adverse effects from the use of the medications will be recorded, with a positive or negative answer in specific questions. The pain level after the therapy and the adverse effects will be documented in the initial patients' record. If in the follow-up, the pain levels are NRS <4 or at least a 50% reduction in pain intensity, this will be considered a positive drug response. Codeine and tramadol will be administrated randomly, in a titrated dosage, depending on the age and co-existing diseases of each patient. Specific dosage ranges and increments will be defined in the finalised protocol. Blood samples, will be stored refrigerated at -20° C until analysis. For analysis, genetic material will be isolated from 2 ml of peripheral blood of each participant and will be applied either Real-time PCR (Polymerase Chain Reaction) or PCR-RFLP (Restriction Fragment Length Polymorphism) for the 16 for the 16 clinically significant polymorphisms of the CYP2D6 gene *1XN, *2, 2A, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41[6].

A sufficient sample size is required in order to draw meaningful conclusions. The aim is to recruit 50 patients per group. After collecting the genetic data, an anonymised Excel spreadsheet will be created to combine all genetic and clinical data for each participant, along with their treatment response. In the final stage

of the analysis, a detailed, high-dimensional model, integrating genetic and clinical data, will be developed, tailored to forecast responses specifically to tramadol and codeine in cancer patients. In order to determine the optimal predictive model, multiple experiments will be performed using different machine learning and deep learning approaches.

All algorithmic approaches will be conducted using the WEKA software, ensuring standardised implementation and reproducibility of results. Furthermore, the study will assess the effectiveness of a tailored Convolutional Neural Network for analysing genetic data (Omics-CNN) [7]. In the initial stages, the Local Outlier Factor method and Principal Components Analysis (PCA) will be applied to identify potential outliers.

Algorithms performance will be reviewed based on discrimination (AUC), overall accuracy, and calibration of predicted probabilities. In the initial analyses, all individual features from each sample will be treated equally, with no predefined weighting on their impact on the final outcome.

Following model training, t-tests and the Minimum Redundancy–Maximum Relevance (mRMR) [7] method will be applied to assess the contribution of individual variables, as well as their combined interactions, in shaping the final predictions. The computational model is expected to provide predictions and useful knowledge, leading to more tailored pain management strategies.

The predictive framework will be used as basis for the creation of an API tool for clinical use in personalised opioid prescribing.

CONCLUSION

The protocol introduces an innovative approach to **opioid** therapy in chronic cancer pain management by integrating machine learning into clinical practice, by combining genetic and clinical data so as to minimise **opioid**-related side effects and support a more personalised approach to patient therapy. The use of such a tool can help identify patients who are likely to respond positively to tramadol or codeine and those at higher risk for adverse effects. Tailoring treatment based on genetic profiles may reduce trial-and-error prescribing, enhance positive outcomes, reduce the risk of adverse effects, and optimise analgesic efficacy.

This study can be expanded to either integrate data of patients under multimodal analgesia, or to examine the role of other genetic factors in **opioid** response. From this perspective, valuable insights could be gained regarding the combined effects of multiple genetic variants. The high performance of deep learning models stems from their ability to generalise effectively to new data. This is why there is a strong demand for integrating large and diverse datasets into these algorithms. However, the high cost of blood analysis, poses significant challenges in expanding by increasing the sample size. To overcome the challenge posed by the high cost of collecting genetic data, model performance will additionally be assessed using open-access genetic datasets, so as to evaluate the generalisability of the algorithm. Ongoing validation and refinement will enhance the model for future clinical application, ultimately improving the quality of life for oncology patients.

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Brief Communication

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Threats to surgical decision-making in a crisis

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ABSTRACT

Surgical decision-making is a complex, high-stakes process requiring a blend of clinical expertise, emotional regulation, situational awareness, and rapid judgment. Like pilots, surgeons often rely on both established protocols and instinct when navigating crisis situations. While structured frameworks—such as "Avoid, Trap, Mitigate"—enhance decision quality, emotional factors like hunger, anger, loneliness, tiredness, pain, and stress (HALT-PS) can significantly impair judgment. These emotions may cause errors of omission, commission, or flawed planning, contributing to surgical complications or "Never Events." Simulation-based training, team communication, and adaptive protocols derived from aviation have been shown to enhance crisis performance and mitigate human error. Over-reliance on technology without contingency planning, such as robotic tools, further jeopardises outcomes. Ultimately, the surgeon bears the burden of decisions that can determine life or death. Recognising and mitigating emotional and systemic vulnerabilities is vital for safe, patient-centred surgical care.

Key Words: *Decision making; emotions; patient safety*

INTRODUCTION

The basic guideline is "would you have this done to yourself, your wife, your child, your parent?"

Mark M. Ravitch (1910–1989)

Surgical decision-making involves a systematic approach to evaluating clinical scenarios, utilising evidence-based guidelines, and considering various factors to ensure optimal patient outcomes. It is a critical process that encompasses the evaluation of patient conditions, the selection of appropriate surgical interventions, and the management of potential risks and complications. It is guided by evidence-based practices and protocols that enable surgeons to navigate complex clinical scenarios effectively. However, there are crisis occasions when a surgeon often goes by their 'gut feeling,' which have a foundation in their training and experience, and yet are substantially emotional. Pilots, too at times confront crisis occasions when they act on their gut instincts and on January 15, 2009, Chesley Sullenberger and First Officer Jeffrey Skiles managed to land US Airways flight 1549 on the Hudson River and save 150 lives. Both pilots and surgeons must make rapid, high-stakes decisions during unexpected emergencies—such as engine failure mid-flight or sudden hemorrhage during surgery. These situations demand exceptional situational awareness, mental resilience, and the ability to prioritise under pressure. Both rely on extensive training, protocols, and experience, but also need adaptability when standard procedures fall short. Surgeons make complex, individual decisions during procedures, impacting a single patient, while pilots make critical decisions in a dynamic environment, potentially affecting many lives. Both professions, however, are vulnerable to errors due to fatigue, stress, and cognitive biases.

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Human factors in Surgical response

Simulation-based training in both fields enhances cognitive flexibility and crisis response. Real-time data, teamwork, and calm leadership are critical to minimising harm. The shared emphasis on non-technical skills and structured responses underpins their ability to perform life-saving decisions within seconds. A study recommended the 'Patient, Procedure, People' protocol, a tool adapted from aviation threat and error management training. It allows surgical teams to improve situational awareness, effective communication, flatten hierarchical gradients, and improve decision-making before responding to critical events [1]. The study found poor decision-making, with resulting errors due to tunnel vision, acute stress reactions (fight–flight or freeze–hide) and limbic hijacking (surprise and startle events). Air Accident Investigation Branch (AAIB) concluded that fatal accidents are frequently caused by pilots flying outside their own personal limits, those of the aircraft, or the environment. Similarly, for a surgeon, patient morbidity or mortality may occur if they work outside their personal capability, with poor procedure selection and patient optimisation, or with a team or theatre environment not suited to the procedure [2]. For the surgeon, another aspect of poor decision making is too much dependence on the surgical tool, like a robot or laparoscope, without an alternative bailout option applied, as described by Abraham Maslow as the "law of the instrument" or "Maslow's hammer" as "it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail" [3]. Both pilots and surgeons must make critical decisions under pressure, but their approaches and priorities differ. Pilots rely on established protocols and automation, aiming to maintain situational awareness and anticipate potential problems. Surgeons, while also valuing situational awareness, may need to act more rapidly in life-threatening situations, sometimes improvising based on their expertise and the specific context.

Surgeons sometimes make terrible decisions when they rely solely on their emotions, which can sometimes change in the blink of an eye, along with the justifications for the actions they've taken or the merits of certain actions. This is because strong emotions intensely focus our thinking and neutralise the influence of other inputs from the environment, logic, various reminders, and past decisions. The evidence-based crisis management framework in surgery has been based on the commercial aviation industry policy of "Avoid, Trap, and Mitigate."Avoid prevents harm through preparation; Trap corrects emerging failures; Mitigate contains crises to stabilise situations, prioritising safety, teamwork, and critical decision-making [4].

In surgery, decision-making situations come with alarming regularity. There are life-or-limb-threatening situations that a surgeon encounters often, and every time he/she is challenged to make a correct decision, because the alternative can prove to be costly for the patient. So, should a particular trauma patient be sent to the operating theatre for early surgery or to radiology for an accurate diagnosis, can a pregnant woman wait for a normal delivery or be taken for a Cesarean section, should this dismembered lower limb be sacrificed or replanted are decisions which a surgeon is expected to take almost every day. Yes, they are trained to do so, and yes, there are Standard Operating Procedures (SOPs) and, most importantly, there is Artificial Intelligence (AI) to fall back upon today, but the ultimate responsibility is that of the surgeon.

However, there are times when we falter, and make a wrong decision, usually by bypassing the SOPs. Why do you think this happens? Over the years, we have, from our experience, realised that six human emotions are the real culprits. We must be aware of them and know how to neutralise them to improve our decision making.

Ken Shubin Stein, who started as a professor at Columbia University Graduate School of Business, then decided to become a neurologist to know how the mind works, uses the acronym **HALT-PS** to describe these six factors that impair our judgment [5]. These are:

- **H**unger
- **A**nger
- **L**oneliness
- **T**iredness
- **P**ain
- **S**tress

These six emotions are a big stop sign. They shouldn't be ignored lest we end up with a surgical complication due to a human error (*act of commission*, *act of omission*, *error of execution*, and *error of planning*), communication error, system failure, or equipment failure [6].There are experiences from everyday life that clearly prove that these six emotions are real culprits in decision-making, and yet are not always clearly linked to bad decision-making. These six emotions somehow don't allow us to see the full picture, which probably includes many important details and many different facets. For instance, having interrupted his dinner a surgical registrar might have to rush to attend a head injury patient but while doing a detailed neurological examination and establishing the Glasgow Coma Scale score, he is still remembering the dinner that awaits him in his cabin, and in this rush forgets to examine the abdomen and so misses a solid organ trauma, which is the cause of shock! He is trained to examine the entire patient, but hunger has clouded

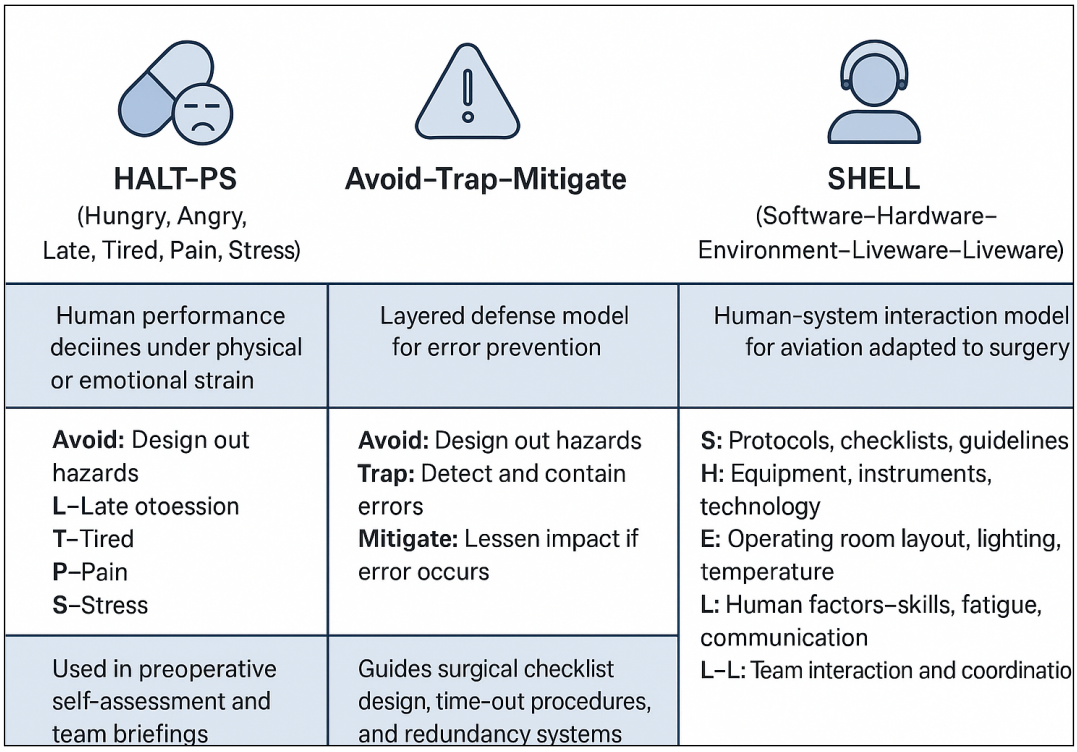

FIGURE 1. Key frameworks (HALT-PS, Avoid–Trap–Mitigate, SHELL) and their application to surgery.

his decision-making. There is a current **lack of robust evidence and empirical data** directly linking specific interventions like the proposed HALT-PS to a quantitative reduction in actual surgical errors. Research in this area often highlights the systemic challenges in tracking and reporting surgical error data and acknowledges that many widely used safety protocols, such as the Universal Protocol, have not been evaluated through randomised controlled studies with actual patient outcomes.

A surgical "Never Event" is a preventable error occurring immediately before, during, or immediately following surgery and to prevent 'Never Event', "one size fits all" safety approach should not be the dictum and each Operating Room should perform a risk assessment relative to the occurrence of Never Events during a specific surgery and make tailored adjustments in the safety standards [7].

Framework and analogy from the aviation industry

Literature always compares the role of surgeons versus pilots whenever there is a crash or accident, but the fact remains that excessive use of the aviation-healthcare safety paradigm in surgery can lead to misleading generalisations and end-user disengagement. Both pilots and surgeons are trained professionals, but a surgical operation is more variable and volatile than aeronautical engineering without any radar or sophisticated gadgets for turbulence control or bailout option in the middle of the surgical procedure when the patient bleeds or gasps, making the surgeon's job highly risky, hazardous, challenging, and unpredictable [8]. The best protocol for a surgeon to follow in a crisis is probably the SHELL model, which was originally developed for aviation human factors analysis. The SHELL model in surgery emphasises interaction between Software (protocols, checklists), Hardware (equipment), Environment (light, noise), and Liveware—both individual (surgeon, anaesthetist) and group (team dynamics). It highlights how human factors influence performance, decision-making, and patient safety within the complex environment of the operating theatre, promoting systems-based surgical safety [9].

Practical Recommendations for Surgeons

In a nutshell, hunger, anger, loneliness, tiredness, pain, and stress are the emotions that are most dangerous to our decision-making, and for a surgeon, they may prove fatal. It's not always possible to assess their impact on us before making important decisions, but it's worth trying, and over time, we can develop greater awareness of these emotions and be able to avoid decisions that we might regret later. Remember, being aware of these emotions doesn't mean they'll disappear, and it's very hard to neu-

tralise them without taking action. So, if necessary, it is better for the surgeon to go for healthy food to combat hunger, call a loved one for a short conversation, lie down for a half-hour rest, or take any similar action to ensure he is the mental state that allows him to make the best decisions.

The cognitive engineering strategies for surgical error management in cardiothoracic surgery are task shedding (task shedding involves deliberately reducing or deferring less critical tasks when cognitive load is high, for example, during a cardiac arrest or unexpected bleeding), intelligent interruption systems (interruptions during surgery (e.g., phone calls, monitor alarms, or conversations) can disrupt concentration and cause mistakes. Intelligent systems ensure that only essential alerts reach the surgeon during critical phases), sterile cockpit (borrowed from aviation, the "sterile cockpit" rule limits nonessential communication during high-risk periods of surgery), short breaks (a 2–3 minute "microbreak" during long valve repairs helps maintain steady hands and sharper decision-making, preventing fatigue-related errors), team strengthening (enhances coordination, mutual trust, and error recovery. Teams that communicate effectively can recognise and correct small errors before they escalate), pre-incision time-out (ensures shared situational awareness and prevents "wrong site" or "wrong patient" errors), safety systems for device interoperability (integrating and coordinating multiple devices (anesthesia monitors, bypass machines, defibrillators, etc.) to share data and avoid conflicting outputs), workload-adaptive associate systems (these are smart, artificial intelligence -assisted systems that dynamically adjust assistance levels based on the surgeon's or team's workload.), and cognitive aids for high-risk/low-frequency situations (structured checklists, flowcharts, or digital prompts that guide decision-making in rare but dangerous situations) [10].

CONCLUSION

Surgical decision-making in crisis situations demands not only clinical expertise but also emotional intelligence and situational awareness. While structured frameworks like "Avoid, Trap, Mitigate" and models such as SHELL enhance safety, the influence of human emotions—hunger, anger, loneliness, tiredness, pain, and stress—can compromise judgment and lead to preventable errors or "Never Events." Recognising and addressing these vulnerabilities through simulation-based training, effective communication, and self-awareness is crucial. Surgeons must balance technology, protocol, and intuition while maintaining composure under pressure. Ultimately, safeguarding patient outcomes depends on integrating technical proficiency with emotional resilience and sound cognitive control during crisis decision-making.

"*It is preferable to use superior judgment to avoid having to use superior skills*".

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Collate acknowledgements in a separate section at the end of the article before the references. List here those individuals who provided assistance during the research.

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