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Original Article

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Pelvic Exenteration for locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) in Greece: A national snapshot survey of current practice

Greek Pelvic Exenteration Collaborative
(Author names and affiliations Appendix 1)

ABSTRACT

Background: Surgical treatment of locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) relies on Pelvic Exenteration, a complex procedure with high morbidity and mortality rates and great disparities in practice across different centers internationally. The aim of this survey is to review the current perioperative management of LARC and LRRC in Greece.

Material and Methods: National Snapshot Survey disseminated online by the Hellenic Surgical Society and Greek Society of Coloproctology.

Results: Most respondents were surgeons, 22% of whom had received fellowships in pelvic exenteration surgery. 83% of the participants reported holding multidisciplinary team meetings, and typically fewer than 10 pelvic exenteration procedures are conducted annually. A total of 28% of the participants employ a validated classification system to describe the operative approach (Pelvic Exenteration Lexicon). Considering outcomes, surgical factors like length of stay (78%), ICU duration (72%), blood loss (70%) and number of blood transfusions (64%) were prioritised, whereas patient-reported outcomes focused on physical functioning (77%), quality of life (75%), and urinary function (75%). For urological reconstructions, percutaneous nephrostomy (87%), cutaneous ureterostomy (75%) and urinary diversion using an ileal conduit (73%) were utilised the most, while plastic reconstructions involved mainly mesh placement (72%), omental flap with/without a skin graft (70%) and pedicled flaps (58%). Most prevalent complications were perineal wound dehiscence, abdominal wall hernia, postoperative ileus, urinary infection and VTE.

Conclusion: Due to its complexity and low volume, experience in LARC/ LRRC is dispersed and differs among individuals. There is a need for structured, validated national guidelines to standardise methods and ensure that patients receive the highest standard of care.

Key Words: *Rectal cancer; locally advanced; recurrent; pelvic exenteration*

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INTRODUCTION

In 2024, it is expected that approximately 106,590 new cases of colon cancer and 46,220 new cases of rectal cancer will be diagnosed in the United States and an estimated total of 53,010 individuals will lose their lives due to these cancers [1].

In Greece, despite the absence of a national cancer registry to furnish reliable statistics [2], there were 1,100 newly documented cases of rectal cancer in 2022, corresponding to an age-standardized incidence rate of 9.1 per 100,000 population [3].

The primary curative treatment for rectal cancer is surgical resection accompanied by Total Mesorectal Excision (TME) [5]. Although resection and TME are associated with low tumour recurrence rates, locally advanced rectal cancer (T3-4N0M0 or T1-4 N1-2M0 tumours), poses greater challenges for achieving complete or R0 resection compared to early-stage disease [6]. Undesirably, even with optimal surgery and supplementary treatments, about 10% of patients encounter a local recurrence, with roughly half of them having solely locoregional disease [7].

The surgical approach to treating LARC and locally recurrent rectal cancers (LRRC) relies on Pelvic Exenteration (PE), a procedure originally outlined by Brunschwig for cervical cancer in 1948 [8]. PE is an extensive surgical procedure aimed at removing these malignancies radically, with the aim of a negative resection margin, by partially or completely excising nearby affected pelvic structures, including rectum, bladder, uterus, fallopian tubes, vagina, as well as major pelvic blood vessels, nerves, and pelvic bones [9]. This procedure has been found to provide a five-year survival rate for LARC between 52% to 65%, and for LRRC between 35% to 50% [10]. However not all LARC/ LRRC cases are suitable for exenteration procedures; the percentage of exenteration procedures among the total referrals of patients with LARC and LRRC, between 2010 and 2014, in a multidisciplinary colorectal cancer center in the United Kingdom, was estimated to be 41% and 16%, respectively [11].

However, it results in increased morbidity and greater functional compromise. This demands specialised perioperative care and the involvement of a multidisciplinary team of health practitioners [12]. Although there has been an effort to standardise the perioperative and anaesthetic considerations in PE and recent guidelines have been published [13], there are wide disparities in practice across different centers internationally.

The purpose of this article is to present a snapshot of the current practice in Greece, related to the perioperative management of patients undergoing a PE for LARC/ LRRC

METHODS

We conducted a cross- sectional study that focused on several important factors that rule the intraoperative management of the patients with LARC/ LRRC treated with a pelvic exenteration procedure. An online survey was structured, using the online platform of Microsoft Forms and it was sent by email to the Greek Society of Coloproctology (GSCP) and the Hellenic Surgical Society (HSS) for validation and subsequently, it was forwarded online to all their members for response. A follow-up email was forwarded after 15 and 20 days, respectively, to serve as a reminder. The results of the survey were transferred to the Microsoft Office Excel application for subsequent analysis and chart formation.

Unless stated otherwise, all percentages described below refer to the number of the responses received in the respective topic. Questions included in the survey are available at the Appendix 2.

RESULTS

We received a total of 60 replies. Except for one radiation oncologist and one medical oncologist, all other participants were surgeons, 22% of whom had undergone some form of specialised training or fellowship in Pelvic exenteration surgery. Nearly half of them (55%) have been treating patients with LARC/ LRRC for 5-20 years (Supplementary Figure 1). At our national institutions, public or private, ten or less Pelvic exenteration procedures are performed most commonly (53%), and only six participants (10%) reported higher numbers.

Pre-operative considerations

In 83 %, a multi-disciplinary team (MDT) or tumour board meeting is hosted and most participants (98%) believe that the implementation of a standardised system and template for reporting outcomes of an advanced pelvic cancer MDT should be considered. The optimal MDT handling LARC/ LRRC, according to our results, should have a designated MDT lead/chair, such as a colorectal, gynaecological or urological consultant (75%) and should be composed of many specialties, including general surgeons (95%), radiologists (86%), pathologists (75%), urologists (75%), medical and clinical oncologists (71% and 55%, respectively), gynaecologists (68%) and a clinical nurse specialist (45%). Other specialties like radiotherapists, neurosurgeons, orthopaedic and plastic surgeons and dietitians are thought to be selectively involved, depending on the case being discussed (Figure 1).

For staging purposes, a pelvic magnetic resonance imaging (MRI) scan is used by all (100%) participants and 52% of them also implement both a Computerised tomography (CT) scan and a positron emission tomography-computed tomography (PET-CT) scan. Endoscopic ultrasound (EUS) is selected by four participants (7%), always as an adjunctive to MRI for local staging (Supplementary Figure 2).

Neoadjuvant long course chemoradiotherapy and total

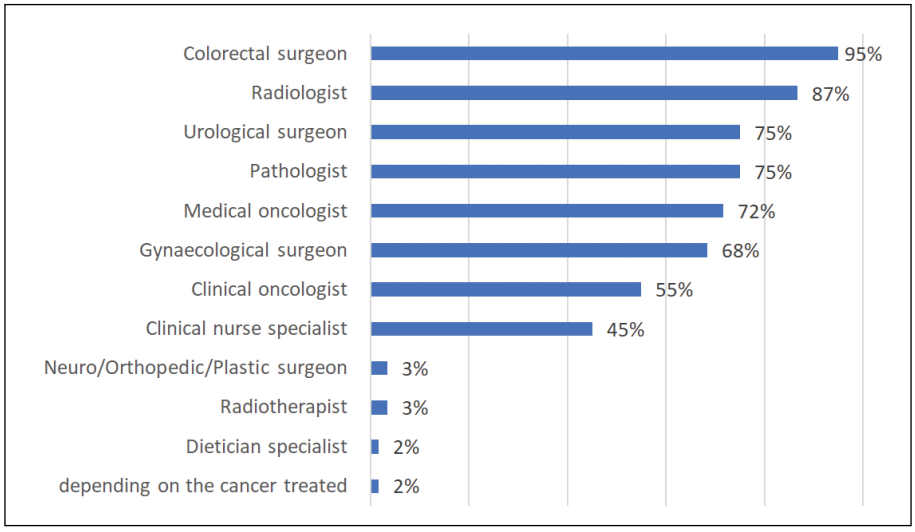

FIGURE 1. Optimal composition of an advanced pelvic cancer multidisciplinary team.

neoadjuvant treatment are the leading forms of neoadjuvant treatment applied (75% and 72%, respectively), while short course radiotherapy and immunotherapy are reported by less than half of the participants (45% and 45%, respectively) (Supplementary Figure 3). Except classical radiotherapy, brachytherapy (28%) and cyberknife (18%) are also reported as alternative/ adjunctive radiotherapy techniques, whereas other methods like proton beam therapy, intraoperative radiofrequency ablation and intraoperative radiotherapy are used infrequently (7%, 7% and 2%, respectively) (Supplementary Figure 4).

In the pre-assessment of patients undergoing PE, 85% of participants strongly believe that all patients should be admitted on the night before surgery for intravenous fluid adjustment and optimisation. The presence of a prehabilitation program to enhance the nutritional status and preoperative fitness of patients undergoing PE is practiced by 28% of the responders. The anaesthetist conducting a PE case is unanimously (97%) suggested that should personally undertake the pre-assessment of the patient.

Cardiopulmonary Exercise Testing (CPET) has been found mandatory (92%) in the pre-assessment process, and in its absence, other essential components commonly reported are image stress testing (80% of the participants, 64% of whom reported its use only if metabolic equivalent of task (MET) <4), preoperative cardiac consultation (67%), resting echocardiography (45%) and spirometry (1%) (Figure 2).

Intraoperative considerations

In the operation theater (OR), a specialised anaesthesiologist team, including nurses or Operating Department Practitioners (ODPs) who possess specific training for collaboration with the anaesthesiologist is perceived mandatory by 65% of participants. If the PE is expected to exceed 12 hours, engagement of an additional consultant anaesthesiologist, trainee anaesthesiologist, or both is considered wise (22%, 5% and 67%, respectively). Regarding the given form of anaesthesia, 53% of the participants believe that total intravenous anaesthesia (TIVA) is suitable for these cases, 5% neglect TIVA, while a significant portion (42%) refrain from expressing an opinion.

In the OR, an Arterial Blood Gas (ABG) machine is considered imperative, by most participants (75%) to be ensured, in order to minimise the need for anaesthesiologists to briefly vacate the operating theatre during Pelvic Exenteration procedures, while nearly half of them also select Thromboelastography (TEG) / clotting tests and Rapid infusers (47% and 43%, respectively) (Supplementary Figure 5).

Maintenance of a readily accessible supply of both blood products and reconstituted blood products, allowing for immediate administration upon request from an anaesthetist is considered standard of practice by most participants (90%) and transfusion of clotting products is thought vital to be guided by TEG monitoring (63%). Before commencing any case, nearly all participants (93%) cross match, group and save packed Red Blood Cells (pRBCs), with 4 units being the commonest (53%). Additionally, 48% reported saving 1 liter of Fresh Frozen Plasma (FFP) units and 22% 1 unit of pooled platelets (Supplementary Figure 6).

Tranexamic acid is preferred to be given intraoperatively, if required, at a dose of 1g or 500mg (42% and 23%, respectively), while its routine use immediately preopera-

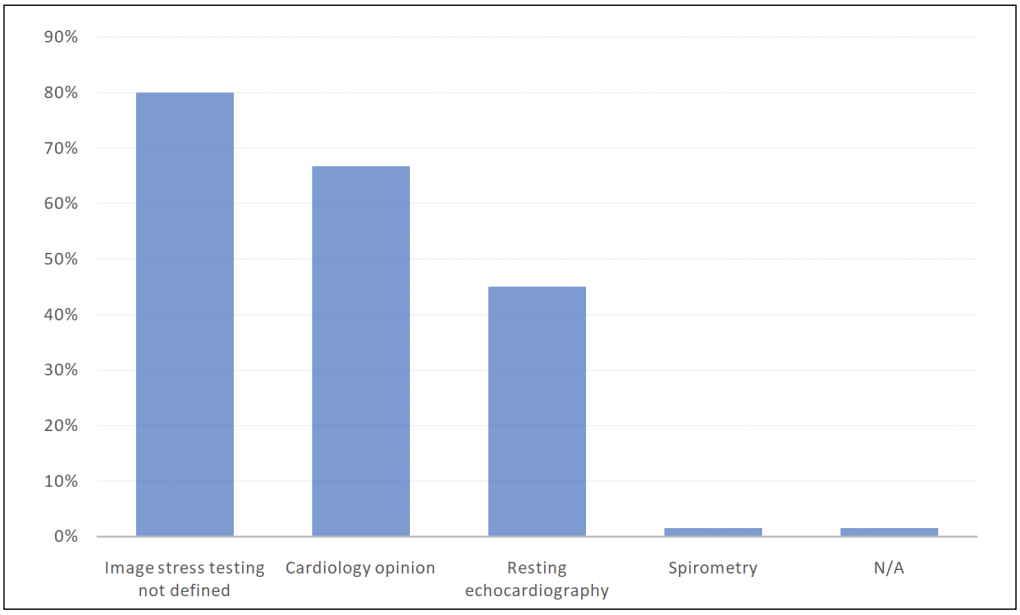

FIGURE 2. Other essential components in the preoperative assessment of Pelvic Exenteration patients, if CPET is unavailable. N/A; no answer.

tively is seldom practised (12%) (Figure 3).

For prevention of venous thromboembolism (VTE), low molecular weight heparins (LMWH) are utilised both preoperatively if the patient is admitted more than 24 hours from the time of surgery, and postoperatively (93%). The three predominantly used agents are enoxaparin (40%), Tinzaparin (28%) and Bemiparine (23%) (Supplementary Figure 7). The typical VTE prevention protocol employed (72%) is both LMWH and thromboembolic deterrent stockings (TEDs), with or without intermittent pneumatic compression devices (IPCs).

Apropos the PE procedure, a validated classification

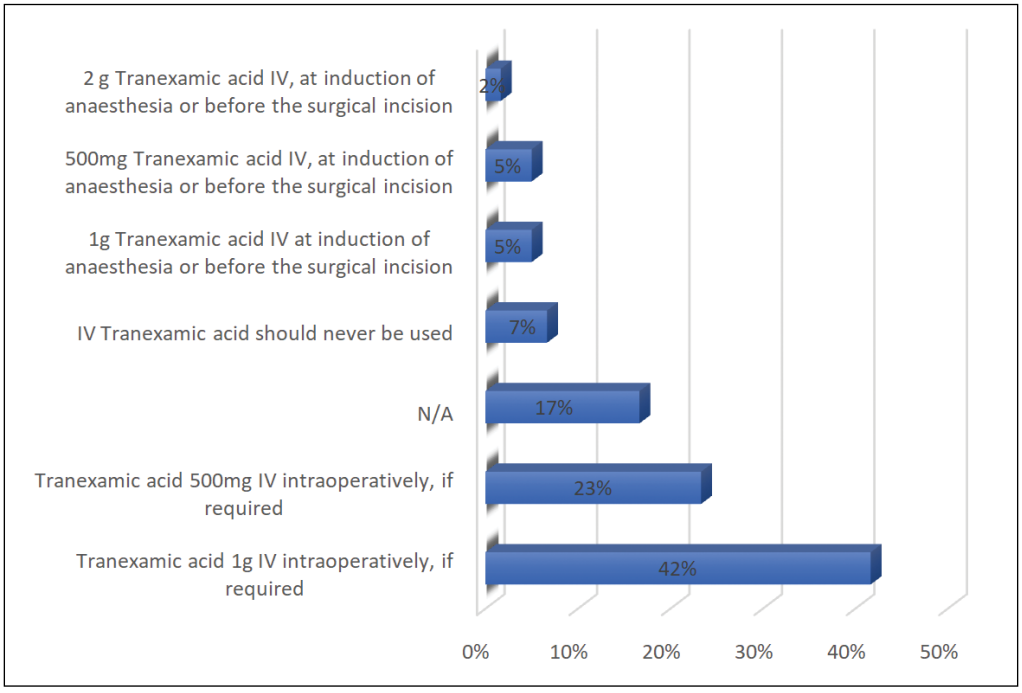

FIGURE 3. Opinions regarding the intraoperative use of IV Tranexamic acid. N/A; no answer.

system to describe the operative approach in rectal cancer (Pelvic Exenteration Lexicon) is reported to be followed by less than one third (28%) of the participants.

Plastic reconstruction options in PE cases include most frequently mesh placement (72%), omental flap with/without a skin graft (70%) and pedicled flaps (58%) (Supplementary Figure 8). Participants who utilize flaps report that the vertical or oblique rectus abdominis myocutaneous flap is the most frequently chosen option (51%) (Figure 4). Urinary diversion techniques that are most frequently utilised are percutaneous nephrostomy (~86%), cutaneous ureterostomy (~75%) and urinary diversion using an ileal conduit (~73%) (Figure 5).

Postoperative considerations

For postoperative pain management, there is an agreement (93%) that PE cases should comply with a careful postoperative pain management protocol that ensures continuous efficacy of regional anaesthesia. Most participants agree with routine, unless contraindicated, placement of epidural anaesthesia (85%) and with selection of tunneled epidural catheters (75%) in order to prolong analgesia up to 10 days. Besides epidural, paracetamol and IV opiated are most commonly involved (69% and 58%, respectively), while non-steroidal anti-inflammatory drugs (NSAIDs) are used less frequently (41%) (Supplementary Figure 9).

Commonest wound related complications are perineal wound dehiscence (73%) and abdominal wall hernia (55%) (Supplementary Figure 10). Postoperative ileus and bowel obstruction, urinary infection and VTE are the most frequently reported gastrointestinal (Supplementary Figure 11), urinary (Supplementary Figure 12) and vascular (Supplementary Figure 13) related complications (86%, 58% and 73%, respectively).

Following a PE procedure, most critical surgery- related outcomes seem to be length of hospital stay (78%), length of Intensive care unit (ICU) admission (72%) and total blood loss (70%) (Figure 6), while overall survival rates with the disease are considered the most vital (survival) outcome (64%). Interpreting the patient-related outcomes, physical status (77%), global quality of life (75%) and urinary function (72%) are considered the most essential factors (Figure 7).

Immediately postoperatively, the majority of the participants (85%) find the anticipated Systemic inflammatory reaction (SIRS) severe, which may result in haemodynamic instability and they consider imperative to transfer the patient to the ICU, ventilated and sedated, until it has subsided. The ability to predict the severity of SIRS on initial pre-assessment of the patient is debated; 40% of the participants agree, 32% disagree and 28% abstain from responding.

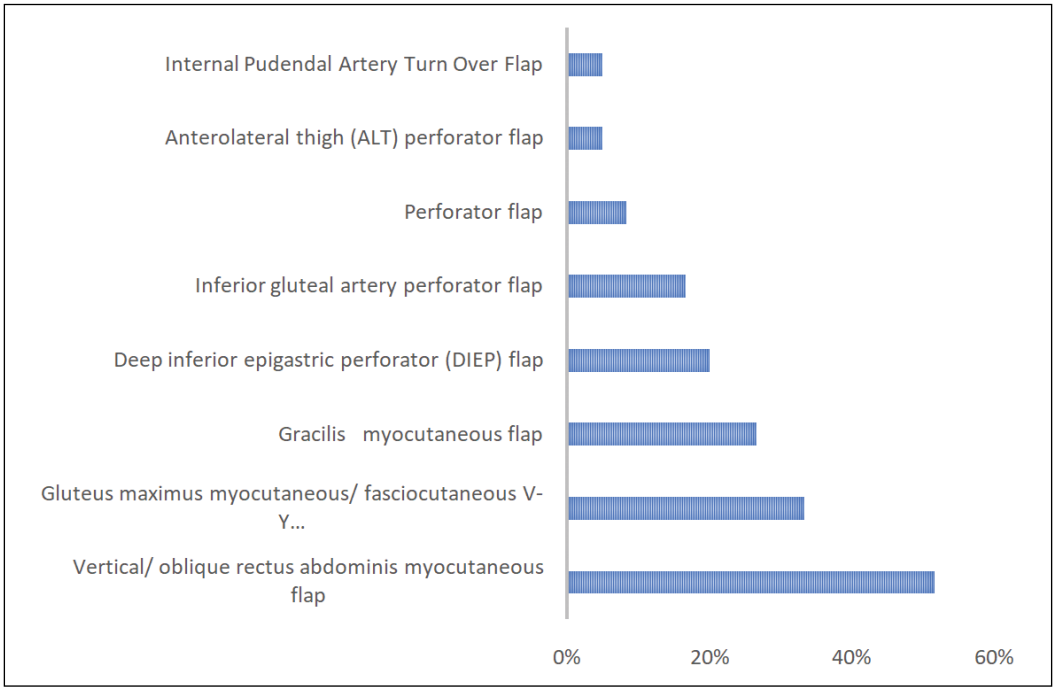

FIGURE 4. Flap preference (excluding the omental flap).

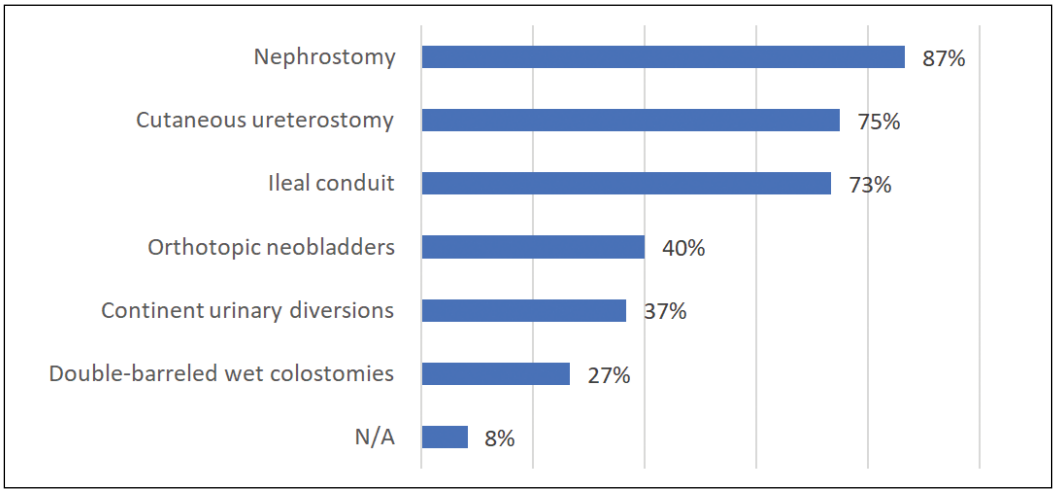

FIGURE 5. Vital equipment in order to minimise the need for anaesthesiologists to briefly vacate the operating theatre, during Pelvic Exenteration procedures. N/A; not answered.

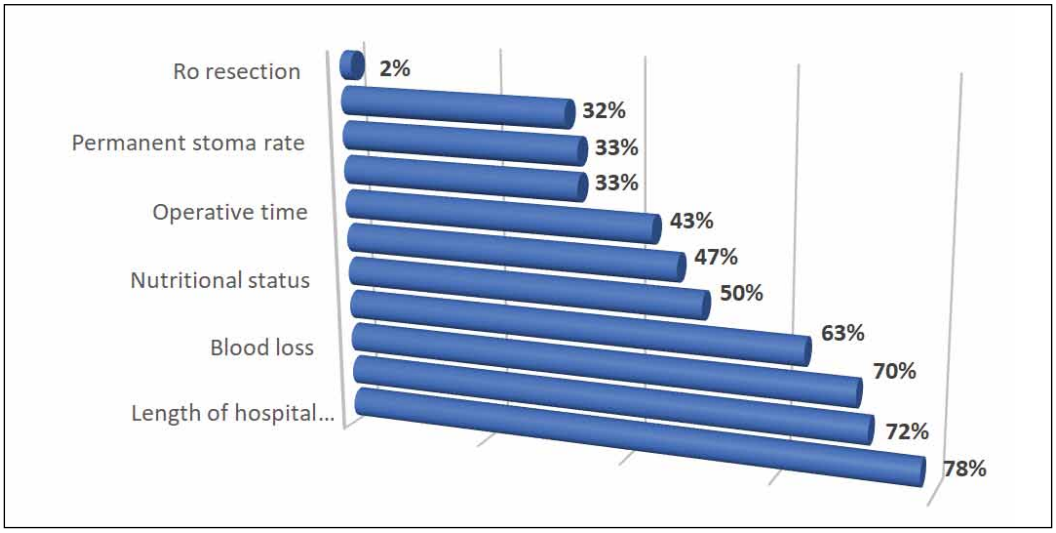

FIGURE 6. Important surgery- related outcomes following Pelvic Exenteration.

DISCUSSION

Effective multidisciplinary perioperative and anaesthetic management is crucial for achieving successful surgical outcomes in patients undergoing PE for LARC/ LRRC. The last few years there has been a collective effort through PELVEX to develop recommendations in order to avoid the significant variation in clinical practice worldwide [13].

Preoperative considerations

Participation in a specialised advanced pelvic cancer MDT meeting is compulsory for high-risk and intricate cases, such as those with LARC or LRRC [9,14-16].

Several studies have indicated a link between enhanced survival rates and discussions during MDT meetings, especially in the case of complex rectal cancers [14,17]. MDT meetings offer additional advantages, including improved communication among clinicians, access to the latest treatments, education and training, and better coordination of care. Although they are essential for the treatment of patients with complex cancer, the substantial resources needed to conduct these meetings must be considered in service planning [12].

Ideally, the core team includes an MDT lead or chair such as a colorectal, gynaeoncology, or urology consultant, an MDT coordinator or secretary, at least two colorectal surgeons, a gynaeoncologist, an urologist, a medical oncologist, a radiation oncologist, a histopathologist, a radiologist, and clinical nurse specialists. Depending on the case, additional specialists may be invited [18].

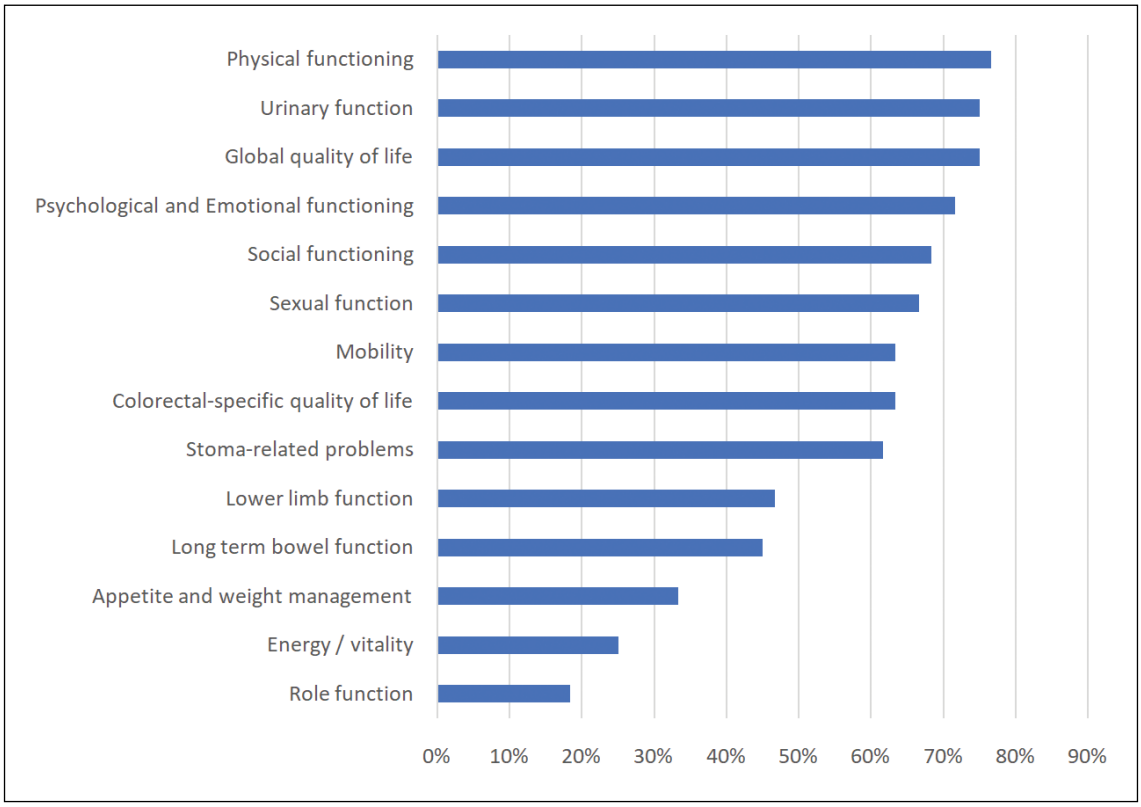

FIGURE 7. Important patient-reported outcomes and functions following Pelvic Exenteration surgery.

Staging of LARC and LRRC should be based on the TNM cancer system [19-21]. Pelvic MRI is the most accurate test to define locoregional spread, local lymph node status and response to therapy with EUS having less value and being used complementary or when MRI is contraindicated [19-22]. For assessing for distant metastases, CT of the chest and CT or MRI of the abdomen are considered efficient [19-21]. In LRRC, or when a pelvic exenteration procedure is planned, a PET-CT may be considered [10,19].

For restaging purposes after neoadjuvant therapy, although repeating the initial staging imaging modalities is essential and is strongly recommended, advanced functional MRI techniques and/or a PET-CT scan should also be considered [19,21,22].

For LARC considered for PE, neoadjuvant treatment is considered mainstream. The 3 commonest regimes are total neoadjuvant treatment (TNT), long course chemoradiotherapy (CRT) and short course radiotherapy (SCRT). National Comprehensive Cancer Network (NCCN) suggests TNT [21], while European Society for Medical Oncology (ESMO) suggests either CRT or SCRT [20]. American Society of Colon and Rectal Surgeons (ASCR) suggests CRT over SCRT, with no suggestions regarding TNT [19].

For LRRC, data is limited. According to ESMO [20], in non irradiated patients planned for surgical resection, a standard-dose CRT or a SCRT followed by chemotherapy is recommended, while in patients who have already received radiation therapy, re-irradiation with lower doses plus chemotherapy is a viable option. A 2022 meta-analysis [23] demonstrated that for LRRC, CRT followed by surgery can improve resection status, long-term disease control, and survival rates.

Patients undergoing PE, do not need routine admission the night before surgery, unless there is need for optimisation [13]. There is strong recommendation regarding the preoperative nutritional and fitness optimisation, which should start long before surgery [10]. It is also strongly recommended that the anaesthesiologist involved in the PE case, should personally undertake the pre-assessment of the patient [10].

CPET is an effective pre-assessment tool, since it can risk-stratify patients and can be a useful predictor of postoperative morbidity and mortality [24]. Should it be unavailable, MET assessment is a viable but less accurate method [13]. Other pre-assessment modalities can be offered based on the comorbidities of each patient.

Immediately preoperatively, a regular dedicated specialist team including the anaesthesiologic, the surgical and the nursing staff, the use of the World Health Organization (WHO) Surgical Checklist and a team brief are essential

to ensure good communication and teamwork and to improve patient outcomes [13]. If the case is anticipated to exceed 12 hours, a second anaesthesiologic consult or senior trainee is advised to assist [10].

Intraoperative Considerations

Patient positioning is of great importance to reduce pressure induced injuries like neuropathies, ulcers and Well leg compartment syndrome (WLCS) [25,26]. Use of pads on pressure points, quality operating tables and mattresses, avoidance of joint over manipulation are important preventive strategies [27].

Regarding anaesthesia, the current consensus is the administration of inhaled volatile anaesthetics; use of total intravenous anaesthesia (TIVA) is not suggested despite its advantages in the postoperative period [13]. In the operating theater, intensive monitoring of the patient is warranted and except the Anesthesiology Control Tower, other modalities like ABG, Rapid Infusers and Thromboelastography (TEG) machines are essential to be readily approachable by the anaesthesiologists by being situated inside or very close to the OR [13].

Patients undergoing PE are very likely to need transfusion of a variety of blood products including pRBCs, FFP and platelets and it should be guided by TEG, if available [10]. Two cross-matched pRBCs are required as a minimum before commencing every case [13]. Tranexamic acid is a useful aid for hemorrhage prevention but with serious complications including death and thromboembolic events [28]. A maximum of 1g is recommended and it can reduce the bleeding by one third; its action varies by timing of administration but it's not statistically significant [29].

For prevention of VTE and Pulmonary embolism, IPCs and TEDs are imperative; prophylactic LMWH should be routinely administered within 24 h of the perioperative period but the consensus is low and it should be individualised for each patient [13].

The essential technical elements of extended and exenteration pelvic surgery should be clearly defined in a standardised thesaurus (Pelvic Exenteration Lexicon), which will enhance data synthesis, enable precise activity documentation for audits, and ultimately lead to better patient outcomes [30,31].

Plastic reconstruction after a PE procedure is complex and should weigh many factors, including the status of the patient, the size of the pelvic and perineal defect, any history of irradiation or previous chemotherapy and the plan for postoperative adjuvant therapy [30,32]. Several approaches have been suggested for reconstructing the pelvic floor and vulvovaginal complex in females.

The Vertical Rectus Abdominis (VRAM) flap followed by the Inferior Gluteal Artery Myocutaneous (IGAM) flap are the most frequently used flaps [33]. Other commonly used techniques are the Transverse Rectus Myocutaneous flap, the Deep Inferior Epigastric Artery Perforator flap, gluteal flaps (Superior/ Inferior Gluteal Artery Perforator flap, Internal Pudendal Artery Perforator flap or Perineal Turnover flap) and thigh flaps (i.e. Anterolateral Thigh flap, Tensor Fascia Lata flap, Gracilis flap, De-epithelised Gracilis Adipofascial flap) [30,34-37]. However, until now, there is no optimal method and even the most advanced techniques fail to fully restore both form and function [38].

Use of the omentum as a pedicle flap, is another option, which can serve as a pelvis filler and can be used as an adjunct when the tissue deficit is quite large or when less invasive reconstructive techniques are selected like primary closure, skin grafts or local skin flaps [39-41]. In selected cases, a primary closure or a bioprosthetic mesh can also be utilised [32]. In cases of neovaginal reconstruction, a bilateral gluteal advancement flap or a VRAM flap are recommended [33].

Following repeat PE for LRRC, re-do reconstruction is challenging, and largely depends on the extent of resection needed to achieve negative margins and the chosen method of primary reconstruction [30].

Urinary reconstruction should effectively maintain renal function, ensure proper urinary outflow, and minimize patient morbidity [42]. In contemporary practice, the most frequently utilised urinary diversions are the ileal conduit (Bricker procedure) and the colon conduit [43]. Though infrequently used, the double barrel wet colostomy is another option [44].

Postoperative considerations

Achieving satisfactory postoperative analgesia can be complex and should employ a multimodal, opioid-sparing approach whenever possible; various analgesic techniques, such as epidural or spinal analgesia, intravenous lidocaine, transversus abdominis plane block, and continuous local anaesthetic wound infusion are effective for postoperative pain control, each with its own risks and benefits [45]. Regional anaesthesia should be carefully monitored by practitioners skilled in managing and adjusting epidural pain management as needed [13].

PE has a well-documented and profound impact on patients with advanced pelvic malignancy with a high morbidity (~18%-87%) and a 30- day mortality between 0% and 9.1% [46]. Additionally, it diminishes Quality of Life (QoL), and physical functioning may never fully return to previous levels [47].

Complications can have various origins, including the perineum and the wound trauma, the renal system, the gastrointestinal tract, the cardiovascular and the pulmonary system. Their frequency depends on several factors such as the previous morbidities of the patient, the choice of urological and perineal reconstruction, the surgical technique and the extent of pelvic resection, the perioperative care of the patient, etc [48].

There is an emerging interest in patient-reported outcome measures (PROMs) as a method for assessing the impact and outcomes of the surgery [10]. Commonly used questionnaires include the AQoL, QLQ-C30, SF-36®, SF-6D®, FACT-C, and the distress thermometer [46]. Although their use has increased over time, there remains a need for standardised use and timing of PROMs to facilitate multicenter studies [49].

Patients undergoing PE typically require transfer to the ICU postoperatively, preferably intubated, for invasive monitoring since they often experience a significant SIRS, which can lead to hemodynamic instability [13].

Post-operative surveillance specific to PE has yet to be established, but follow-up should generally align with protocols for primary rectal cancer and it is best conducted by the surgeon who performed the operation, since they are familiar with the intricacies of the case, with further consultation of other members of the MDT if imposed by the clinical case [10]. Patients are typically kept under medical surveillance for a minimum of five years, and there is no evidence suggesting that a shorter-interval follow-up schedule should be routinely used in more complex cases [10].

In Greece, the National Health System lucks centralisation of complex cancer surgery into high-volume centres. There are severe and widening disparities across the country and survival rates remain unacceptably poor for cancer patients. There are challenges and equally opportunities that are needed to develop radical, yet sustainable plans, which are comprehensive, evidence-based, integrated, patient-outcome focused, and deliver value for money.

Limitations

Although our survey was distributed to the members of the Greek Society of Coloproctology and the Hellenic Surgical Society, the actual responding population cannot be described, and respondents with biases may select themselves into the sample. Additionally, lack of centralisation of cancer services precludes accurate national data and comparisons of results, between different units, and there is insufficient information on the patient-selection process, the criteria for resectability and the peri operative outcomes [11] .

CONCLUSION

Pelvic exenteration surgery has significantly evolved over recent decades, transitioning from a palliative procedure in gynaecologic practice to a potential curative option for patients with advanced pelvic malignancies. It is now considered the standard of care for surgical oncologists for patients with locally advanced and recurrent rectal cancer. However, there is great diversion in clinical practice and treatment protocols among exenteration centres.

Although guidelines in this field have already been published, further studies are needed in various aspects of the perioperative and anaesthetic management of patients undergoing pelvic exenteration procedures. Such complex procedures are also imperative to be centralised, and specialised exenteration centres should be established to ensure standardisation and that quality standards are met.

As stated by Kontovounisios, 2024 [50], "the triad of success in PE surgery, encompassing objective measures such as survival, and subjective measures including quality of life and health economics, is based around "one-third selection process, one third decision-making and one-third surgical technique".

Incorporating collaboration, teaching, and research opportunities into the "one-third selection process, one-third decision-making, and one-third surgical technique" triad will enable specialist surgeons to perform more precise surgery in dedicated institutions and will offer compassionate care through a clinical approach focused on direct personal interaction with patients.

Conflict of interest: *None*

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Appendix 2

ONLINE SURVEY

1. First & Last name:

Needed for authorship in the manuscript only. The answers are completely confidential and the identity of the participants will remain anonymous.

2. Correspondence email address:

3. Which age group are you in?

- ◯ ≤ 30
- ◯ 31 - 40
- ◯ 41 - 50
- ◯ 51 - 60
- ◯ 61 - 70
- ◯ >70

4. What is your gender?

- ◯ Male
- ◯ Female
- ◯ Prefer not to say

5. What is your profession?

- ◯ Surgeon
- ◯ Medical oncologist
- ◯ Radiation oncologist
- ◯ Nurse

6. As a surgeon, have you undergone any specialized training or fellowship program specifically in Pelvic Exenteration surgery?

- ◯ Yes
- ◯ No
- ◯ N/A

7. How many years have you been treating patients with locally advanced or recurrent rectal cancer?

- ◯ <5 years
- ◯ 5-10 years
- ◯ 10-20 years
- ◯ >20 years
- ◯ N/A

8. Does your institution host a specialized, multi-disciplinary team or tumor board meeting?

- ◯ Yes
- ◯ No
- ◯ N/A

9. Could you specify the optimal composition of an advanced pelvic cancer multidisciplinary team?

You may select multiple options as necessary.

MDT lead/chair (such as colorectal, gynaecological or urological consultant)

- ◯ Colorectal surgeon
- ◯ Gynaecological surgeon
- ◯ Urological surgeon
- ◯ Medical oncologist
- ◯ Clinical oncologist
- ◯ Pathologist
- ◯ Radiologist
- ◯ Clinical nurse specialist
- ◯ N/A

10. Do you believe that the implementation of a standardized system and template for reporting outcomes of advanced pelvic cancer Multidisciplinary Team (MDT) should be considered?

- ◯ Yes
- ◯ No
- ◯ N/A

11. Could you specify the imaging modalities that you consider indispensable for staging locally advanced and recurrent rectal cancer in your professional practice?

You may select multiple options as necessary.

- ◯ CT scan
- ◯ MRI scan
- ◯ PET / CT scan
- ◯ N/A

12. What neoadjuvant treatment options are applied at your institution, for locally advanced rectal cancer?
You may select multiple options as necessary.

- ◯ Neoadjuvant chemoradiotherapy – long course
- ◯ Neoadjuvant chemoradiotherapy – short course
- ◯ Total Neoadjuvant Treatment
- ◯ Immunotherapy
- ◯ None
- ◯ N/A

13. Do you offer neoadjuvant chemoradiotherapy for locally recurrent rectal cancer, if indicated?

- ◯ Yes
- ◯ No
- ◯ N/A

14. What other radiotherapy techniques does your institution offer?
You may select multiple options as necessary.

- ◯ Intraoperative radiotherapy (IORT)
- ◯ Brachytherapy
- ◯ Proton beam therapy
- ◯ Cyberknife
- ◯ No other radiotherapy techniques are offered
- ◯ N/A

15. Do you have a prehabilitation program in your institution to enhance the nutritional status and preoperative fitness of patients undergoing Pelvic Exenterations?

- ◯ Yes
- ◯ No
- ◯ N/A

16. How many Pelvic Exenteration operations are performed at your institution annually?

Field not required

17. Which Pelvic Exenteration outcomes do you consider important in your practice?
You may select multiple options as necessary.

- ◯ Length of hospital stay
- ◯ Operative time
- ◯ Blood loss
- ◯ Number of blood transfusions required
- ◯ Length of ICU stay
- ◯ Return of bowel function
- ◯ Discharge destination
- ◯ Permanent stoma rate
- ◯ Analgesia use
- ◯ Nutritional status

18. Which patient-reported outcomes and functions do you consider important in your practice?
You may select multiple options as necessary.

- ◯ Urinary function
- ◯ Psychological and Emotional functioning
- ◯ Physical functioning
- ◯ Colorectal-specific quality of life
- ◯ Global quality of life
- ◯ Sexual function
- ◯ Long term bowel function
- ◯ Mobility
- ◯ Social functioning
- ◯ Role function
- ◯ Energy / vitality
- ◯ Lower limb function
- ◯ Appetite and weight management
- ◯ Stoma-related problems

19. Which survival outcomes do you consider important?

Please rank them from 1 to 5, with 1 being the most important.

Overall survival
1
2
3
4
5
N/A

Disease free survival
1
2
3
4
5
N/A

Disease specific survival
1
2
3
4
5
N/A

Survival with disease
1
2
3
4
5
N/A

Local recurrence free survival
1
2
3
4
5
N/A

20. Which of the listed complications do you consider important for the overall survival of patients?

You may select multiple options as necessary.

- ◯ Perioperative mortality
- ◯ Postoperative complications
- ◯ Complication severity
- ◯ Surgical reintervention
- ◯ Haemorrhage
- ◯ Hospital readmission
- ◯ Late or long-term complications
- ◯ Unplanned ICU admission
- ◯ Cause of postoperative mortality
- ◯ Intraoperative complication rate

21. What urological reconstructive options are available at your institution?

You may select multiple options as necessary.

- ◯ Ileal conduit
- ◯ Continent urinary diversions
- ◯ Orthotopic neobladders
- ◯ Double-barreled wet colostomies
- ◯ Cutaneous ureterostomy
- ◯ Nephrostomy
- ◯ None
- ◯ N/A

22. What plastic reconstructive options are available at your institution?

You may select multiple options as necessary.

- ◯ Abdominal— vertical or oblique rectus abdominis myocutaneous/muscle flap
- ◯ Deep inferior epigastric perforator (DIEP) flap
- ◯ Gluteal region— myocutaneous or fasciocutaneous VY-plasty
- ◯ Inferior gluteal artery perforator flap
- ◯ Upper thigh—anterolateral thigh with or without vastus lateralis flap
- ◯ Gracilis flap
- ◯ Gluteal fold/perineal— internal pudendal artery perforator or perineal turnover
- ◯ Perforator flap
- ◯ Omentum
- ◯ Mesh
- ◯ None
- ◯ N/A

23. What are the most common wound complications following Pelvic Exenterations in your practice?
You may select multiple options as necessary.

- ◯ Perineal wound dehiscence
- ◯ Perineal flap loss or dehiscence
- ◯ Abdominal wall hernia
- ◯ Perineal hernia
- ◯ N/A

24. What are the most common gastrointestinal complications following Pelvic Exenterations in your practice?
You may select multiple options as necessary.

- ◯ Anastomotic leak
- ◯ Postoperative ileus
- ◯ Bowel obstruction
- ◯ Gastrointestinal tract injury or perforation
- ◯ N/A

25. What are the most common urinary complications following Pelvic Exenterations in your practice?
You may select multiple options as necessary.

- ◯ Anastomotic leak
- ◯ Ureteric stricture
- ◯ Urinary tract infection
- ◯ N/A

26. What are the most common vascular complications following Pelvic Exenterations in your practice?
You may select multiple options as necessary.

- ◯ Venous thromboembolism
- ◯ Limb ischaemia
- ◯ Lower limb compartment syndrome
- ◯ N/A

27. Do you believe it would be more beneficial for the anesthetist conducting a Pelvic Exenteration case to personally undertake the pre-assessment of patients involved?

Strongly agree
- ◯ Agree
- ◯ Not sure
- ◯ Disagree
- ◯ Strongly disagree

28. Should a Cardiopulmonary Exercise Testing (CPET) be part of the preoperative assessment of all patients undergoing Pelvic Exenteration?

Strongly agree
- ◯ Agree
- ◯ Not sure
- ◯ Disagree
- ◯ Strongly disagree

29. Should CPET be unavailable, what are the other essential components in the preoperative assessment of Pelvic Exenteration patients?
You may select multiple options as necessary.

- ◯ Cardiology opinion
- ◯ Resting echocardiography
- ◯ Imaging stress testing
- ◯ Imaging stress testing for patients with more than two clinical risk factors and poor functional capacity <4 METs
- ◯ N/A

30. Which blood transfusion products do you consider indispensable prior to commencing every Pelvic Exenteration case?
You may select multiple options as necessary.

- ◯ Less than 4 units of packed cells
- ◯ 4 units of packed cells
- ◯ More than 4 units of packed cells
- ◯ 1 unit of pooled platelets
- ◯ 1L of fresh frozen plasma units
- ◯ N/A

31. What is your opinion regarding the use of IV Tranexamic acid intraoperatively?

- ◯ Routinely use of 500mg Tranexamic acid IV, at induction of anaesthesia or before the surgical incision
- ◯ Routinely use of 1g Tranexamic acid IV at induction of anaesthesia or before the surgical incision
- ◯ Tranexamic acid 500mg IV intraoperatively, if required
- ◯ Tranexamic acid 1g IV intraoperatively, if required
- ◯ IV Tranexamic acid should never be used
- ◯ N/A

32. In your practice, is it common for patients undergoing Pelvic Exenteration to necessitate the transfusion of more than two units of Packed red blood cells (pRBCs)

- ◯ Yes
- ◯ No
- ◯ N/A

33. What specialized equipment is imperative to be ensured, in order to minimise the need for anaesthesiologists to briefly vacate the operating theatre, during Pelvic Exenteration procedures?

You may select multiple options as necessary.

Arterial Blood Gas machine

- ◯ Thromboelastography (TEG) / clotting tests
- ◯ Rapid infusors
- ◯ N/A

34. Is Thromboelastography (TEG) monitoring useful to guide the administration of clotting products during Pelvic Exenteration procedures?

- ◯ Yes
- ◯ No
- ◯ N/A

35. Is it imperative to maintain a readily accessible supply of both blood products and reconstituted blood products, allowing for immediate administration upon request from an anaesthetist, thereby eliminating any potential time delays?

- ◯ Yes
- ◯ No
- ◯ N/A

36. Should it be considered standard practice to admit all Pelvic Exenteration patients on the night before surgery for intravenous fluid adjustment and optimisation?

- ◯ Yes
- ◯ No
- ◯ N/A

37. What is your current practice on Thromboembolic prophylaxis in Pelvic Exenteration cases?

You may select multiple options as necessary.

- ◯ Thromboembolic deterrent (TED) stockings
- ◯ Intermittent Pneumatic Compression Devices
- ◯ LMWH preoperatively if patient is admitted more than 24 hours from surgery
- ◯ LMWH postoperatively
- ◯ N/A

38. What is your preferred agent for venous thromboembolism prophylaxis?

- ◯ Enoxaparin (Clexane)
- ◯ Tinzaparin (Innohep)
- ◯ Bemiparin (Ivor)
- ◯ Fondaparinux (Arixtra)
- ◯ Unfractionated Heparin
- ◯ N/A

39. What type of operating table and mattress do you use for Pelvic Exenteration cases?

Field not required

40. What strategies do you utilize to prevent pressure ulcer formation during Pelvic Exenteration procedures?

You may select multiple options as necessary.

- ◯ Removal of patient's gown and other sheets in order to have the skin in direct contact with the mattress
- ◯ Careful pressure point protection padding, particularly at the sacrum
- ◯ N/A

41. What strategies do you utilize to prevent leg compartment syndrome and position- related neuropathies of the lower extremities during Pelvic Exenteration procedures?

You may select multiple options as necessary.

- ◯ Careful vigilance on leg positioning
- ◯ Frequent leg and knee repositioning (i.e. every two hours)
- ◯ Limiting hip and knee flexion/ abduction
- ◯ N/A

42. Is it mandatory to employ a specialized anaesthesia team, comprised of either nurses or Operating Department Practitioners (ODPs) who possess specific training for collaboration with the anesthetist on Pelvic Exenteration cases?

- ◯ Yes
- ◯ No
- ◯ N/A

43. Is Total Intravenous Anaesthesia (TIVA) suitable for Pelvic Exenteration cases?

- ◯ Yes
- ◯ No
- ◯ N/A

44. Would it be wise to engage the assistance of an additional anaesthetic consultant or trainee if the anticipated duration of a case is expected to exceed 12 hours?

- ◯ Anaesthetic trainee
- ◯ Anaesthetic consultant
- ◯ Both required
- ◯ Not required (trainee/consultant)
- ◯ N/A

45. Should all Pelvic Exenteration patients receive epidural anaesthesia provided there are no contraindications??

- ◯ Yes
- ◯ No
- ◯ N/A

46. Is it advisable to utilize tunneled epidural catheters in order to deliver prolonged analgesia (up to 10 days) while minimizing catheter-associated complications?

- ◯ Yes
- ◯ No
- ◯ N/A

47. What is your preferred analgesic regime for managing postoperative pain, following Pelvic Exenteration procedures?
You may select multiple options as necessary.

- ◯ Epidural anaesthesia
- ◯ IV opiates
- ◯ Paracetamol
- ◯ NSAIDs
- ◯ N/A

48. Should Pelvic Exenteration cases comply with a careful postoperative pain management protocol that ensures continuous efficacy of regional anaesthesia, with qualified practitioners who can implement modifications in epidural pain control as needed?

- ◯ Yes
- ◯ No
- ◯ N/A

49. Do you think Pelvic Exenteration cases may undergo a large systemic inflammatory reaction (SIRS) which may result in instability? Is it possible that cases of Pelvic Exenteration might undergo a significant systemic inflammatory reaction syndrome (SIRS), potentially leading to hemodynamic instability?

- ◯ Yes
- ◯ No
- ◯ N/A

50. Is it possible to predict the severity of the Systemic Inflammatory Response Syndrome (SIRS) based on initial preassessment workup?

- ◯ Yes
- ◯ No
- ◯ N/A

51. Should patients affected by SIRS, go to the ICU, ventilated and sedated, until the SIRS has improved?

- ◯ Yes
- ◯ No
- ◯ N/A

52. Would you agree that, at the bare minimum, the final pathology report ought to incorporate all core elements as provided by the International Collaboration on Cancer Reporting?

- ◯ Yes
- ◯ No
- ◯ N/A

53. Do you implement a separate follow-up / surveillance protocol on patients undergoing Pelvic Exenterations?

- ◯ Yes
- ◯ No
- ◯ N/A

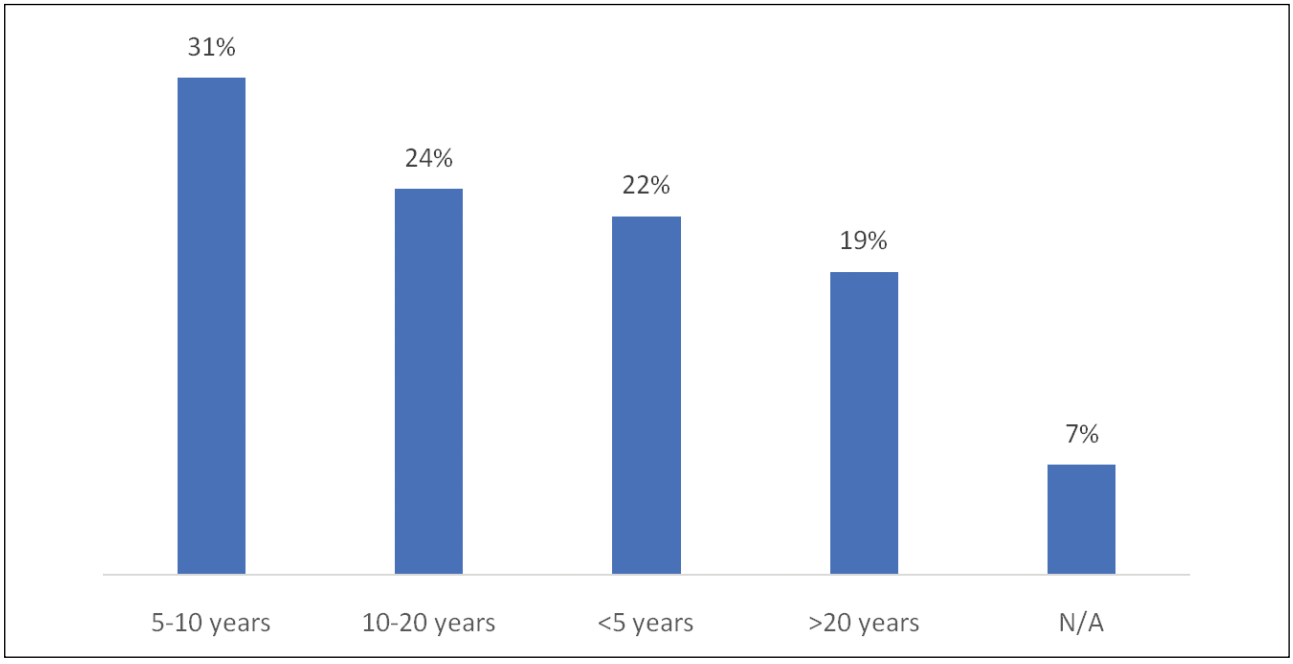
54. Do you employ a validated classification system to describe the operative approach in extended and Pelvic Exenteration surgery for rectal cancer (Pelvic Exenteration Lexicon)?

- ◯ Yes
- ◯ No
- ◯ N/A

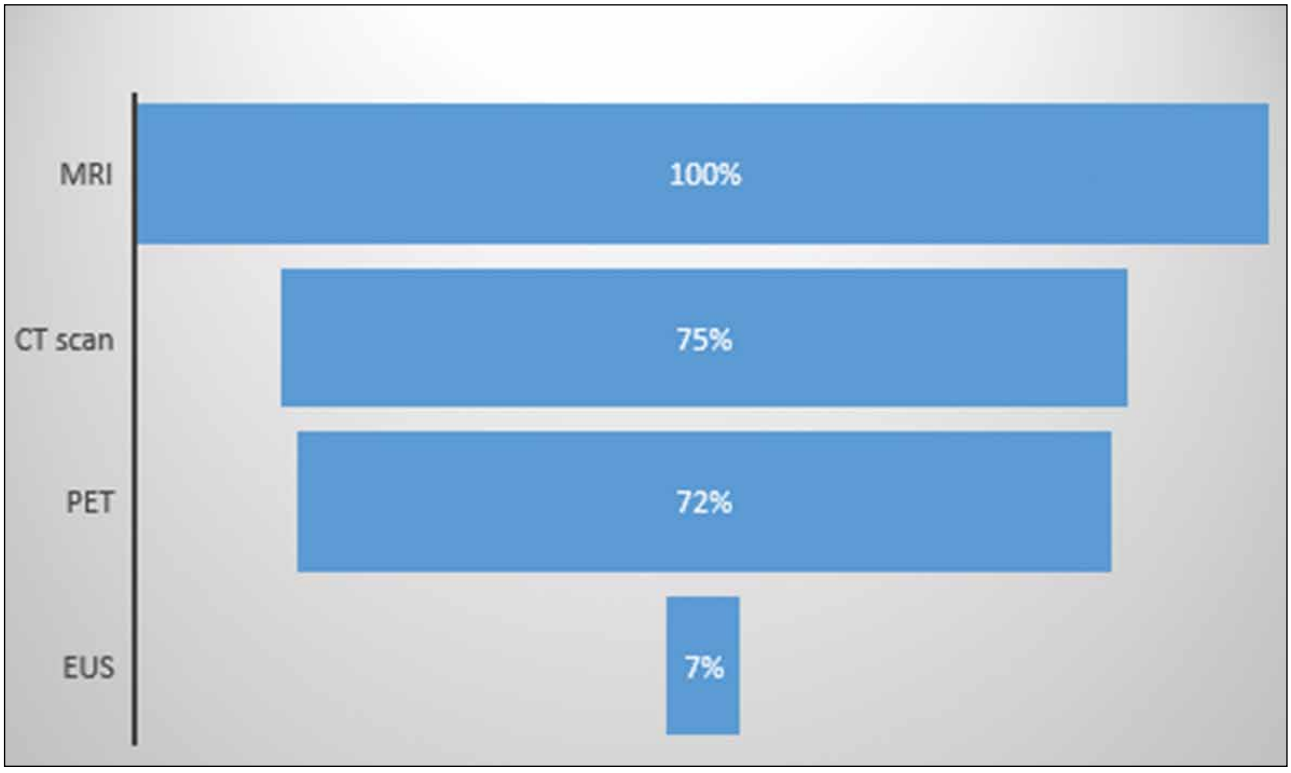
55. Additional comments

Field not required

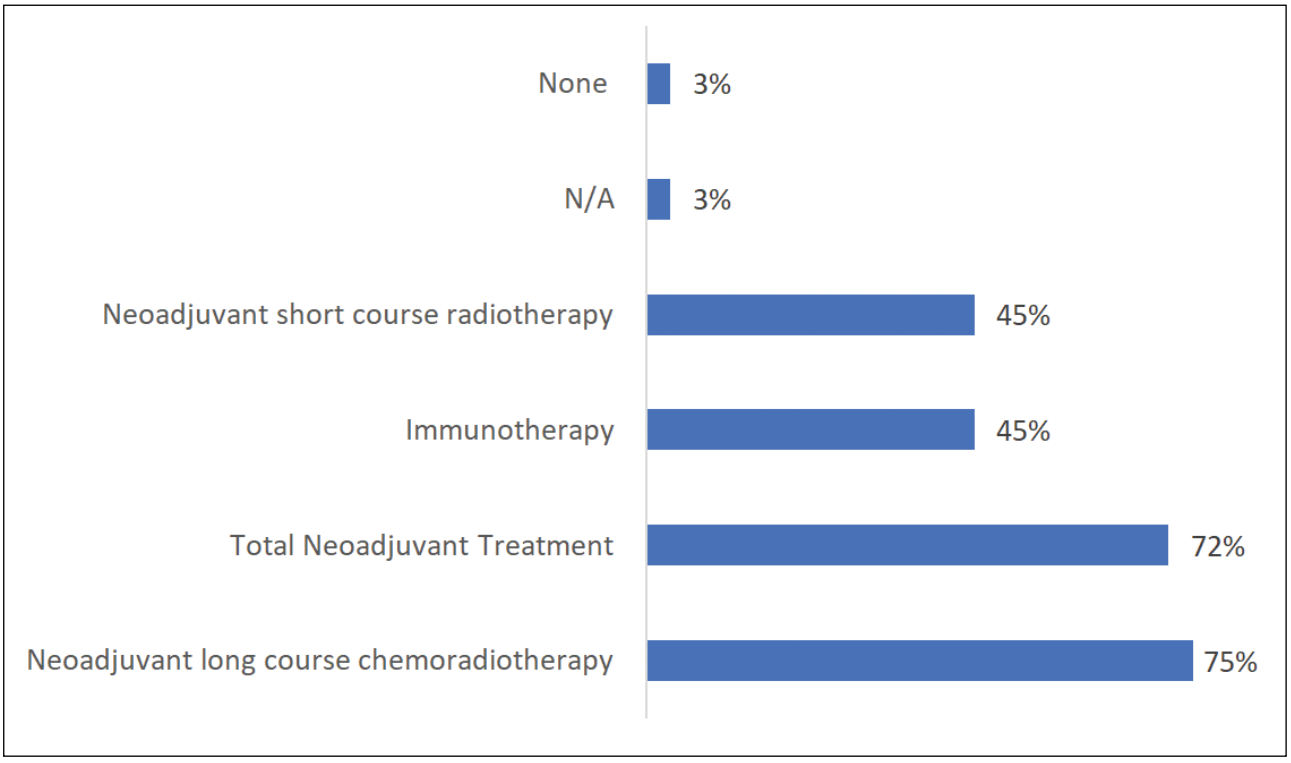
Supplementary



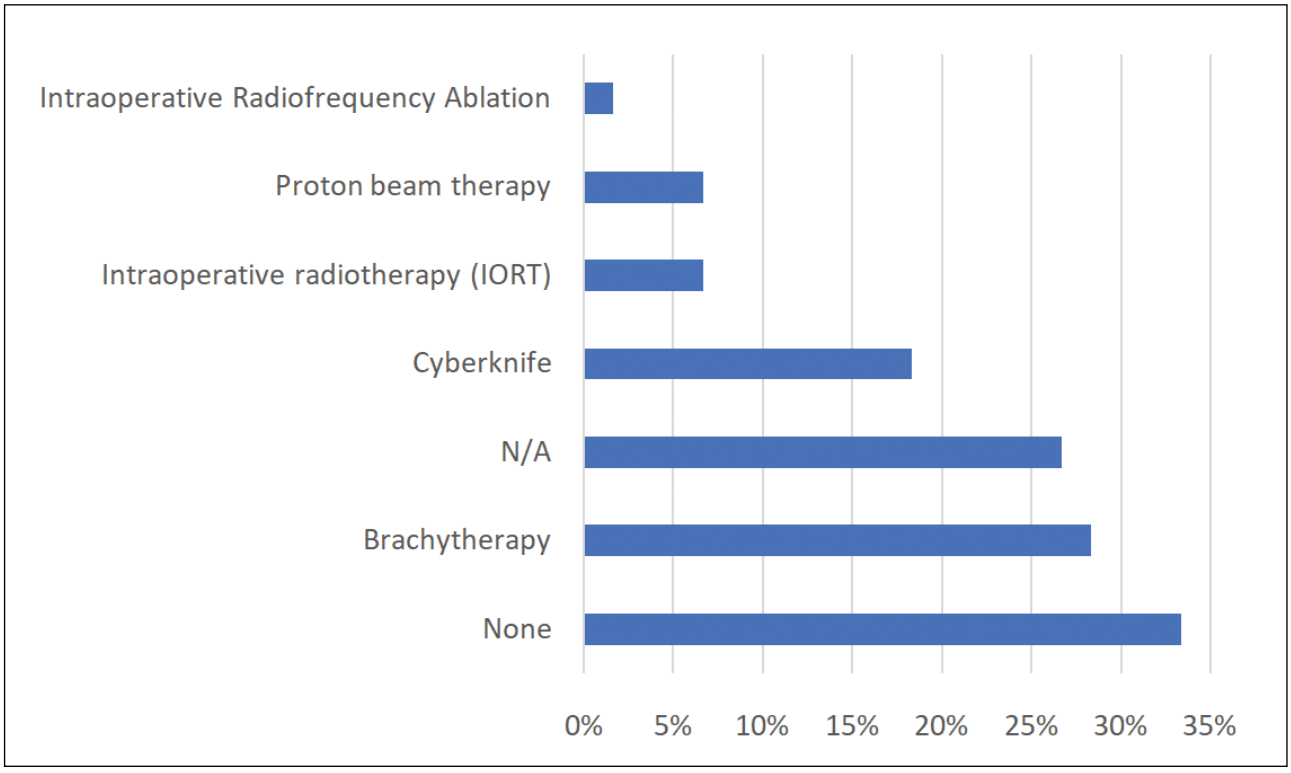
SUPPLEMENTARY FIGURE 1. Number of years patients with locally advanced or recurrent rectal are being treated. N/A; not answered.



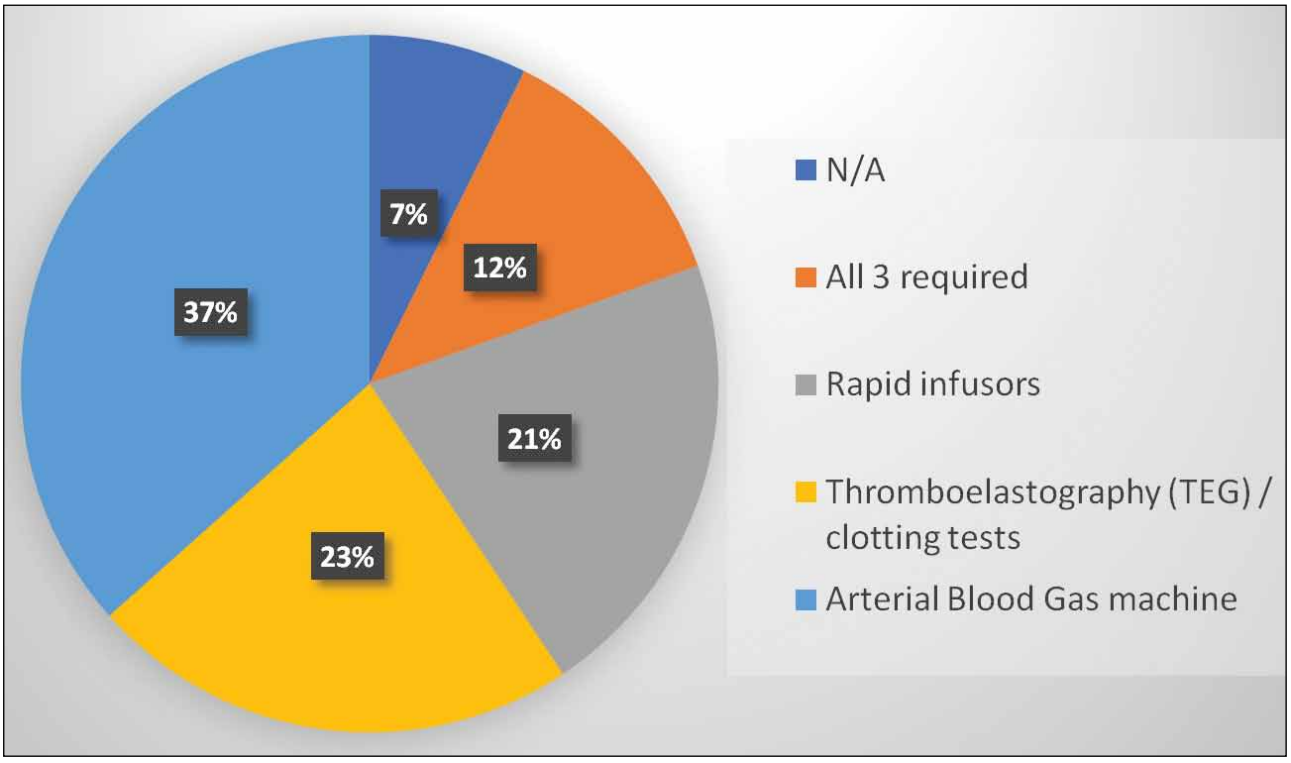
SUPPLEMENTARY FIGURE 2. Imaging modalities indispensable for staging. MRI; magnetic resonance imaging, CT scan; Computerised tomography scan, PET; positron emission tomography-computed tomography scan, EUS; endoscopic ultrasound.



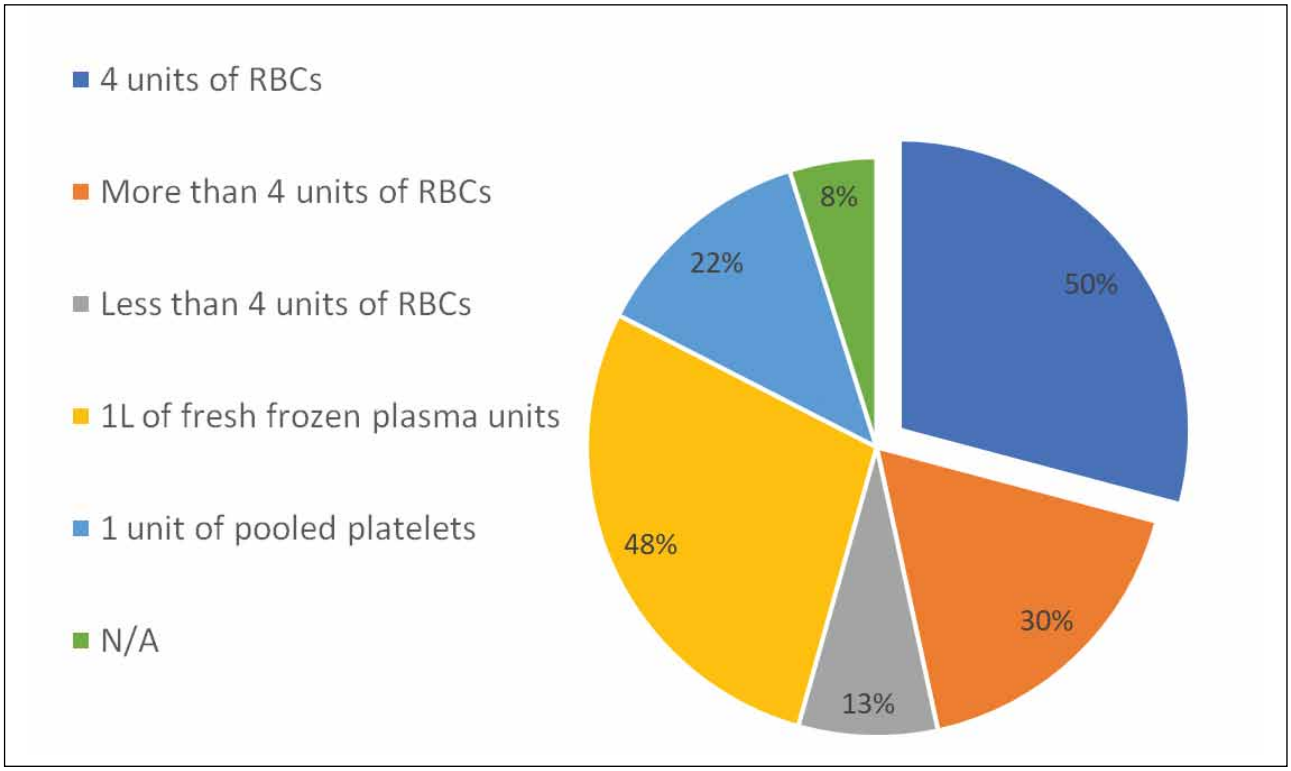
SUPPLEMENTARY FIGURE 3. Neoadjuvant treatment options applied. N/A; not answered.



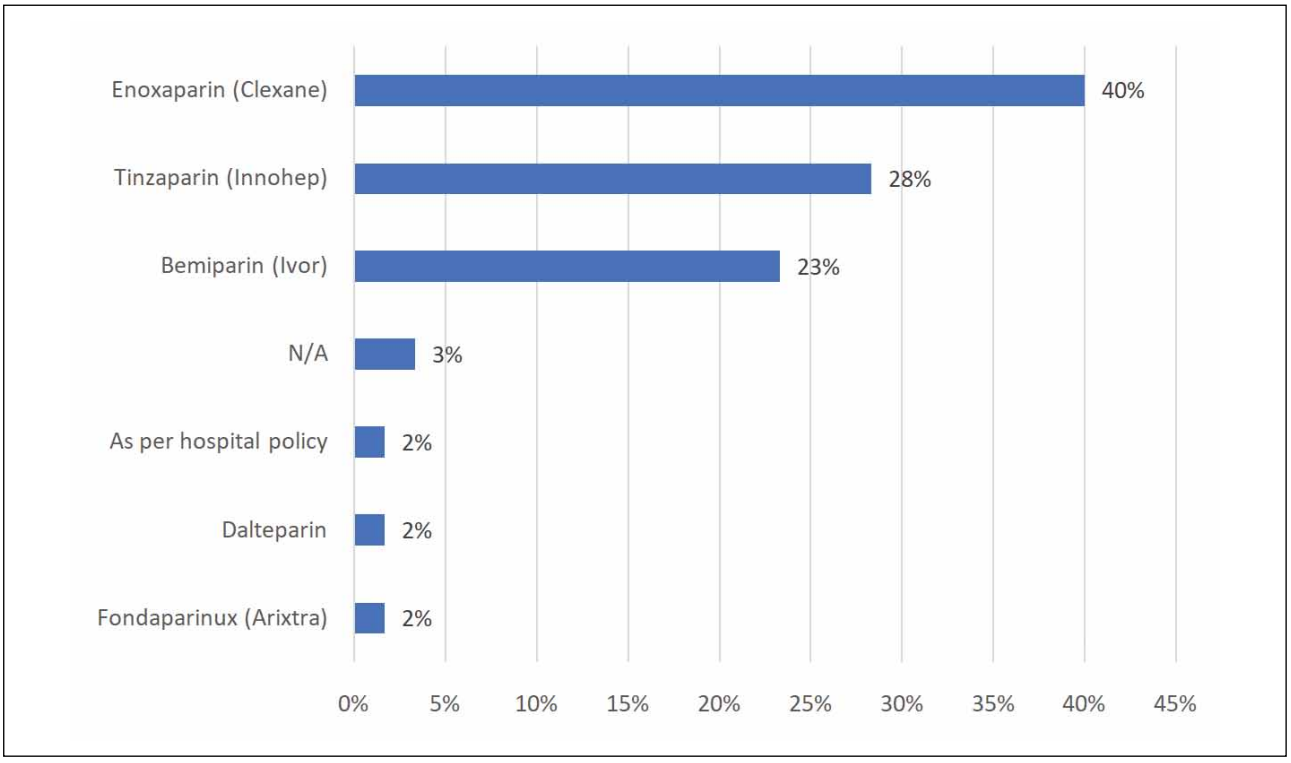
SUPPLEMENTARY FIGURE 4. Alternative radiotherapy techniques offered. N/A; not answered.



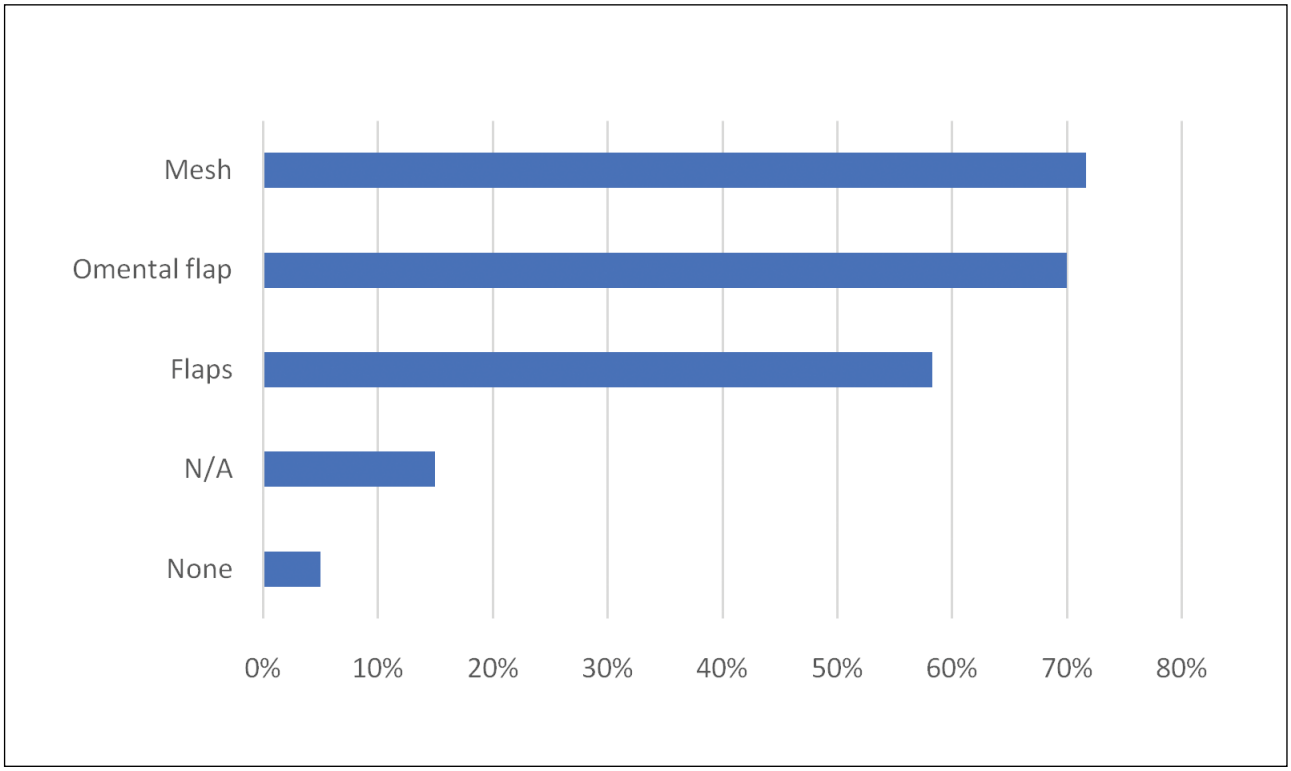
SUPPLEMENTARY FIGURE 5. Vital equipment in order to minimise the need for anaesthesiologists to briefly vacate the operating theatre, during Pelvic Exenteration procedures. N/A; not answered.



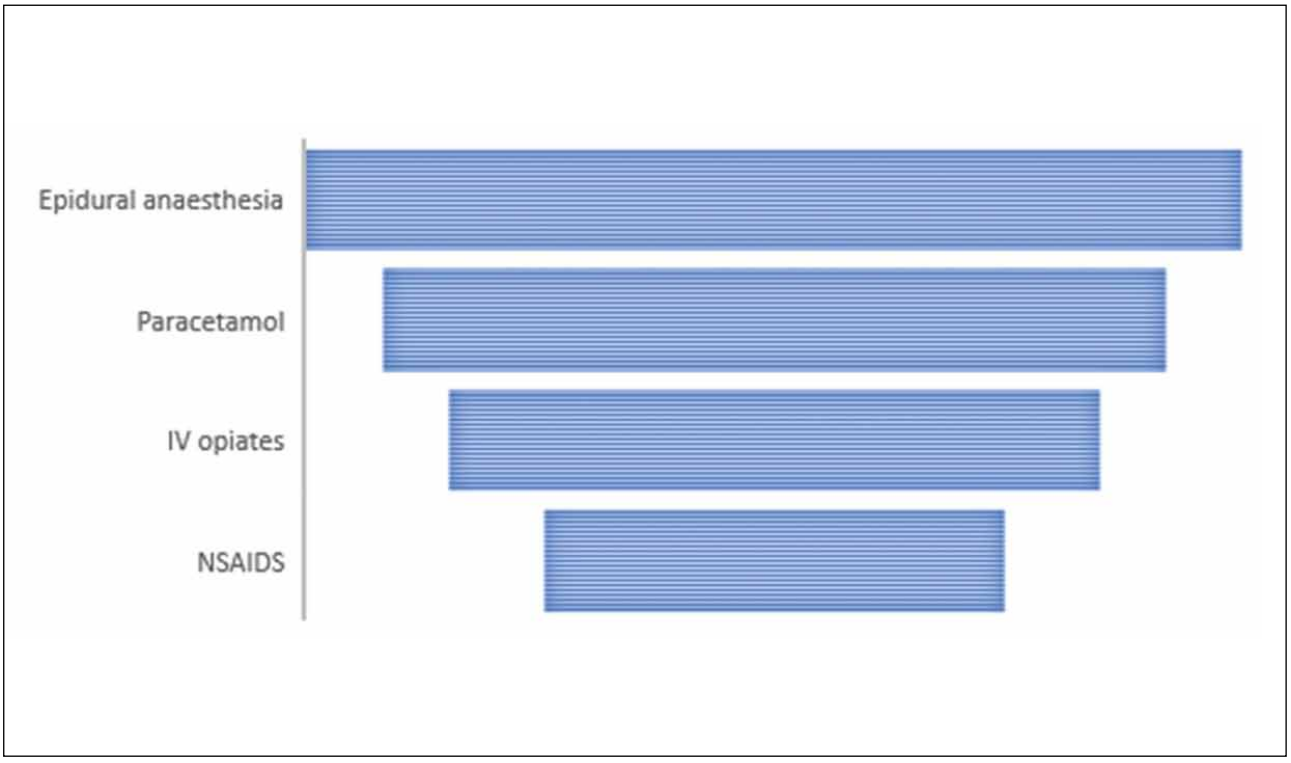
SUPPLEMENTARY FIGURE 6. Blood transfusion products that are considered indispensable prior to commencing any Pelvic Exenteration case. RBCs; red blood cells, N/A; not answered.



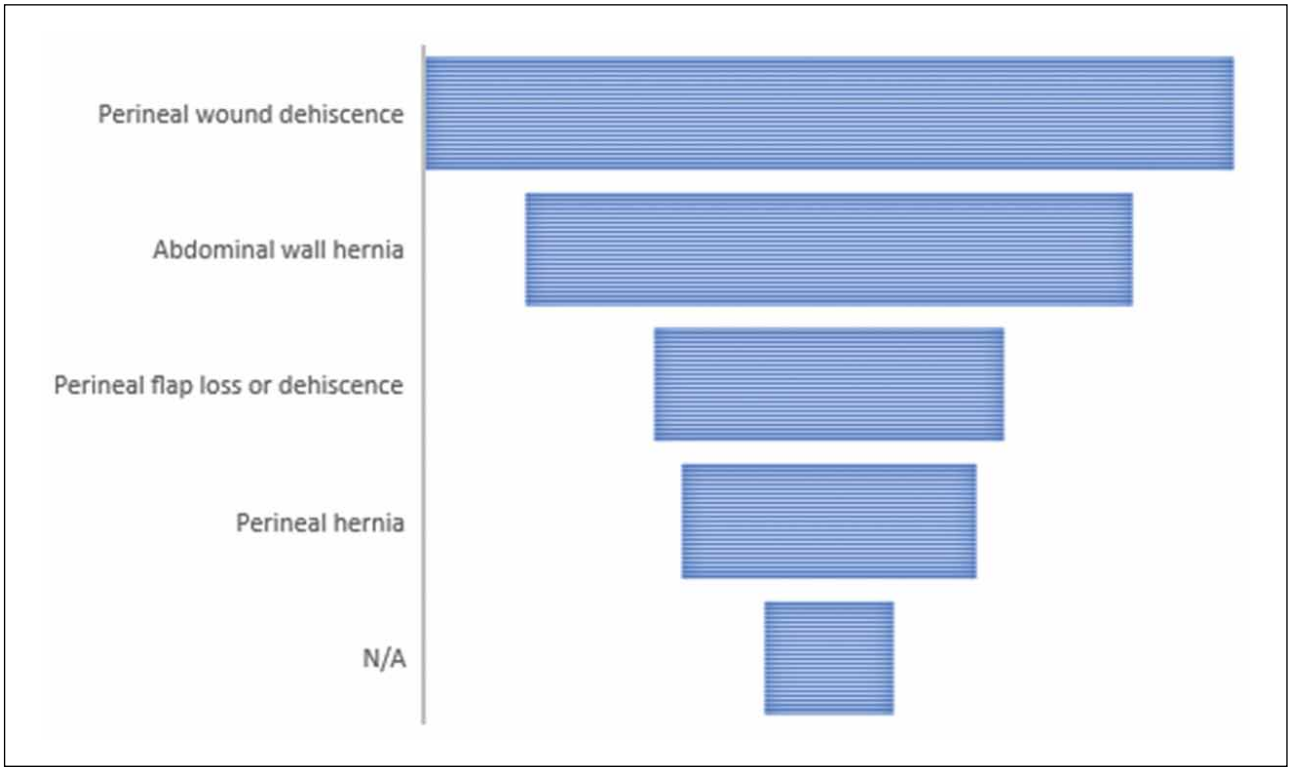
SUPPLEMENTARY FIGURE 7. Preferred agent for venous thromboembolism prophylaxis. N/A; not answered.



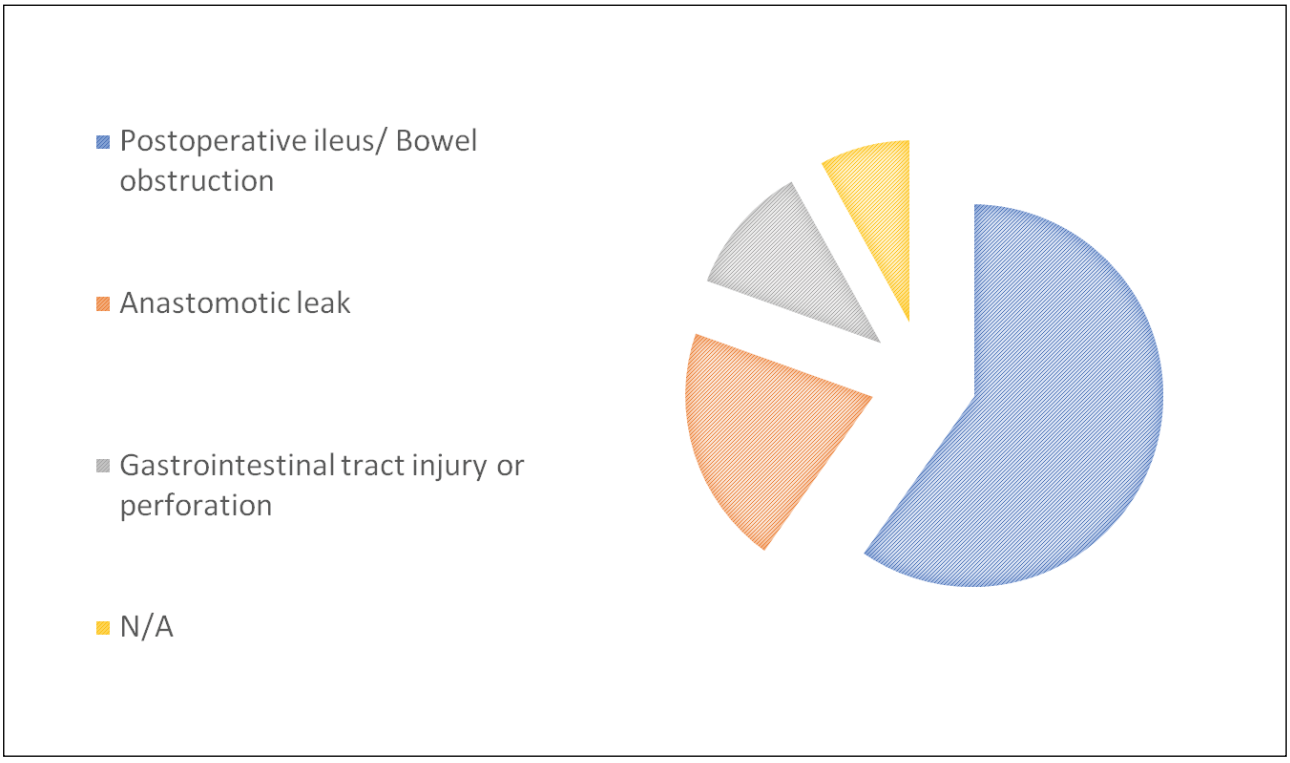
SUPPLEMENTARY FIGURE 8. Plastic reconstruction options. N/A; not answered.



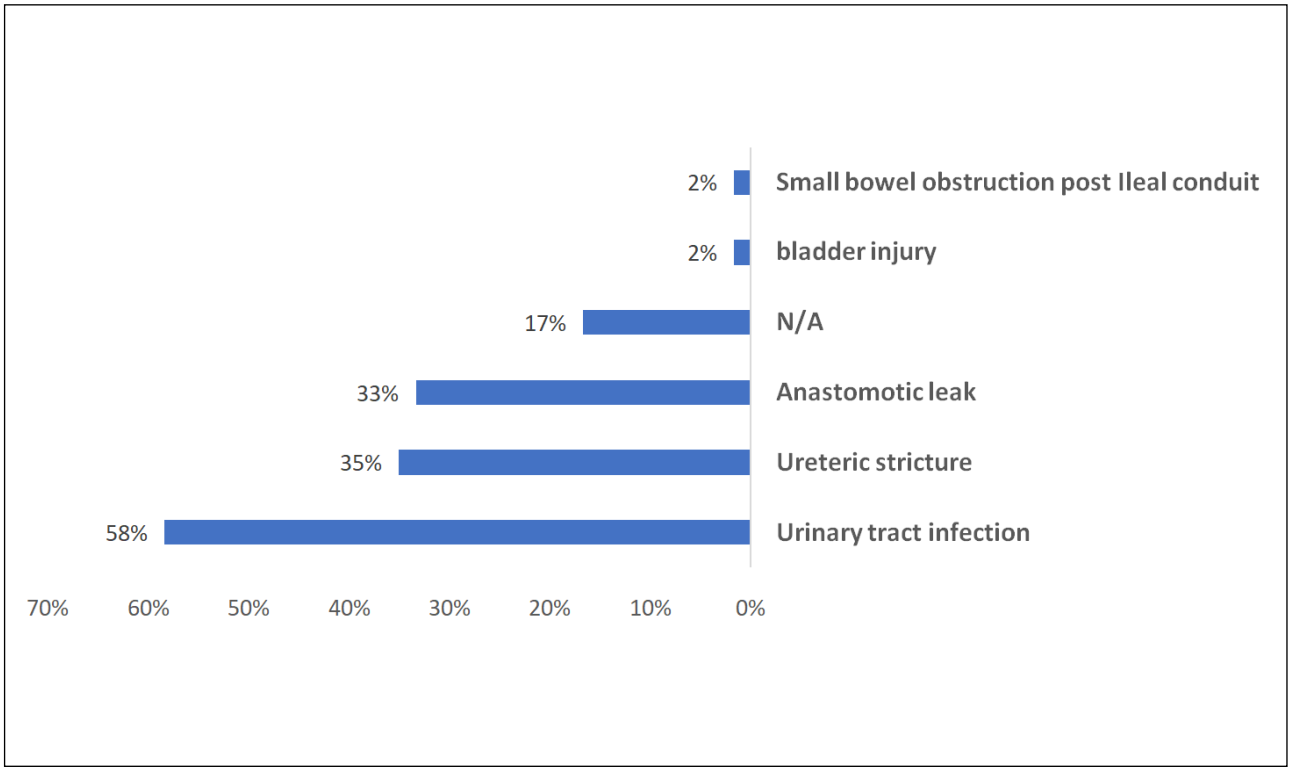
SUPPLEMENTARY FIGURE 9. Preferrable analgesic regime. N/A; not answered, NSAIDS; nonsteroidal anti-inflammatory drugs



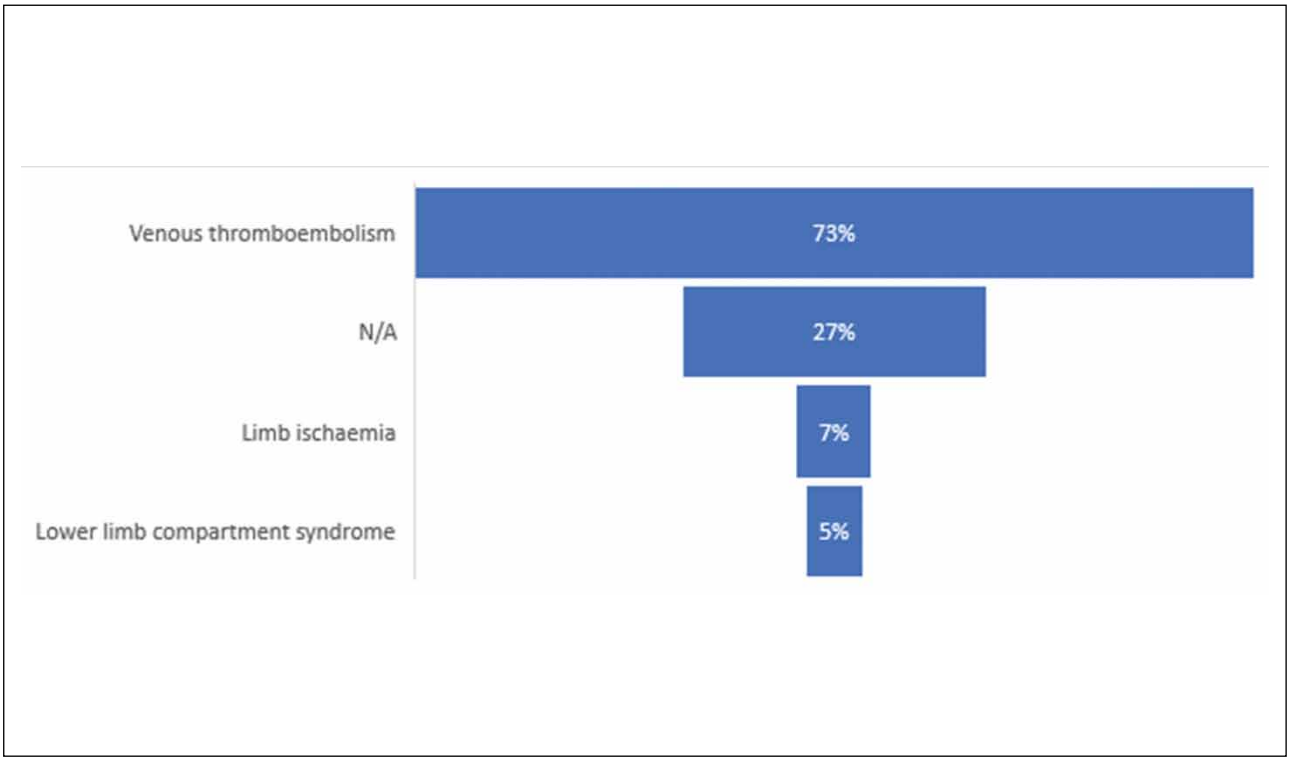
SUPPLEMENTARY FIGURE 10. wound complications following Pelvic Exenterations. N/A; not answered.



SUPPLEMENTARY FIGURE 11. Gastrointestinal complications following Pelvic Exenterations. N/A; not answered.



SUPPLEMENTARY FIGURE 12. Urinary complications following Pelvic Exenterations. N/A; not answered.



SUPPLEMENTARY FIGURE 13. Vascular complications following Pelvic Exenterations. N/A; not answered.

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Breast milk: A modulator of the immature immune system in the management of necrotising enterocolitis in preterm neonates

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ABSTRACT

Necrotising enterocolitis remains (NEC) a major source of morbidity and mortality among preterm infants. The use of breast milk is a major protective factor against NEC, with its anti-infective nutritional and immunological properties. Breast milk, expressed either from the mother's own milk, or in the form of pasteurised donor milk, is the preferred nutritional source of enteral feeding for very low and extremely birth weight infants. Although there is a lack of definite data, breast milk is superior to preterm commercial formulas. However, breast milk seems not only to protect the immature bowel of preterm neonates but also treat the immature host defense system of the gut. The present review presents the currently available data in the literature on the diverse aspects of the role of breast milk not only as a useful feeding strategy to prevent NEC, but also as a means to treat the immature gut of preterm infants.

Key Words: *Breast milk; intestinal microbiota; necrotising enterocolitis; premature neonates; preterm formula*

INTRODUCTION

Necrotising enterocolitis (NEC) is the most common acquired neonatal disease of the gastrointestinal tract (GIT). The pathogenesis of NEC is not clearly elucidated and consequently questions arise on how to treat or prevent the disease [1]. NEC incidence may vary significantly between different neonatal intensive care units. The overall prevalence of NEC is estimated to be 1 to 3 per 1000 live births [2]. Ninety per cent of NEC affected neonates are premature, and 14% of them are weighing less than 1000g. Notably, 50% of the extremely low birth weight neonates may need a surgical intervention. Despite advancements in the treatment of NEC, the mortality rates in premature neonates remains high, ranging from 10% to 50% [1,2].

Advances in medical knowledge have demonstrated that breast milk (BM) is the most favourable source of nutri-

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tion of neonates and its health, nutritional, immunological, developmental, and physiological benefits are universally established [3]. In addition, numerous studies have shown that BM minimises the occurrence and severity of NEC in premature neonates by reducing the influence of risk factors in the development of NEC [4,5]. On the basis of these data, the present review aims to investigate the effectiveness of BM in the management of NEC. We sought to test the hypothesis that after reviewing the current literature, we could propose BM not only as a means to prevent NEC, but as a modulator of the immature gut of premature neonates.

METHODS

The review of the literature was performed through PubMed and Google Scholar databases. Inclusion criteria concerned original and review articles, systematic reviews and meta-analyses published from January 1, 1980 to December 31, 2023, without language restrictions. The search strategy was performed using the Boolean operators AND/OR. The search terms used were: human milk OR breast milk OR breast feeding OR enteral nutrition OR donor milk OR human-milk- based fortifiers AND premature neonates OR low birth weight neonates OR very low birth weight neonates OR extremely low birth weight neonates AND intestinal microbiota OR bioactive factors AND necrotizing enterocolitis OR experimental necrotizing enterocolitis OR intestinal inflammation. Furthermore, the references of the articles were investigated by hand for related articles. All articles were selected systematically for inclusion and critically evaluated.

Necrotizing enterocolitis

1. Factors associated with pathogenesis of NEC in premature neonates

Although it is generally accepted that NEC is a multifactorial disease, preterm birth, the gastrointestinal microbiota and the intestinal immaturity are the major risk factors for the pathogenesis of NEC in premature neonates. Intrauterine infection is the leading cause of preterm birth and recent research focuses on the association of uterine microbiome and preterm birth [6]. The role of gastrointestinal microbiota is very important in protecting mucosal integrity and alterations in its synthesis may lead to sepsis, NEC and systemic inflammatory bowel disease. Intestinal immaturity related factors such as impaired gut motility, digestion, absorption, barrier function, immune defense and circulatory regulation, may be responsible for the pathogenesis of NEC in premature neonates [7]. Furthermore, additional factors such as genetics, the type of diet, e.g. human milk versus formula, the exposure to antibiotics and the mode of delivery, all may contribute to NEC development [8-10].

2. Gastrointestinal microbiota: from fetal life to early postnatal days

2a. Fetal gastrointestinal microbiota

Although GIT is thought to be sterile in normal fetuses, with microbial colonisation of the gut beginning at birth from vaginal bacteria in vaginal delivery or from maternal skin surface and the surrounding milieu in caesarian section, cultured-dependent studies have discovered microorganisms in amniotic fluid, fetal membranes, umbilical cord, and placenta [11]. Moreover, several studies based on non-cultured dependent studies by using high throughput 16S ribosomal RNA gene analysis, revealed the presence of substantially diverse assemblages of bacteria, such as *Enterococci and Staphylococci*, isolated from human meconium, obviously suggesting that this material was composed during fetal life [12,13].

2b. Early postnatal life

The early postnatal life comprises a period of roughly 7-9 days, during the course of which the development of intestinal microbiota is settled [14]. In full-term neonates, the first bacteria that colonize the intestine include *Streptococcus*, *Staphylococcus*, *Escherichia coli*, *Lactobacillus*, and *Enterobacter* species. These bacteria by consuming oxygen produce a low oxygen environment, giving the opportunity to grow and, finally, prevail anaerobic bacteria species such as *Clostridia*, *Bifidobacterium* species and members of *Firmicutes* phyla [14]. However, other factors, including the mode of delivery and diet play a significant role in the initial colonization. More specifically, neonates born vaginally are seeded with maternal vaginal flora, such as *Lactobacillus* and *Prevotella* species, while those born by caesarian section are colonised by skin flora, such as *Staphylococcus* and *Corynebacterium* [15]. Moreover, neonates born by caesarian delivery show a decreased amount of *Bifidobacteria* and a delay in colonization [15]. BM is another potential provider of bacteria to the neonatal gut such as *Staphylococcus*, *Streptococcus, Lactobacillus* and *Weissella* species. Nevertheless, full term neonates fed with formula show a different microbial pattern, promoting the presence of *Enterobacteriacea*e, *Bacteroides* species, and *Clostridium difficile* [16]. Yet, there is a controversy concerning the amount of *Bifidobacteria* provided by formula fed neonates, which may reflect the different composition of formulas [15].

Preterm neonates are characterised by some unique characteristics, usually derived from an unexpected delivery due to an inflammation of the maternal/fetal membrane. For instance, preterm neonates are fed earlier and usually by formula milk, they are exposed to antibiotics and they are usually grown up in a hospital environment that is host to many atypical bacteria [16]. Consequently, the preterm intestinal microbiota is characterised by a decreased overall diversity and a different microbial load than those of full-term neonates, consisted by bacteria, such as *Escherichia coli*, *Staphylococcus* and *Klebsiella* species, facultative anaerobes, such as *Enterobacteriaceae*, *Enterococcaceae*, and *Weissella* and decreased proportion of beneficial bacteria such as *Bifiiobacteria* and *Lactobacillus* [17].

2c. The impact of the preterm intestinal microbiota in the pathogenesis of NEC

Intestinal dysbiosis with lower microbiota diversity has been found to be related with the development of NEC in preterm neonates. Mai et al. [17], by comparing the intestinal microbiota of premature neonates with NEC with this of unaffected control neonates, found an increase of 34% of *Proteobacteria* and a decrease of 32% of *Firmicutes,* in samples collected one week but less than 72 hours prior to NEC, but not in matched samples. Similarly, Torrazza et al. [11], by analysing fecal samples of premature neonates, using 16S rRNA methods, at two, one and zero weeks prior to NEC development, found a higher proportion of phylum *Proteobacteria* (61%) and *Actinobacteria* (3%) two weeks and one week respectively compared to controls, and lower numbers of *Bifidobacteria* and *Bacteroides*. Additionally, certain bacteria of the *Klebsiella* genus were found before the NEC presentation. A prospective control study evaluated the intestinal microbiota between premature neonates, who developed NEC, and unaffected controls. They revealed that in the early onset of NEC, the abundances of *Clostridium sensu stricto* were much higher than those of case controls, while in the late onset of NEC, Gammaproteobacteria (*Escherichia coli, Shigella*, and *Cronobacter*) predominated and were significantly higher than controls [18]. They suggested that the precise infectious agent of NEC may change by the age of premature neonates, while antibiotics administration may have an impact on the microbial diversity [18]. Moreover, in a control study, Heidi et al. [19] reported the existence and plethora of *Clostridium perfringens* and *Bacteroides dorei* in meconium samples of preterm neonates (aged 24-29 weeks) who developed NEC, compared to those who did not. They suggested that the pre-existence of a NEC-linked gut microbiota with *Clostridium perfringens* and *Bacteroides dorei* in the meconium, predisposes to a NEC-associated microbiota development. Conflicting are the findings of Wang et al. [20] and McMurtry et al. [21]. The former noticed low microbiota diversity in neonates with NEC, an increase in *Gammaproteobacteria* and decrease in other bacteria species, suggesting the impact of a single dominant microorganism responsible for NEC. The latter reported that bacterial diversity tended to decrease with the severity of NEC and lack of Clostridia in lethal cases of NEC, suggesting the perception of bacterial dysbiosis. In summary, it seems that the intestinal microbiota of preterm neonates, who develop NEC later, is different than those who do not. Most studies suggest that there is not a distinct pattern of intestinal colonisation associated with NEC development, while the age of onset may be an additional contributing factor to the microbial colonisation of the intestine.

3. The GIT host defense system

3a. Physical barriers

Epithelial cells represent the physical barrier of the intestinal lumen from the other parts of the human body. The integrity of this barrier is sustained by the presence of tight junction among epithelial cells comprised by enterocytes, goblet cells and Paneth cells. Enterocytes not only provide a physical barrier, but also produce a substantial number of immunomodulatory factors [22]. The recognition of bacteria is first made by Toll like receptors (TLRs) molecules expressed by enterocytes. Among different TLRs molecules, TLR4 is implicated in the pathogenesis of NEC [23]. Goblet cells, first recognised at 9 to 10 weeks of gestation, are involved in the secretion of mucin glycoproteins, which generate the mucus layer of the intestine. Mucus layer supports the underlying epithelium from digestive enzymes and bacterial toxins, and any loss in its production or composition may allow bacteria invasion and induction of NEC [24]. Paneth cells are specialised epithelial cells located in the crypts of Lieberkühn secreting defensins and other anti-microbial peptides that kill invasive pathogens, frame the intestinal microbiota, protect the intestinal stem cells from pathogens, trigger the stem cells differentiation, and participate to the regeneration of blood vessels after injuries to the gut.[24] According to the hypothesis of McElroy et al. [25], Paneth cells have a pivotal role in the onset of NEC in premature neonates. Destruction of Paneth cells by microbial toxins leads to bacterial invasion, severe inflammation, pneumatosis intestinalis and vascular closure in the submucosa, triggering the ultimate pathway to NEC. Tight junctions

between epithelial cells restrict the translocation of bacteria, while helping the absorption of macromolecules produced during the process of digestion [25]. Immaturity in the composition and function of tight junctions lead to increased permeability of the epithelial barrier to the products of bacteria such as lipopolysaccharide, which in turn stimulate the secretion of several pro-inflammatory cytokines by the epithelial cells, involving tumor necrosis factor (TNF), IL-6, IL-8, all of them contributing to the distinctive inflammatory process of NEC [25].

3b. The gut immune system-the role of enterocytes in NEC

Directly below the epithelial barrier, specific immune cells reside that are capable of initiating immune feedback. These include macrophages, dendritic cells, T cells and B cells. Furthermore, specialised epithelial cells, called microfold cells (M cells), are believed to act as an antigen sampling system. Any damage to M cells may lead to an increased uptake of microorganisms, as it may be seen during gut inflammation [26].

Activation of the immune system is achieved by the recognition of a pathogen-associated molecular pattern by the host immune pattern recognition receptors (PRRs). TLR4 is an important PRR that recognises lipopolysaccharide (LPS), a crucial endotoxin in the pathogenesis of NEC and its activation in the premature gut is required for the development of NEC [27]. Accordingly, strategies that inhibit TLR4 signaling, including amniotic fluid, breast milk, and genetic deletion of TLR4 from the intestinal epithelium in animal models, constrict the NEC severity [28,29].

The expression of CD14 (cluster of differentiation 14, the co-receptor of LPS) on enterocytes is thought to be an important factor in the induction of NEC [30]. Enterocytes are capable of producing large amount of interleukin-8 (IL-8) in response to LPS, bacteria or inflammatory cytokines, and compared to control neonates, premature infants have higher levels of IL-8 in NEC affected tissue and serum [31]. In conclusion, enterocytes are not exclusively a physical barrier but also participate in gut homeostasis by secreting and activating various immunomodulatory factors in response to various strains of NEC-associated bacteria.

BM

A substantial number of short- and long-term studies have documented BM as the normative standard for infant feeding and nutrition [31]. The beneficial properties of BM are based not only on nutrients, but also on various bioactive compounds with growth, anti-pathogenic and anti-inflammatory properties, that play a pivotal role in neonate health and survival [31] (Figure 1). BM is a potential native immune system that protects mother's offspring through three ways: a) inhibition of pathogen binding, b) prebiotic activity, and c) immune control, and adjustments of infection [32]. The impact of immunomodulating components of BM on NEC are shown in Table 1.

Immunomodulating components of BM and protection against NEC

Lactoferrin

Lactoferrin is an iron-binding glycoprotein that acts as a part of inherent immune system and is found in human BM [33]. It acts by many mechanisms which target in the protection of intestine from systemic infection and NEC in premature neonates: a) in stomach, under the influence of pepsin is transformed to lactoferricin which acts against gram-negative bacteria by disrupting their cell-membrane, b) synergistically with lysozyme may kill gram-negative bacteria in the stomach, c) it may bind to TLR4 and CD14 receptors blocking the adherence of bacteria to the intestinal epithelium, d) it promotes the apoptosis of infected intestinal epithelial cells, e) it stimulates the growth of commensal bacteria, and f) reduces the production of inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and IL-8 via blockage of nuclear factor κB [33,34]. Published studies demonstrated that prophylactic enteral lactoferrin supplementation prevented late-onset sepsis and NEC in preterm neonates [32,33]. In contrast, the findings of a recent study revealed that lactoferrin enteral supplementation did not decrease incidence of NEC and infection [34].

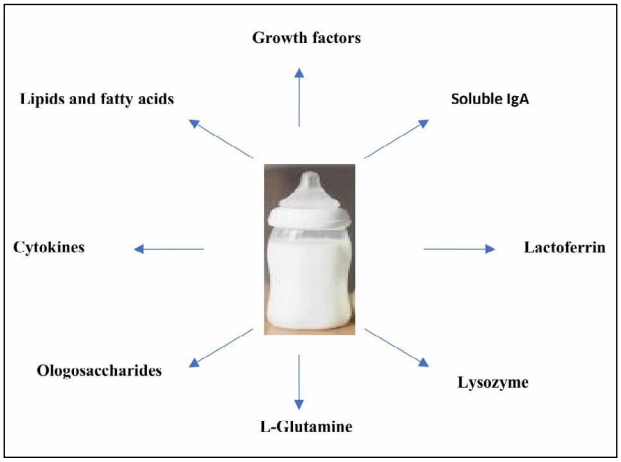

FIGURE 1. Summary of immunomodulating components of BM and protection against NEC.

TABLE 1. Immunomodulating components of BM against NEC.

Component	Role in NEC protection	Reference
Lactoferrin	a. acts against Gram-bacteria in the stomach b. synergistically with lysozyme kills Gram- bacteria in the stomach c. binds to the TLR4 and CD14 receptors blocking the adherence of bacteria to the intestinal epithelium d. promotes the apoptosis of infected intestinal epithelial cells e. stimulates the growth of commensal bacteria f. reduces the production of inflammatory cytokine IL-1β, TNF*-α, IL-6, IL-8	32-34
Lysozyme	a. synergistically with lactoferrin degrades the outer wall of pathogens bacteria protecting the intestine b. protects the intestinal epithelial. From NEC	35-36
Oligosaccharides	a. inhibit pathogens from adhering with epithelial cells of intestine b. preserve the growth of lactobacilli and bifidobacterial c. reduce the incidence of NEC	37-41
Cytokines *TNF-α, IL-6, IL-6, IL-12, IL-2, INF-γ, TGF-β, IL-7, IL-10, IL-18, G-CSF*	a. contribution in the pathogenesis of NEC b. anti-inflammatory properties (IL-10)	42-46
L-glutamine	a. stimulates intestinal cell proliferation and small bowel growth b. antioxidant, anti-apoptosis and anti-inflammation activities which are involved in the pathogenesis of NEC	47-50
Secretory IgA	a. entraps microbes in the mucus of intestine b. downregulates pro-inflammatory bacterial antigens on commensal bacteria	51-52
Lipids and fatty acids - Saturated and monounsaturated fatty acids - Long-chain Polyunsaturated fatty acids (LCPUFA)	a. promotes intestinal barrier b. regulate the intestinal inflammation	53-54
Growth factors *EGF, HB-EGF, IGF1/IGF2, VEGF, EPO, G-CSF*	a. maintain intestinal homeostasis b. protect intestinal barrier	55-57

TLR4: toll like receptor 4, CD14: cluster of differentiation 14, TNF: tumor necrosis factor, INF-γ: interferon gamma, TGF-β: tumor growth factor beta, G-CSF:granulocyte colony stimulator factor, EGF: epidermal growth factor, HB: heparin binding, IGF: insulin like growth factor, VEGF: vascular endothelial growth factor, EPO: erythropoietin

Lysozyme

BM lysozyme is an antibacterial immune-active enzyme, which in synergy with lactoferrin, binds to lipopolysaccharide in the outer wall of bacteria, resulting in degradation of internal proteoglycan matrices of bacterial membranes [35]. It has been also found that lysozyme is secreted by Paneth cells in the GIT in response to enteric pathogens [35]. Concerning NEC, it has been suggested that neonates with NEC have reduced concentration of Paneth cells [25]. As a result, the role of lysozyme in protecting breast fed neonates from intestinal inflammation and NEC is significant [36].

Oligosaccharides

The human milk oligosaccharides (HMOs) consistof three to 32 sugars in size, that they are not digestible by the human intestinal tract, and represent roughly 20% of the whole carbohydrate concentration of BM [37]. HMOs lie on the position of microbial receptors and inhibit pathogens from adhering with epithelial cell walls of the intestine. Also, it has been found that they preserve the growth of *lactobacilli* and *Bifidobacteria* in the gastrointestinal tract, and reduce the presence of pathogens [38]. Studies have shown that only *Bifidobacteria* and *Bacteroides* are able to consume HMOs by encoding the complex array of glycosidases necessary to transport and digest HMOs [39]. In a randomised control study of 75 preterm neonates (birth weight less than 1500 g and gestational age equal or less than 34 weeks), Armanian et al. [40] investigated the effect of enteral supplementation with a probiotic mixture of short- and long- chain oligosaccharides versus no intervention on incidence of NEC in preterm neonates fed exclusively BM. They noticed a reduced incidence of NEC in the group with probiotic supplementation. Moreover, it has been demonstrated that the concentration of HMOs

can predict NEC, as lower concentration is associated with higher incidence of NEC [41].

Cytokines

Cytokines represent protein hormones that interfere in both natural and specific immunity of the newborn infant. BM is the main source of cytokines, specifically anti-inflammatory cytokines, for neonates that are in general deficient of these proteins [42]. Cytokines have antimicrobial, anti-inflammatory and immunomodulatory activities, providing passive protection and modulating the immunological system of the host. Furthermore, cytokines include chemokines, which stimulate movements of other cells, interleukins and interferons [43]. The spectrum of cytokines of BM encompasses pro-inflammatory cytokines (Tumor Necrosis Factor-a, IL-6, IL-8, -1L-12, IL-2 and Tumor Necrosis Factor-γ) and anti-inflammatory cytokines (Transforming Growth Factor-β, IL-7, IL-10, Granulocyte -Colony Stimulating Factor) [42]. Maheshwari et al. [44] studied the level of cytokines in blood in extremely low birth weight neonates who develop NEC in early neonatal period, and found that the diagnosis of NEC was associated with elevated blood levels of IL-1β, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1/CC, C-reactive protein, and lower blood levels of TGF-β, and IL-2. Emami et al. [45], in an experimental NEC study, investigated the anti-inflammatory properties of IL-10, and found an increase in its concentration, suggesting a protective role in the pathogenesis of NEC by weakening the degree of intestinal inflammation. Moreover, Wang et al. [46] investigated the levels of pro-inflammatory cytokines IL-1, and TNF-α and anti-inflammatory IL-10 in premature neonates with NEC and compared them with premature and full-term neonates without NEC. The results showed a statistically significant increase of the above-mentioned cytokines in patients who developed NEC, suggesting a role in the pathogenesis of NEC.

L-glutamine

L-glutamine is present in BM and can stimulate intestinal cell proliferation and small bowel growth, by supplying metabolic nourishment to intestinal epithelial cells. Studies in cells and experimental models indicated that L-glutamine exerts multiple biological activities such as antioxidants, anti-apoptosis and anti-inflammations, which are involved in the pathogenesis of NEC [47]. A lack of glutamine has been proposed to be a risk factor for NEC [48]. In addition, Pawlik et al. [49] reported a lower incidence of NEC after enteral administration of glutamine in a clinical study that included 106 very low birth weight premature neonates versus the control group. However, other studies showed no effect on the incidence of NEC in premature neonates after enteral supplementation with glutamine [50]. More studies are needed to investigate the beneficial intestinal effects of glutamine.

Breast milk secretory IgA

Secretory IgA (sIgA) are derived from the enteromammary and bronchomammary immune system and contribute to the defensive character of BM. BM sIgA has an immunomudulatory role in the GI as a result of entrapping dietary antigens and microbes in the mucus, or down-regulating the expression of pro-inflammatory bacterial antigenic determinants on commensal bacteria [51]. A recent study revealed the important role of BM IgA concentration, as IgA deficiency and reduced IgA-bound bacteria in the intestine was associated with increased risk of NEC development [52].

Breast milk lipids and fatty acids

The effect of BM lipids and fatty acids on gut development is not well-studied, but a lot of mechanisms have been suggested by which fatty acids may modulate the risk of intestinal injury and inflammation. Among different categories of fatty acids, long-chain polyunsaturated fatty acids (LCPUFA) have been reported to contribute to NEC prevention, because of their effect on intestinal barrier function and their critical role in regulating inflammation [53]. Several animal studies have shown that LCPUFA supplementation reduces NEC incidence, but despite these promising results, most current preterm human infant studies did not find any benefit of LCPUFA supplementation regarding the risk of NEC development [53,54].

Growth factors

BM growth factors, such as lactadherin, epidermal growth factor, heparin-binding epidermal growth factor and transforming growth factor-β2, have been reported to contribute to NEC prevention, by maintaining homeostasis of intestinal epithelium, facilitating intestinal mucosal barrier maturation or playing a role in GTI epithelium development pre- and postnatally [55,56]. More specifically, animal and human studies' findings about growth factors administration in NEC experimental models are promising and suggest a potential protective role, as decline incidence and severity of NEC [56,57].

Human-milk based fortifiers

Several studies indicate that BM alone provides insufficient nutrients for preterm infants and cannot meet the

increased demands for growth particularly in extremely premature newborns [58]. So, human milk fortification is currently recommended and widely accepted, in order to improve the nutritional profile of this population [58]. The recent availability of human-milk-based fortifiers overcame the concerns existing about the association between the administration of cow's milk-based fortifiers and NEC [59]. A recent meta-analysis of randomised control trials revealed that there was a reduction in the incidence of NEC with human milk-based fortifiers compared with cow's milk-based fortifiers [60]. However, further trials are required before this therapeutic strategy can be routinely implemented for preterm infants.

Human donor milk and prevention of NEC

Despite the fact that some immunomodulatory constituents of human milk are reduced after pasteurisation of donor milk, its beneficial effects are not completely lost. Although premature neonates receiving their own mother's milk have better feeding tolerance and lower incidence of NEC, there is no evidence that pasteurised donor milk does not administer some health benefits as does mother's own milk [61]. In a randomised trial, Schanler et al. [62] found an increased incidence of NEC in premature neonates fed with formula or donor BM compared with those premature neonates fed with their own mothers' milk. In addition, Christofalo et al [5] in a randomised controlled trial noticed that extremely preterm neonates who received bovine-based preterm formula showed significantly greater duration of parenteral nutrition and higher percentage of surgical NEC compared to those premature neonates fed with either donor human milk or human milk-based human milk fortifier. So, regarding the prevention of NEC, donor milk seems to maintain some of the immunological advantages of fresh human milk [63].

CONCLUSION

Prematurity and low birth weight due to prematurity remains a leading cause of neonatal mortality and morbidity. NEC is known to participate largely among gastrointestinal complications in this age group due to immature immunologic and host defense gastrointestinal systems. BM is considered as a tissue similar to plasma as it contains a variety of immunomodulatory components such as immunoglobulins, cytokines, lactoferrin, lysozyme and other factors that potentially deliberate protection against a diverse range of diseases. Despite ongoing research on the pathogenesis of NEC, the understanding of this devastating disease has increased slowly in recent years. Intestinal epithelial barrier, intestinal microbiota and the immature immunologic environment of the gastrointestinal tract have a crucial influence in the development of NEC, particularly in premature neonates. However, there is ongoing evidence that BM contains multiple components that aid to prevent, and modulate the immature immune system of premature neonates. From this point of view, BM is considered not only a choice of diet but rather a modulator of the immature immune system of the preterm neonate.

Conflict of interest: *None*

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Review

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Acute abdomen in the era of immune checkpoints inhibitors - what the surgeon needs to know: A narrative review

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ABSTRACT

Immune checkpoint inhibitors (ICI) have been approved for the treatment of a variety of malignancies. Immune-related adverse events are rare and might affect a lot of different organs including the intestines. Enterocolitis is a common complication characterised by symptoms such as diarrhoea, abdominal pain, and vomiting. In rare circumstances, bowel perforation, obstruction, or even toxic megacolon might appear. The proper therapeutic management of these conditions is based on case reports or case series. Conservative management is the standard of care in the case of ileus, however, the safety of performing a bowel anastomosis has not been answered yet. This study aims to raise awareness among the medical community, and specifically surgeons, regarding the intestinal complications of ICI, as the uprising administration of these targeted therapies makes this knowledge necessary.

Key Words: *Immune checkpoint inhibitors; acute abdomen; ileus; enterocolitis; immune-mediated colitis; immunotherapy adverse events*

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INTRODUCTION

Immunotherapy is a targeted therapy used as first-line treatment for a variety of malignancies including melanoma, non-small cell lung carcinoma (NSCLC), microsatellite-instability (MSI) high and mismatch repair deficiency (dMMR) colorectal cancer [1] and others. Programmed cell death 1 (PD1) and programmed cell death ligand 1 (PDL1) are two well-studied molecular targets, the blockade of

which results in the inactivation of T-cells, preventing immune response. Pembrolizumab and nivolumab are anti-PD-1 immune checkpoint inhibitors (ICIs), while atezolizumab, avelumab, and durvalumab are anti-PD-L1 ICIs. Anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies, such as ipilimumab and tremelimumab, suggest another category of ICIs, which aim at tumor reduction [2]. Immune-related adverse events (irAEs) may affect a variety of organs, such as the liver, colon, endocrine glands, lungs, and skin [2]. Life-threatening immune-related side effects are rare, however, enterocolitis is quite common, usually presenting with diarrhoea, abdominal pain, vomiting, and nausea [3]. In the emergency setting, bowel perforation, obstruction, or even toxic megacolon may appear [2]. This article aims to raise awareness of this relatively new clinical entity, as a high percentage of gastroenterologists and surgeons are not acquainted with it.

METHODOLOGY

A comprehensive literature search was performed from September 1st 2024 to October 31st 2024 across several major databases, including PubMed, Scopus, and Web of Science, to gather relevant information. Keywords such as "immune checkpoint inhibitors", "PD-1 antibodies", "PD-L1 antibodies", "enterocolitis", "intestine", and "intestinal adverse events", were used. The selection criteria were focused on articles published in the English language. Unfortunately, no randomised control studies and no meta-analyses were found, indicating the rare character of this clinical entity.

EPIDEMIOLOGY AND PREDICTIVE MARKERS

Patients treated with anti-CTLA-4 therapy carry a higher risk of developing enterocolitis compared to anti-PD-1 therapy alone (8-20% vs 1.3%, respectively [4]), however, a combination of ICIs has the greatest probability of developing colitis [3]. In particular, in a meta-analysis conducted by Wang et al [5] with 8,863 participants, the incidence of GI irAEs during PD-1/PD-L1 inhibitor monotherapy with 1.3% for all-grade colitis, 0.9% for severe colitis and 1.2% for severe diarrhoea, while combination ipilimumab and nivolumab resulted in the highest incidences of all-grade colitis (13.6%), severe colitis (9.4%) and severe diarrhoea (9.2%) among ICIs. The median period from the initiation of treatment to symptom onset is approximately three months [6]. The GI symptoms present usually after three weeks of treatment but they can appear anytime [7]. High suspicion index and clinical experience lead to earlier diagnosis, which explains the rising incidence of any grade irAEs [8].

Other predisposing factors include previously treated inflammatory bowel diseases (IBD), high doses of ICIs, microbiota rich in firmicutes and poor in Bacteroidetes, previous hepatitis or HIV infection, and other autoimmune diseases [3], which should be taken into consideration before beginning ICI therapy. Predictive biomarkers that could predict the development of toxicities have been described in terms of ipilimumab such as oeosinophils [9] and interleukin-17 [10]. A single-center study by Pavan et al [11] in patients treated with anti-PD-1/PD-L1 therapy for advanced NSCLC revealed an association between low neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and irAEs, with multivariate analysis confirming PLR as an independent predictive biomarker.

PATHOPHYSIOLOGY

Antibody PD-1 blockages result in the inactivation of T cells [2]. Blocking the PD-(L)1 axis leads to an increased number of CD8+ cells, especially near the tumour site, with high expression of the cytotoxic granzyme B pathway [12]. The inhibition of the PD-L1 by the innate immune system and the inhibition of colitis through a regulatory population of CD4+CD25-PD-1 T cells have been associated with the pathophysiology of ICI-induced colitis although more data are needed [5]. PD-1-induced colitis induces a high concentration of mucosal and intraepithelial CD8+ T-cells population [3,2]. The Th17/ IL-17 axis is also responsible for the production of chemokines CXCL8 and GM-CSFF by intestinal epithelial cells, which attract neutrophils, forming a mucosal barrier [12]. Neutrophil infiltration is a common characteristic of ICI-mediated colitis (IMC) biopsies after both anti-CTLA-4 and anti-PD1 therapy [12].

Anti-CTLA4 antibodies prevent the interaction between CTLA-4 receptor, which is found on regulatory T-cells, and its ligand, B7 [2]. This intervention results in increased CD28 activity, and promotes a direct response of the cytotoxic T-cells against tumour cells [2]. Toxicity from anti-CTLA-4 antibodies is dose-dependent, whereas toxicity from anti-PD-1/PD-L1 is independent of doses [8]. For example, severe-grade toxicities due to Pembrolizumab were similar at doses of 10 mg/kg and its FDA-approved dosage of 2 mg/kg [13].

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Diarrhea is the most frequent symptom, usually without blood in stool, associated with urgency [2]. Rectum and sigmoid colon are affected in the majority of patients, however, the small intestine might also be involved [3], which can result in bowel obstruction [2]. Enteritis may exist without the presence of concomitant colitis [14]. Endoscopy reveals focal areas of inflammation with pen-

etrating oeosinophils and neutrophils, as well as ulcerations in almost 80% of the cases, which can lead to perforation [3]. At first, two types of enterocolitis were identified; active colitis with neutrophilic crypt microabscesses, atrophy and cell apoptosis, and lymphocytic colitis with increased intraepithelial lymphocytes [15]. The level of diarrhoea is not correlated with endoscopic findings [14]. Histological findings include lamina propria expansion, villous bleeding, intraepithelial neutrophils/ lymphocytes, and increased crypt/gland apoptosis [7]. These pathologic features are non-specific and commonly seen in IBD as well [14]. On the other hand, crypt rupture with adjacent histiocytes, either isolated or forming granulomas, suggests a rather unusual finding, which was identified in almost half of the biopsies of ICI-mediated colitis [15]. Collins et al [4] classified gastrointestinal (GI) irAEs into four clinicopathologic categories: acute colitis, microscopic colitis, acute gastritis, and coprostasis, reporting one case of necrotising enterocolitis and generally good response to corticosteroids.

Differential diagnosis includes cytomegalovirus (CMV) colitis, hepatitis, Clostridium difficile, celiac disease, and IBD [3]. Fecal lactoferrin, fecal calprotectin, stool culture, Clostridium difficile antigen, and serology studies including CMV, are essential laboratory tests in order to rule out infection and IBD [2,14,7]. The use of immunochemistry to rule out CMV colitis is also suggested [15]. Young age and the presence of Paneth cells favor the diagnosis of IBD [15]. A thorough medical history, laboratory and serology tests, endoscopy and histopathology, are required to set the diagnosis of ICI-mediated colitis and differentiate it from other types of colitis.

GI AEs are classified into four categories based on the seriousness of the clinical manifestation, in order to guide the therapeutic management [2]. Grade 3 and Grade 4 ICI-induced colitis are defined as severe irAEs with more than 7 diarrhoeic stools per day [2]. Intense abdominal pain, fever, sepsis and rectal bleeding are warning signs which indicate that a Computed Tomography (CT) should be upfront performed to exclude complications such as perforation, abscess formation, and toxic megacolon [2].

THERAPEUTIC MANAGEMENT

Intravenous or oral rehydration, based on the severity of the symptoms, is essential for fluid restoration and resuscitation, as well as electrolyte replacement. Loperamide may also be useful to reduce the frequency of diarrhoea [8]. The first-line treatment for ICI-induced colitis is corticosteroid therapy, budesonide, prednisone or methylprednisolone, dependent on the grade of diarrhoea, after an infectious cause is ruled out [2]. The majority of patients, 60-80% respond positively [3]. Corticoid resistant colitis may require infliximab, mycophenolate mofetil, or vedolizumab alternatively [2]. However, TNF-a inhibitors should be avoided in case of possible colonic perforation [3]. In severe cases, withdrawal and permanent discontinuation of ICIs is required [2,16]. Readministration of anti-CTLA-4 in patients with previous ICI-induced enterocolitis is associated with increased possibility of relapse [6]. In addition, it should be taken into consideration that the administration of cortisone may conceal fever and other clinical manifestations of a possible bowel perforation [7]. The key-points of ICI-induced GI irAEs, including symptoms, differential diagnosis, diagnostic and therapeutic management are provided in Table 1.

TABLE 1. Key-points regarding ICI-related GI irAEs.

Symptoms	Clinical condition	Differential diagnosis	Laboratory exams	Imaging	Therapeutic management
Diarrhoea, fecal incontinence, rectal bleeding, mucus in stool, anemia, weight loss	Enteritis, colitis, Enterocolitis	IBD	Fecal calpronectin , fecal lactoferrin	Endoscopy with biopsies (pathology including immunochemistry)	ICI withdrawal Fluid and electrolyte administration Loperamide
Abdominal pain, psepsis	Bowel perforation, abscess formation, peritonitis	Infection (CMV, hepatitis, Clostridium difficile)	Stool culture, Cl. Difficile antigen, serology for CMV	CT abdomen	Corticosteroids
Vomiting Nausea	Bowel obstruction	Celiac disease			Infliximab, Mycofenolate Mofetil vedolizumab
Fever	Toxic megacolon				Surgery, bowel resection with or without anastomosis

Yasuda et al [17] published the first case of nivolumab-related small bowel perforation where an end ileostomy was performed. Kim et al [18] reported a case of proximal jejunum perforation in a patient with NSCLC treated with Pembrolizumab, who underwent resection and primary anastomosis without postoperative complications. Another case with small bowel perforation and concomitant inflammatory changes of the ileum was reported in a 65-year-old woman treated with Pembrolizumab [3]. No signs of colon or rectal involvement were detected, resection of the small bowel with primary anastomosis was performed, pathology revealed non-caseating granulomatous inflammation and the patient reinitiated pembrolizumab after a few weeks. Primary small bowel anastomosis with a linear staple is reported in several cases without postoperative complications [19]. Kiraci et al [20] published a case report of Pembrolizumab-related appendiceal perforation in a patient treated for advanced melanoma. Conservative management of contained perforation of the appendix in frames of IMC (ICI-mediated colitis) has also been reported [21]. The perforation can be associated with the presence of stricture distal to the dilated loop [22], or it can be a result of rapid tumor regression [23]. In patients treated with immunotherapy, who develop acute abdominal pain, with or without diarrhoea, urgent imaging should be performed to exclude life-threatening surgical complications, such as perforation [20].

Calini et al [24] published a retrospective cohort of 31 patients treated with ICIs who underwent elective or urgent colorectal procedures. Colonic perforation was the main indication for urgent surgery, in which a stoma was performed, while it was associated with a significant risk of postoperative mortality. Even elective cases with curative intention were associated with high morbidity, while only one patient (5,9%) developed an anastomotic leak. Multivisceral resection that was performed in almost half of the elective cases might have contributed to the high morbidity rates. In the same study, mortality was up to 22.2% in the emergency group and 4.5% in the elective one. In the NICHE study [25], where a combination of ipilimumab and nivolumab was administered in 40 patients as neoadjuvant therapy, the anastomotic leakage was 10%. Laparoscopic primary closure of the defect was performed in a case of cecum perforation, which developed in a patient with oesophageal cancer treated with nivolumab by Cho et al [7]. On the contrary, fulminant pancolitis with multifocal areas of ulcerations resistant to conservative treatment leading to GI bleeding and perforation has also been described [26]. However, the safety of an anastomosis or primary closure in the acute setting is not established yet.

Intestinal pseudo-obstruction causing ileus is another very rare manifestation of ICI-related GI irAEs. Prolonged abdominal distention, bloating, vomiting, and constipation are the main symptoms [27], while the median onset is 36 days [16]. A colonoscopy typically reveals mucosal oedema. Imaging should be performed to exclude malignancy progression and possible perforation. Therapeutic management is based on case reports and consists of cessation of immunotherapy [16] in combination with corticosteroid treatment [27]. Administration of infliximab has also been reported for cortisone-resistant cases [28]. Ileus was most frequently reported in PD-1 treatment, while no statistical difference exists between monotherapy and combination therapy [16], in contrast with colitis. Early diagnosis, prompt treatment, and close monitoring of the patients are important to prevent life-threatening complications such as perforation and peritonitis [27]. No surgical intervention is reported for ICI-related bowel obstruction. However, even in this case, close monitoring of the patient is required.

CONCLUSIONS

The increasing use of ICI in oncology will lead to a concomitant rise in ICI-related GI irAEs. A high index of clinical suspicion and experience leads to earlier diagnosis and better outcomes. ICI enterocolitis is a contemporary disease that most surgeons are not acquainted with and it can cause acute abdomen. A multidisciplinary approach and good cooperation among oncologists, gastroenterologists, pathologists, and surgeons are required to achieve the ultimate clinical outcomes. The possibility of bowel perforation in the emergency setting must be excluded soon to avoid mortality. The safety of primary bowel anastomosis or primary closure in patients treated with anti-PD1 and anti-PDL1 is a question not answered yet. Last but not least, ICI-related bowel obstruction requires drug withdrawal and nonoperative management. More structured clinical studies are necessary to guide surgical decision making.

Ethical standards declaration: *Ethical approval was not obtained from the medical research ethics committee, due to the nature of this study.*

Conflict of interest: *There are no conflicts of interest to declare.*

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Systematic Review

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Incidence of cancer after paediatric solid organ transplant recipients: A Scoping Review

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ABSTRACT

Background: To investigate the incidence of post-transplant malignancies in paediatric recipients of solid organ transplants.

Materials and Methods: We searched MEDLINE, Scopus and Web of Science up to January 2025 for observational studies reporting on cancer incidence in children who underwent solid organ transplantation (SOT). Data extraction and quality assessment were performed by two independent reviewers. Data on incidence rates, types of malignancies, and patient demographics were extracted and analysed.

Results: Sixteen studies with a total of 26,310 paediatric transplant recipients were included. The cumulative incidence of cancer after kidney transplantation ranged from 10.2% at 15 years to 27% at 25 years. For liver transplantation, the incidence was 22% at 25 years, with a range from 3.4% to 7.1% incidence of post-transplant lymphoproliferative disorders (PTLD). Following heart transplantation, the incidence was 30.5% at 10 years.

Conclusions: Paediatric solid organ transplant recipients face a significant risk of developing cancer, particularly PTLD. Regular monitoring and early intervention are essential for improving long-term outcomes.

Key Words: *Paediatric transplantation; cancer incidence; post-transplant lymphoproliferative disorders; prognosis; scoping review*

INTRODUCTION

Paediatric solid organ transplantation (SOT) stands as a cornerstone of modern medicine, offering a lifeline to children grappling with end-stage organ failure [1]. Among the organs transplanted most frequently in paediatric patients are the kidneys, liver, and heart [2]. These life-saving procedures have revolutionised the management of various paediatric conditions, providing hope for improved quality of life and long-term survival [2]. Despite the remarkable progress in paediatric SOT, the necessity for prolonged immunosuppressive therapy remains a significant challenge [3]. The heightened risk of rejection necessitates the use of potent immunosuppressive agents, which in turn predispose recipients to complications, including infections and malignancies [3]. The frequency of transplantation and the severity of underlying diseases contribute to the increased susceptibility to complications, underscoring the need for vigilant monitoring and tailored therapeutic strategies [4].

The immunocompromised state resulting from long-term immunosuppression makes paediatric solid organ

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transplant recipients particularly vulnerable to malignancies [5]. Extensive literature has documented an elevated incidence of various cancers in this population, ranging from skin cancers, such as squamous cell carcinoma and melanoma, to lymphomas and solid tumours affecting various organ systems [6-8]. Studies have highlighted the multifactorial nature of cancer development post-transplantation, implicating factors such as the intensity and duration of immunosuppression, viral infections, genetic predisposition, and environmental exposures [9], [10]. While transplantation extends life expectancy and enhances quality of life, the heightened risk of malignancy poses formidable challenges in paediatric transplant care [6]. The prevalence of malignancies in paediatric patients following SOT represents a significant clinical challenge.

Paediatric solid organ transplant recipients face a spectrum of malignancies, ranging from skin cancers to lymphomas and solid tumours [11]. The incidence and types of cancer vary depending on factors such as the type of transplanted organ, duration of immunosuppressive therapy, and age at transplantation [12]. In this scoping review the authors aim to conduct a comprehensive analysis of the incidence and types of post-transplant malignancies in paediatric recipients of kidney, liver, and heart transplants.

METHODS

This scoping review has been reported in accordance with the Preferred Reported Items for Systematic Review and Meta-Analysis (PRISMA) statement [13].

Data sources

A systematic search was conducted in MEDLINE (via PubMed), Scopus and Web of Science up to 1 January 2025. The search strategy is presented in Supplementary Table 1. Keywords included «paediatric», «solid organ transplant», «cancer» and «malignancy".

Study Selection

Observational studies in the paediatric population (under 18 years) who had undergone kidney, liver, or heart transplantation and documented the incidence of malignancies were included in the present study. Exclusion criteria included studies focusing solely on adult populations, case reports, and reviews without original data. After removing duplicate entries, two independent reviewers (A.S. and G.S.) screened the titles and abstracts of all retrieved articles. Full-text versions of potentially relevant studies were then assessed according to predefined

TABLE 1. Occurrence of malignancy after kidney transplantation.

	Study	Transplant Year	Average Transplant Age	No. of Patients	No. of Kidneys (%)	No. of Cancers (%)	Average Cancer Age	Cancer Type (N)	Cumulative Incidence
Solid organ transplantation	Kitchlu 2019 [18]	1/7/1991 - 31/12/2014	NA	951	400 (42)	25 (6)	18.7	NA	NA
	Enden 2020 [19]	1/1/1982 - 31/12/2015	7.9	233	137	14 (10.2)	18.7	NHL (10)	NA
	Yanik 2017 [17]	1987 - 2011	NA	17,958	7,822 (43.6)	102	NA	NHL	NA
	Debray 2009 [7]	1/1996 - 7/2007	10.6	1,326	505 (38)	17	NA	PTLD (15)	NA
	Simard 2011 [16]	1970 - 2007	11.66	536	330	26	27.4	Non-melanoma skin (7)	NA
Kidney transplantation	Francis 2017 [14]	1/1963 - 12/2013	NA	NA	1,734	289 (16.7)	14.7	Non-melanoma skin (196)	27% at 25 years
	Ploos van Amstel 2015 [22]	1972 - 2010	13.23	NA	249	54	33.5	Non-melanoma skin (40)	41% at 30 years
	Yabuuchi 2021 [21]	1983 - 2016	11.43	NA	356	12 (3.4)	18.5	PTLD (5)	14.7% at 30 years
	Koukourgianni 2009 [20]	4/1987 – 3/2007	9.7	NA	219	16 (7.3)	NA	PTLD (10)	10.2% at 15 years

Abbreviations: Non-Hodgkin lymphoma, NHL; Posttransplant Lymphoproliferative Disorders, PTDL

eligibility criteria, considering only publications in English. Any discrepancies were resolved through consensus or by consulting a third reviewer (G.T.).

Data extraction

Data was extracted independently by two reviewers (A.S and G.S.) using a data extraction form in Microsoft Excel. The population demographics included the type of organ transplanted (kidney, liver, or heart), with a focus on paediatric patients under 18 years of age. The incidence of malignancies was recorded across the three organ types, with each study presenting the total number of patients (n) and the corresponding percentages (%) for cancer incidence where applicable. Additionally, the mean age at transplantation was noted for each study, with values reported in years. The statistical representation of the cancer data was presented through absolute numbers (n) for the incidence of specific cancers and percentages (%) to denote the prevalence of each malignancy within the study populations. Furthermore, the studies also provided cumulative incidence rates, with cancer types categorised by organ system.

RESULTS

Search results and study characteristics

The flow diagram depicting the study selection process is presented in Figure 1. From the initial search, 1,445 articles were identified. All articles underwent title and abstract screening. Thirty-one studies were retained for full-text assessment. Sixteen studies did not meet the

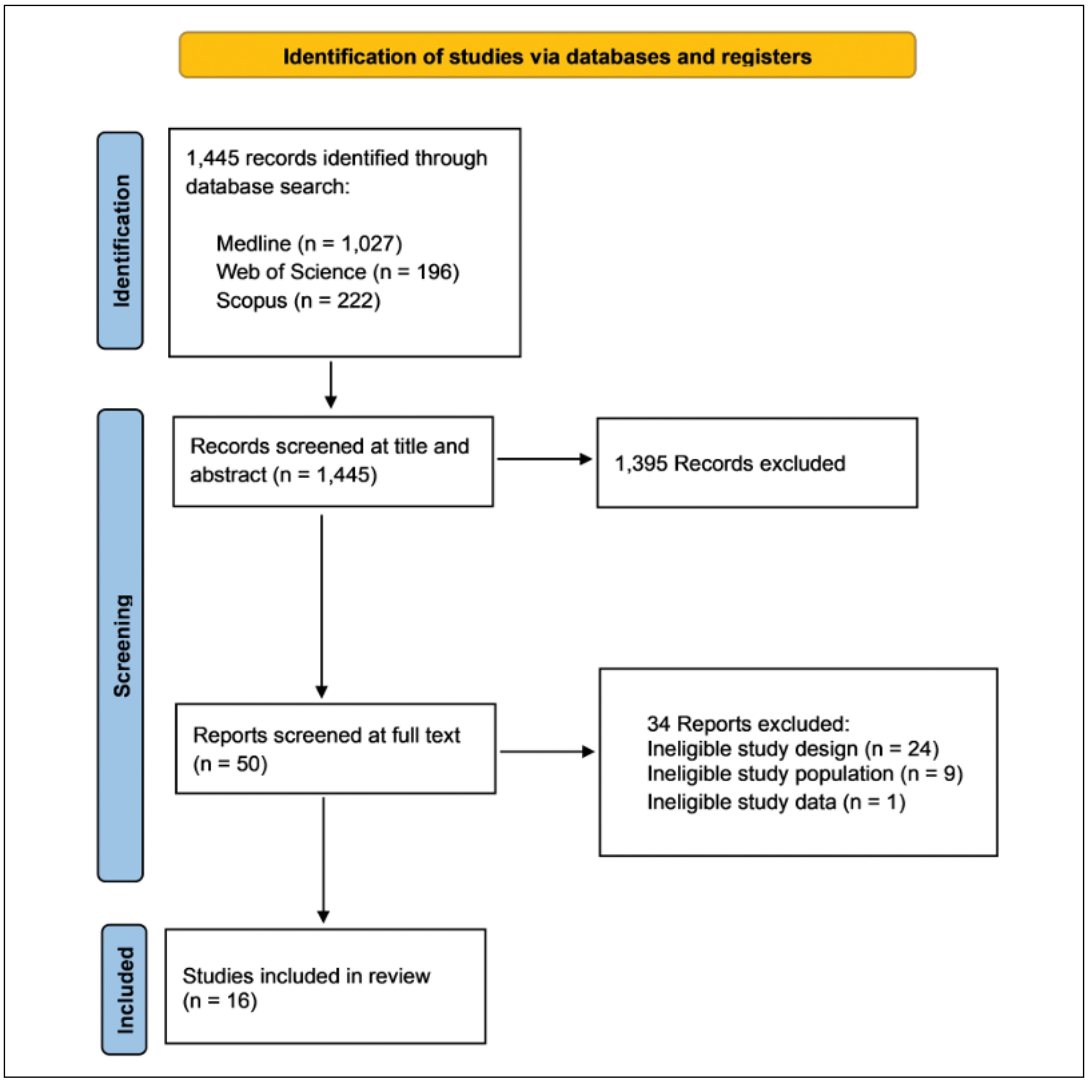

FIGURE 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the identification inclusion and exclusion of studies.

inclusion criteria and were subsequently excluded. Finally, sixteen observational studies were selected for the scoping review [7,14-28]. Five studies evaluated the risk of malignancy in paediatric patients post SOT [7,16-19], four after kidney transplantation [14,20-22], three after liver transplantation [15,24,25] and one after heart transplantation [23]. Three studies specifically assessed the risk of post-transplant lymphoproliferative disorders (PTLD) following heart [26,27] and liver [28] transplantation in paediatric populations. In total, 26,310 paediatric patients were included across the fifteen studies. All data were extracted from registries.

Malignancy post kidney transplantation

Data from nine studies were utilised to assess the occurrence of malignancy following kidney transplantation in paediatric patients [7,14,16-22]. Data is presented in Table 1. Specifically, the study by Kitchlu et al. (2019) includes data from 1991 to 2014 [18]. Out of 951 individuals undergoing SOT, 42% developed cancer, with a mean age of cancer onset at 18.7 years. In the study by Enden et al. (2020), lasting from 1982 to 2015, with a mean transplantation age of 7.9 years, out of 233 individuals examined, 10.2% developed cancer, predominantly lymphomas (NHL), with a mean age of cancer onset at 18.7 years [19]. The study by Yanik et al. (2017) includes data from 1987 to 2011 [17]. Out of 17,958 individuals examined, 43.6% developed cancer, with the majority suffering from NHL. The study by Debray et al. (2009) includes data from 1996 to 2007, with a mean transplantation age of 10.6 years [7]. Out of 1,326 individuals examined, 38% developed cancer, with PTLD being the predominant cancer type. The study by Simard et al. (2011) includes data from 1970 to 2007, with a mean transplantation age of 11.66 years [16]. Out of 536 individuals examined, 26% developed cancer, with the majority having non-melanoma skin cancer. The study by Francis et al. (2017) includes data from 1963 to 2013, without reference to the mean transplantation age [14]. Out of 1,734 individuals examined, 16.7% developed cancer, with the majority having non-melanoma skin cancer. The study by Ploos van Amstel et al. (2015) includes data from 1972 to 2010, with a mean transplantation age of 13.23 years [22]. Out of 249 individuals examined, 21.7% developed cancer, with the majority having non-melanoma skin cancer. The study by Yabuuchi et al. (2021) includes data from 1983 to 2016, with a mean transplantation age of 11.43 years [21]. Out of 356 individuals examined, 3.4% developed cancer, with PTLD being the predominant cancer type. Lastly, the study by Koukourgianni et al. (2009) includes data from 1987 to 2007, with a mean transplantation age of 9.7 years [20]. Out of 219 individuals examined, 7.3% developed cancer, with PTLD being the predominant cancer type.

Malignancy post liver transplantation

Eight studies were utilised to evaluate the likelihood of malignancy following liver transplantation in paediatric patients [7,15,16,18,19,24,25,28]. Data is presented in Table 2. Specifically, the study by Kitchlu et al. (2019) reports that out of 951 individuals examined, 30% underwent liver transplantation, while 7% developed cancer, with a mean age of cancer onset at 9.2 years [18]. In the study by Enden et al. (2020), out of 233 individuals examined, 3.8% developed cancer, with B-cell lymphoma being the predominant cancer type [19]. The study by Debray et al. (2009) reports that out of 1,326 individuals examined, 45% underwent liver transplantation, while 42% developed cancer, with PTLD being the predominant cancer type [7]. The study by Simard et al. (2011) reports that out of 536 individuals examined, 24% underwent liver transplantation, while 6% developed cancer, with NHL being the predominant cancer type [16]. The study by Aberg et al. (2008) includes data from 1982 to 2005 [25]. Out of 78 individuals examined, 6% developed cancer, with non-melanoma skin cancer being the predominant cancer type. The study by Aberg et al. (2018) includes data from 1982 to 2013 [15]. Out of 923 individuals examined, 14% developed cancer, with NHL being the predominant cancer type. The study by Karakoyun et al. (2017) includes data from 1997 to 2015, with a mean transplantation age of 5.4 years [24]. Out of 206 individuals examined, 13% underwent liver transplantation, and PTLD was the predominant cancer type. Lastly, the study by Dogan et al. (2024) reports on 112 paediatric liver transplant recipients. Among them, 43.75% developed EBV DNAemia, and 16.3% developed PTLD [28]. The predominant PTLD subtype was EBV-related B-cell lymphoma, while the mean time to PTLD diagnosis was 41.3 months post-transplant [28].

Malignancy post heart transplantation

Seven studies were utilised to assess the likelihood of malignancy following heart transplantation in paediatric patients [7,16,18,19,23,26,27]. Data is presented in Table 3. Specifically, the study by Kitchlu et al. (2019) reports that out of 951 individuals examined, 23% underwent heart transplantation, while 14% developed cancer [18]. In the study by Enden et al. (2020), out of 233 individuals examined, 4.7% developed cancer, with NHL being the predominant cancer type [19]. The study by Debray et al. (2009) reports that out of 1,326 individuals examined, 8% underwent heart transplantation, while 4% developed cancer, with PTLD being the predominant

TABLE 2. Occurrence of malignancy after liver transplantation.

	Study	Transplant Year	Average Transplant Age	No. of Patients	No. of Livers (%)	No. of Cancers (%)	Average Cancer Age	Cancer Type (N)	Cumulative Incidence
Solid organ transplantation	Kitchlu 2019 [18]	1/7/1991 - 31/12/2014	NA	951	283 (30)	19 (7)	9.2	NA	NA
	Enden 2020 [19]	1/1/1982 - 31/12/2015	4.9	233	53	2 (3.8)	18.6	B-cell lymphoma (1) - Skin (1)	NA
	Debray 2009 [7]	1/1996 - 7/2007	4.4	1,326	605 (45)	42	NA	PTLD (34)	NA
	Simard 2011 [16]	1970 - 2007	11.66	536	128	6	27.4	NHL (5)	NA
Evaluation of PTLD	Dogan 2024 [28]	2010 - 2022	5.3	NA	112	8 (16.3)	NA	PTLD	7.1%
Liver transplantation	Aberg 2008 [25]	1982 - 2005	NA	NA	78	2 (6)	NA	Non-melanoma skin	NA
	Aberg 2018 [15]	1982 - 2013	NA	NA	923	37	NA	NHL (14)	22% at 25 years
	Karakoyun 2017 [24]	1997 - 2015	5.4	NA	206	13	8.6	PTLD (7)	3.4%

Abbreviations: Non-Hodgkin lymphoma, NHL; Posttransplant Lymphoproliferative Disorders, PTDL

cancer type [7]. The study by Simard et al. (2011) reports that out of 536 individuals examined, 11.4% underwent heart transplantation, while 4% developed cancer, with NHL being the predominant cancer type [16]. The study by Webber et al. (2006) includes data from 1993 to 2002, with a mean transplantation age of 6.1 years [26]. Out of 1,184 individuals examined, 8.2% developed cancer. The study by Arshad et al. (2019) includes data from October 1992 to October 2018, with a mean transplantation age of 5.6 years [27]. Out of 202 individuals examined, 11.9% underwent heart transplantation, while 9.9% developed cancer. The above two studies specifically evaluated the

TABLE 3. Occurrence of malignancy after heart transplantation.

	Study	Transplant Year	Average Transplant Age	No. of Patients	No. of Hearts (%)	No. of Cancers (%)	Average Cancer Age	Cancer Type (N)	Cumulative Incidence
Solid organ transplantation	Kitchlu 2019 [18]	1/7/1991 - 31/12/2014	NA	951	218 (23)	30 (14)	NA	NA	NA
	Enden 2020 [19]	1/1/1982 - 31/12/2015	10.3	233	43	2 (4.7)	17.3	NHL (2)	NA
	Debray 2009 [7]	1/1996 - 7/2007	8.6	1,326	104 (8)	4	NA	PTLD (4)	NA
	Simard 2011 [16]	1970 - 2007	11.66	536	61	4	27.4	NHL (3)	NA
Evaluation of PTLD	Webber 2006 [26]	1993 - 2002	6.1	NA	1,184	56	8.2	PTLD	NA
	Arshad 2019 [27]	10/1992 - 10/2018	5.6	NA	202	24 (11.9)	9.9	PTLD	30.5% at 10 years
Heart transplantation	Gambino 2007 [23]	11/1985 - 1/2005	9.7	NA	43	15	NA	PTLD (8)	NA

Abbreviations: Non-Hodgkin lymphoma, NHL; Posttransplant Lymphoproliferative Disorders, PTDL

occurrence of PTLD. Lastly, the study by Gambino et al. (2007) includes data from November 1985 to January 2005, with a mean transplantation age of 9.7 years [23]. Out of 43 individuals examined, 15% underwent heart transplantation, and PTLD was the predominant cancer type in the study.

DISCUSSION

In this scoping review we evaluated the frequency for cancer occurrence following SOT in the paediatric population. Summarily, the results indicate a significant association between transplantation and cancer occurrence, with 819 patients overall developing cancer out of 26,310. The main types of cancer reported include PTLD, particularly NHL, and non-melanoma skin cancers. Following kidney transplantation, the cumulative incidence ranges from 10.2% after 15 years to 27% after 25 years, after liver transplantation, a 22% incidence is reported after 25 years, and a range from 3.4% to 7.1% incidence regarding the likelihood of PTLD development, and finally, after heart transplantation, a 30.5% incidence is reported after ten years. The likelihood of cancer occurrence post kidney transplantation increases over time, while the risk of cancer occurrence is significantly higher post heart transplantation.

The data from the scoping review confirm the overall trend presented in the literature review. Based on the research data, an increase in cancer risk is significant, with some studies reporting an even greater risk in paediatric patients compared to adults [6,29,30]. The type of cancer varies, with common types being non-melanoma skin cancers and PTLD [6]. Additionally, the average age of cancer onset after transplantation is significantly younger compared to general populations, making monitoring and prevention of malignancy even more critical for transplant recipients [17,29].

Immunosuppression is a critical part of transplant therapy, as it helps prevent rejection of the transplanted organ [31]. However, continuous immunosuppression may have adverse effects, including an increased risk of cancer occurrence [31]. Excessive suppression of the immune system, especially over time as seen in paediatric transplantations, may allow cancer cells to develop and further spread, as the normal mechanisms for controlling cancer cells are compromised [32]. This can lead to the development of lymphomas, non-melanoma skin cancers, and other types of cancer [32]. Additionally, immunosuppression may affect the action of normal immune cells that fight cancer cells, making the body's response to cancer more difficult and allowing cancer cells to further spread [5,10]. Therefore, immunosuppression presents a double-edged impact: on one hand, it protects the transplanted organ from rejection, but on the other hand, it may increase the risk of cancer occurrence.

Paediatric transplant patients also face various other factors that can lead to cancer occurrence. Besides immunosuppression, other factors influencing cancer risk include genetic predisposition, pre-existing infections, exposure to carcinogens, and disruptions of the immune system [33]. Transplant recipients, due to the need for long-term pharmacological treatment and immunosuppression, are susceptible to increased exposure to carcinogens and immune system disruptions, which can create an environment conducive to cancer development [34]. Research data confirm that transplant patients have an increased risk of cancer compared to the general population [30]. Additionally, it is observed that cancer occurrence post-transplantation is more common in specific organs, such as the kidney and heart, compared to others [35].

When cancer is discovered in children following transplantation, management usually takes a comprehensive strategy based on the type and stage of cancer, as well as the patient's condition. Therapeutic options may include surgical intervention, chemotherapy, radiotherapy, and in some cases, immunotherapy or outcome-based therapy [6,17]. It is essential to consider the child's sensitivity due to their young age and tailor the treatment accordingly [33]. The prognosis after cancer occurrence post SOT in paediatric patients depends on various factors, including the type of cancer, disease stage, selected treatment, and overall health status of the patient [36]. Early diagnosis and appropriate treatment can significantly improve survival prospects [37]. However, the prognosis may be poorer compared to adults due to the young age of patients, their sensitivity to treatment, and the potential recurrence of cancer [14,22]. Prognosis also depends on the ability to respond to treatment and manage complications, such as graft rejection and immunosuppression-related complications [22]. Additionally, prognosis is influenced by the presence of potential transplantation complications, such as graft dysfunction or the development of other new diseases [19].

The present study has several limitations that should be considered. Although the participants were numerous overall, the search strategy yielded only 1,445 studies, and data heterogeneity limited the generalisability of findings. Future research should adopt broader search strategies and standardised reporting methods to improve data comparability. Additionally, many studies lacked critical variables, such as the average age of transplantation or detailed immunosuppression protocols, making interpretation and clinical implementation challenging. While these findings should be applied with caution due to the quality and variability of the included studies, they highlight the importance of targeted monitoring for high-risk paediat-

ric transplant recipients. Future studies should focus on standardising methodologies, conducting multi-center comparative analyses, and extending follow-up durations to better understand late-onset malignancies and improve clinical care for this vulnerable population.

In summary, the present scoping review evaluated the likelihood of malignancy occurrence post SOT in paediatric patients. The results of the review highlighted the high rate of cancer occurrence post transplantation, with lymphatic system cancers being the most frequent type in this population group. Additionally, it was observed that paediatric patients undergoing SOT face challenges regarding the occurrence and management of cancer, often requiring careful monitoring and tailored treatment. Future studies are recommended to systematically assess this risk, conducting statistical synthesis of the data.

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Living donor liver transplantation could solve shortage of liver grafts in Greece

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ABSTRACT

Organ shortage remains a major challenge in Greece, with low deceased donor rates limiting liver transplantation options. Living Donor Liver Transplantation (LDLT) offers a viable alternative, reducing waiting times, improving graft quality, and enabling elective scheduling. While LDLT introduces risks to donors, stringent medical and ethical evaluations mitigate these concerns. The successful completion of initial LDLT cases in Greece demonstrates its potential to address graft shortages. This article highlights the advantages, challenges, and future prospects of LDLT, advocating for its broader adoption as a transformative solution for liver transplantation in Greece.

Key Words: *Living donor; liver transplantation; Greece; organ shortage; donation*

Organ shortage, especially for liver transplants, remains a major worldwide health problem [1]. With increasingly high demand on one hand and limited availability of deceased donor organs on the other, patients commonly experience protracted waiting times, which in turn negatively impact both their survival and quality of life. Living Donor Liver Transplantation (LDLT), first performed in 1989, represents a significant alternative to deceased donor transplantation, which represents the principal source of liver grafts in the Western world [2,3]. By utilising liver segments from selected living individuals, LDLT offers a potential solution to this major issue. In Greece, deceased donation suggests the only source of graft, whilst unfortunately, deceased donor rates remain low [4]. At this point, the establishment and development of LDLT programs could revolutionise the landscape of liver transplantation, potentially reducing waiting lists and improving Greek patient outcomes.

During LDLT, an adequate portion of a healthy liver from a living donor is transplanted to a compatible recipient with end-stage liver disease [5]. One of the crucial advantages of this approach is that it significantly reduces waiting times, as the procedure can be scheduled electively [6]. This flexibility allows for optimal timing of the surgery, which can be decisive for patients whose health may otherwise significantly deteriorate while awaiting a suitable organ from a deceased donor [6,7]. Minimisation of the cold ischaemia time is another advantage of LDLT, which can further improve graft function and reduce post-transplant complications. For Greece, where the number of deceased donors remains largely inadequate, LDLT offers a significant benefit in terms of scheduling and quality of grafts. Livers from selected living donors are generally healthier, as donors undergo extensive medical evaluations to ensure the absence of liver diseases or other contraindications. Consequently, good quality grafts from healthy living donors tend to demonstrate better post-transplant function hence primary graft non-function ratings are reduced contrary to deceased donor grafts, especially those from marginal or extended criteria donors [8].

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LDLT indeed offers numerous benefits, yet it also introduces major risks, particularly concerning the safety and well-being of the healthy individual who serves as the donor. Potential complications from LDLT include bile leaks, bleeding, infections,and, in rare cases, life-threatening issues [5]. The possibility of complications, as in any other major surgical procedure, highlights the importance of thorough medical evaluations and informed consent processes to ensure that healthy donors fully comprehend the risks involved. Notably, according to established guidelines the live donor risk includes a benchmark 0% mortality and <5% major morbidity rate [9].

Despite the increasing number of liver transplants being performed in Greece over the past years, the demand has consistently exceeded supply. This has been the result of several cultural, religious, and educational factors not adequately addressed by the Greek state [4]. Notwithstanding, some efforts to raise awareness about the importance of organ donation, Greece continues to hold one of the lowest deceased donor rates in the European Union [10]. Greece could effectively mitigate the current shortage of liver grafts by encouraging the development and acceptance of living donation programs. Most importantly, the successful performance of the first two LDLT procedures in Greece in early 2024 was a promising step towards establishing LDLT as a standard practice in the country.

Ethical considerations also play a pivotal role in the decision to proceed with LDLT. The procedure involves a healthy individual undergoing surgery for the benefit of another, which raises concerns about potential coercion and the ethical implications of subjecting a person to potential risks without direct medical benefit. To address these concerns, LDLT programs in Greece and elsewhere implement rigorous protocols for evaluating donors, including psychological assessments and independent donor advocacy, ensuring that donors make informed and voluntary decisions.

In Greece, the successful completion of the first 2 LDLT cases provides a proof of concept that could pave the way for future procedures. As LDLT becomes more common, the experience gained by Greek transplant teams will likely lead to improved surgical techniques, better post-operative care, and enhanced overall outcomes for both donors and recipients. Nonetheless, for LDLT to become a sustainable and effective solution to Greece's organ shortage, a supportive framework is mandatory [10]. This includes training and resources for transplant teams, as well as public education initiatives to raise awareness about the benefits and risks of living donation. Moreover, Greece could benefit from partnerships with other countries that hold well-established and efficient LDLT programs to help the exchange of knowledge and the adoption of best practices. At this point, developing a culture of living donation demands for addressing public concerns and dispelling myths about organ donation is of paramount importance. The Greek Transplant Organization in conjunction with the Ministry of Education and the Ministry of Health need to promote educational campaigns that highlight the success stories of LDLT recipients and donors, emphasising the life-saving potential of living donation. Additionally, efforts to streamline the legal and administrative aspects of LDLT will be essential to make the process more accessible and efficient.

Establishment and dissemination of LDLT represents a significant opportunity to address the ongoing organ shortage in Greece. We firmly believe that LDLT, as a safe and efficient alternative to deceased donor transplants, can reduce waiting times, improve patient outcomes, and foster a new culture of living donation. By building a robust LDLT framework and encouraging public acceptance, Greece can and needs to take meaningful steps toward overcoming its organ donation challenges and improving the lives of countless individuals in need of a liver graft. This effort, however, will not be fruitful if it is not collective, and all included parties need to work consistently and be fully aware of the benefits and challenges of LDLT.

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Case Report

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Laparoscopic hiatal hernia augmentation following sleeve gastrectomy using a "mesh sling" tethered to ligamentum teres – Case report of a novel technique

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ABSTRACT

Symptomatic hiatal hernia following sleeve gastrectomy is a well known and documented complication. The gold standard for its treatment is to perform a hiatal hernia repair combined with conversion of the sleeve to a gastric bypass. However, in some patients a gastric bypass may not be indicated or the patient may be unwilling for the conversion. In these situations, the ligamentum teres augmentation combined with hiatal hernia crural repair seems to be the most effective and popular, according to a literature survey. To avoid damaging the sleeve, the use of prosthetic materials to augment the hiatal repair is generally not recommended. In this case report, for a patient who presented with a hiatal hernia with severe reflux following a sleeve gastrectomy, we describe a novel technique where a sling composed of a strip of composite mesh was loosely placed around the gastroesophageal junction and tethered to a shortened ligamentum teres.

Key Words: *Hiatal hernia; sleeve gastrectomy; ligamentum teres augmentation; mesh sling; case report*

INTRODUCTION

Hiatal hernia and reflux symptoms are not uncommon following a sleeve gastrectomy for morbid obesity. In these patients, the initial line of therapy is the maximum allowed dosage of proton-pump inhibitors for 8 weeks. If this fails, conversion of the sleeve to a gastric bypass is an accepted and proved surgical solution [1]. However, if the patient declines this procedure or if a gastric bypass is not indicated, the most popular surgical option is the use of the ligamentum teres for augmentation with hiatal hernia repair [2]. The other viable options are hiatal augmentation using the LINX® system and the posterior rectus sheath flap technique [3,4]. In hiatal hernias following a gastric bypass, the fundus of the remnant stomach can be mobilized and used for plication. Several papers have been published on the favorable outcomes of the ligamentum teres augmentation technique in the literature over the last decade [5,6]. However, in some patients the ligamentum teres may be unavailable due to its shorter length or distorted due to adhesions. We hereby describe a novel surgical alternative in our patient who presented with a symptomatic hiatal hernia following sleeve gastrectomy. A sling prepared with a composite mesh was placed around the gastroesophageal junction and tethered to a shortened ligamentum teres, as the entire length of the ligamentum teres was unavailable to fully encircle the gastroesophageal junction.

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CASE REPORT

The patient was a 45-year-old woman that presented to the ER with a sudden, severe central chest pain and difficulty in breathing for the past six hours. She had no previous history of cardiac conditions. Her ECG, ECHO and cardiac enzymes were found to be within normal limits, essentially eliminating any acute cardiac event. She had a history of gastroesophageal reflux disease (GERD) and had undergone an endoscopy two months ago that showed a 'large hiatal hernia'. She has been on proton pump inhibitors and was following a controlled diet. She suffered from acute episodes of reflux one -two times per week. She confirmed that she did not have GERD or a hiatal hernia prior to the laparoscopic sleeve gastrectomy that she underwent in another center in 2016. Her BMI was 23.20 on presentation to the ER. An abdominal CT scan was obtained, which revealed a 'Small hiatus hernia with suture material/staplers along the lateral aspect of the gastric fundus.' All of this was explained to the patient, including the need for a semi-urgent surgery to address the hiatal hernia, which was the cause for her current acute symptoms. The options offered to her were a hiatal hernia repair with ligamentum teres augmentation (strongly preferred option) OR hiatal hernia repair with conversion of the sleeve to a gastric bypass (less preferred option as she did not need further weight loss). She readily consented for the hiatal hernia repair with Ligamentum teres augmentation option.

Surgical technique

The patient was positioned in the reverse Trendelenburg position after intubation. The pneumoperitoneum was achieved via a Veress needle and maintained at 12 mmHg. All four ports (one 12 mm for camera and three 5 mm for instruments) that were used were placed in the left upper and lateral quadrants. A 30-degree angled laparoscope was placed in the 12-mm port. Next, a Nathanson retractor was placed just below the xiphoid process for liver retraction, providing adequate visualisation. Adhesions to the ligamentum teres and posterior surface of the left lobe of liver due to the previous surgery were identified and taken down with sharp dissection. A 5-mm-long Ligasure was used to enter the lesser sac via division of the gastrohepatic ligament. The right crus was identified and dissected free from the oesophagus and left crus. Part of the sleeve was seen to be stuck in the hiatal hernia, which was circumferentially dissected and reduced back into the abdomen after widening the hiatus anteriorly (Figure 1). The lower oesophagus was then mobilized for about 4 cm into the abdomen from within the mediastinum. Using monofilament non-absorbable sutures, both the crura were stitched together posterior to the oesophagus. Two stitches were also placed anteriorly. Since the ligamentum teres was involved in the dense adhesions as mentioned above, its full length could not be harvested to encircle the gastroesophageal junction to provide the buttress. So a sling was fashioned using a 6 x 2cm long strip of composite mesh, which was then encircled around the gastroesophageal junction and fixed to the short ligamentum teres using several interrupted non-absorbable monofilament stitches (Figure 2). Fatty tissue in the vicinity was also interposed between the mesh sling and the lower oesophagus to avoid direct contact (Figure 3).

A 38 Fr-size gastric calibration tube was then passed through the mouth and used to determine the tightness of the crural repair and the sling repair. The attending gastroenterologist was called in to do an endoscopy to confirm that the gastroesophageal junction was well within the abdominal cavity and the adequacy of the repair. All the port sites were closed after haemostasis was confirmed (Figure 4).

RESULTS

In the postoperative period, the patient recovered uneventfully. Her symptoms at presentation were relieved. She was discharged on postoperative day 3. In a recent communication with the patient 3 months after the surgery, she complained that she had an episode of vomiting following a rapid intake of food. She was advised to watch her food/liquid intake and to inform if vomiting occurs again. She had no more similar incidents so far.

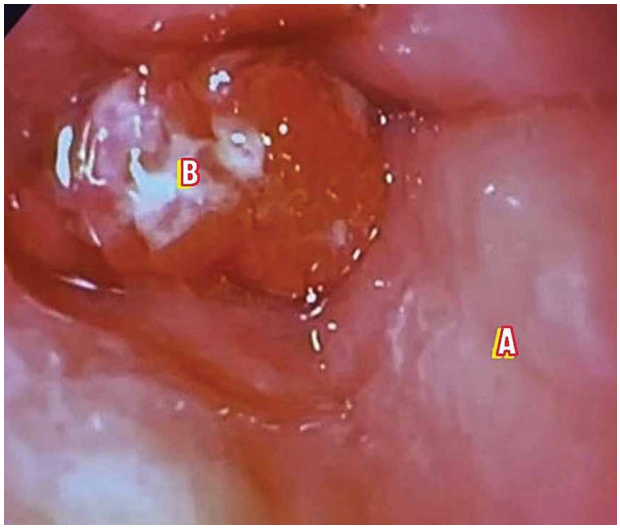

FIGURE 1. Endoscopy showing the gastro-esophageal junction (A) with a hiatal hernia (B).

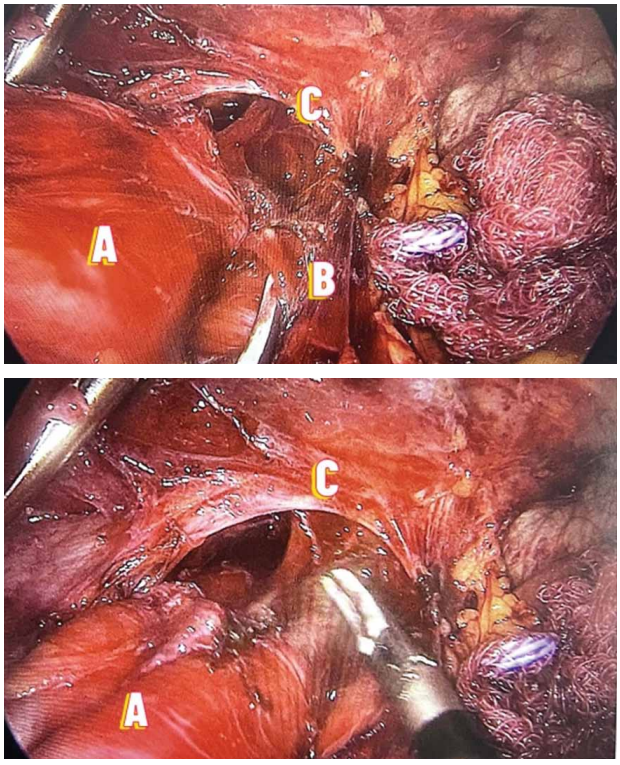

FIGURE 2. Proximal sleeve (A) was seen to be stuck in the hiatal hernia (C); left crus dissection (B).

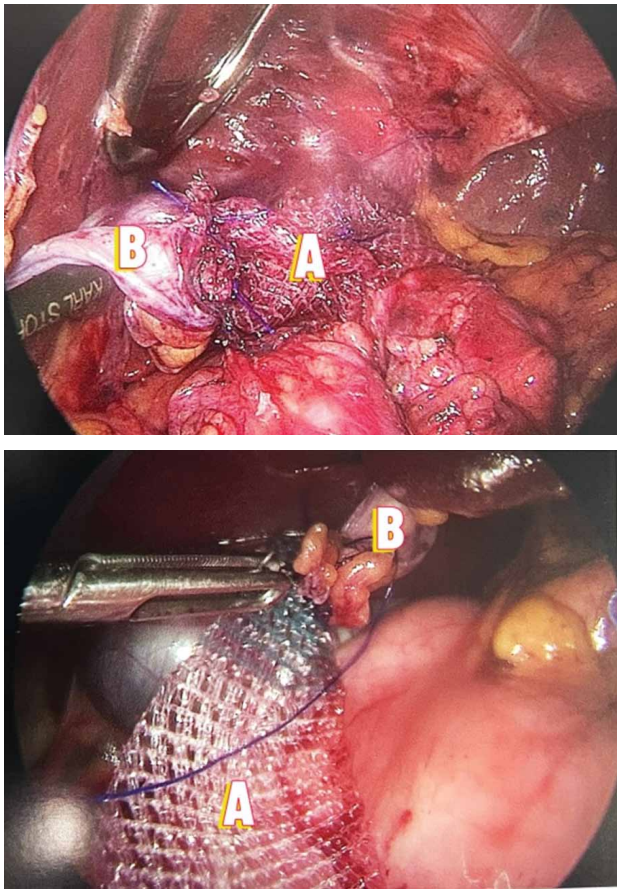

FIGURE 3. Composite mesh sling 6 x 2cm length (A); fixed to the short ligamentum teres (B).

She was followed again up after 12 months and remains symptom-free.

DISCUSSION

GERD is well known and documented complication following a sleeve gastrectomy in patients who did not have a hiatal hernia prior to the surgery. Studies have shown 15% - 33% of people who undergo a sleeve gastrectomy experience reflux symptoms, out of which 3.5% have a hiatal hernia [8]. It must also be remembered that a migrated sleeve is usually not reducible spontaneously because the staples cause adhesions that prevent its return into the abdominal cavity. Therefore, it is prudent to repair a hiatal hernia that is identified preoperatively concomitantly with the sleeve gastrectomy. Some surgeons have proposed a technique called Nissen sleeve gastrectomy to avoid or prevent post-sleeve hiatal hernia in the absence of a hiatal hernia during the initial operation. This technique was shown to be effective to control GERD following a sleeve gastrectomy but was associated with poor weight loss and other postoperative complications [10,11]. A newer technique is the Sleeve-Collis-Nissen Gastroplasty described by da Silva et al, which is a complex procedure and not thoroughly evaluated yet [12].

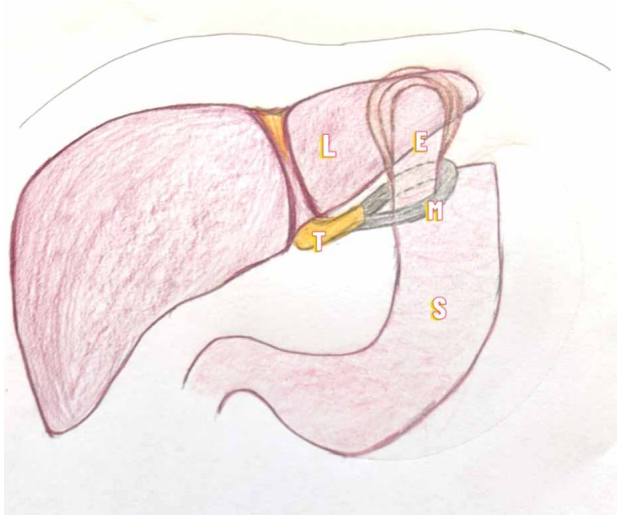

FIGURE 4. Diagram showing the completed procedure (L – left lobe of liver; E – lower esophagus; T – ligamentum teres; M – mesh sling; S – gastric sleeve).

The ligamentum teres augmentation of a hiatal hernia repair not associated with bariatric surgery is not a new

technique. Between 1964 and 1967, Rampal , Pedinielle and Marchal described in French publications the technique of using the ligamentum teres to augment a hiatal hernia repair in 1964 [13,14,15]. By 1990, Narbona et al had published a large series of their experience with 100 patients using this technique and long term follow-up [16]. The benefit of this method is the use of the patient's own tissue to augment the hiatal hernia repairs. Of course at that time this procedure was performed in patients with primary hiatal hernia and not following bariatric surgery.

In our patient, the ligamentum teres repair option was preferred over a gastric bypass given that she did not need further weight loss, unwillingness of the patient to undergo a gastric bypass and dealing with the inherent complications of a bypass. Obviously a fundoplication could not be performed in this situation since the fundus was resected during the sleeve gastrectomy. The entire length of the ligamentum teres was unavailable due to the dense postoperative adhesions. So a sling made of a thin long strip of composite mesh was constructed to extend the ligamentum teres length. The mesh sling augmentation works in two ways:

1. The ligamentum teres with mesh sling lies posterior to the lower oesophagus in direct contact with the crural suture repair, where adhesions will form.
2. The pulling/tugging effect of the sling on the gastroesophageal junction keeps it within the abdominal cavity and reduces chance of upward migration; much like a fundal wrap would function.

Using synthetic meshes to augment hiatal repair may cause dysphagia, odynophagia, oesophageal erosions or damage to the sleeve. Biologic meshes are expensive and studies show no real difference in long-term recurrence rates [17]. In our technique, the composite mesh sling was folded in such a way that the smooth film surface was in contact with the gastroesophageal junction in order to avoid mesh erosion or dense adhesions leading to stricture formation. Nearby fatty tissue was interposed between the mesh sling and the lower oesophagus to further avoid direct contact.

The ligamentum teres buttress technique was found to be useful in hiatal hernias after gastric bypass and for recurrent hiatal hernias following sleeve gastrectomy as well [18,19]. Dore et al published a very interesting paper comparing two procedures for the relief of reflux symptoms after sleeve gastrectomy [20]. The Roux-N-Y gastric bypass was compared to a ligamentum teres repair, and they concluded that short term outcomes of ligamentum teres repair are comparable, if not better, than bypass. Chaudhry et al evaluated this technique for hiatal hernia after mini-gastric bypass and reported favorable outcomes [21]. More recently, another novel technique described by Vigneswaran et al using the posterior rectus sheath as a pedicle flap to augment hiatal hernia repair was published [4]. This technique seems to be a viable alternative to the ligamentum teres repair, where the patient's own tissue is utilized. A comparative study between these two techniques regarding long term outcomes would be productive and provide more clarity.

In conclusion, for symptomatic hiatal hernias following sleeve gastrectomy when there is no fundus available to wrap and if the entire length of the ligamentum teres is also unavailable, our novel technique with a composite mesh sling is a useful and easily reproducible alternative.

Approval by Ethics Committee: *Yes*

Informed Consent Obtained: *Yes*

Conflict of Interest: *NIL*

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Case Report

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Transient aphonia in a patient undergoing laparoscopic cholecystectomy: A case report

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ABSTRACT

This case report presents an otherwise healthy 36-year-old female patient who underwent laparoscopic cholecystectomy due to acute cholecystitis and postoperatively exhibited transient aphonia.

Key Words: *Laparoscopic cholecystectomy; transient aphonia; self-limiting aphonia; post-cholecystectomy aphonia*

INTRODUCTION

Laparoscopic cholecystectomy is widely accepted as the standard of care for treating cholecystitis in the acute setting [1]. Although considered a minor surgical procedure and associated with minimal systemic complications, administration of general anaesthesia may still lead to significant adverse events [2-5]. CO2 inflation, steep patient position and prolonged operative time may predispose to the emergence of neurological complications especially in prone patients [4,5]. Neurological disorders after surgery are not uncommon in high-risk patients [6]. However, only rarely have they been reported in the literature in young healthy patients undergoing abdominal surgery [7-10]. In this study, we report the case of a young patient presenting aphonia immediately after laparoscopic cholecystectomy.

CASE REPORT

A 36-year-old female patient was referred to our department after diagnosis of acute cholecystitis. Personal and family medical history were insignificant. After initial evaluation and appropriate supportive treatment, she was scheduled for a laparoscopic cholecystectomy. Routine preoperative lab tests, including complete blood count (CBC), liver function tests (LFTs), renal function, coagulation studies, electrolytes and lipid profile were obtained along with preoperative electrocardiogram (ECG).

In the operating room, a standard laparoscopic cholecystectomy was performed without any intraoperative complication. The procedure was performed under general anaesthesia. Anaesthetic regimen included propofol and fentanyl for induction and remifentanil used for maintenance, without any adverse reaction. Cholecystectomy was performed under a low intra-abdominal pressure of CO2 (10-11mmHg). Awakening and extubation were uneventful. Following extubation, it became obvious that the patient was unable to speak, although she could follow verbal commands. There was no deterioration of respiration, and all vital signs remained normal. Muscle tone was intact. Emergency neurological consultation was performed in the operating room. No other neurological deficit was observed other than the inability to speak. Emergency otorhinolaryngology evaluation with laryngoscopy revealed normal vocal cord movement. The patient was kept in the resuscitation room for monitoring and possible airway management in case of emergency. After 45 minutes, her voice started gradually to recover, with full recovery within three hours after extubation.

Postoperative course was otherwise insignificant. Prior to discharge the patient was re-evaluated by a neurologist and psychiatrist and scheduled for imaging (brain MRI, carotid and lumbar artery ultrasound) and detailed

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coagulation studies to rule out underlying causes of the event. The patient has been followed-up for the last four months. No similar symptoms have been exhibited during this time.

DISCUSSION

Transient postoperative aphonia after abdominal surgery is rare and limited case reports describe such episodes across the literature [2-5]. Differential diagnosis includes transient ischemic attack (TIA), conversion disorder, non-reversed pharmacological effect and vocal cord injury during airway management [2-5]. TIA is described as a focal neurological deficit lasting for minutes with full neurological recovery [6]. It can be attributed to transient hypoxia, hypotension or embolism and predisposes to ischaemic attack in the near future. Several surgical diseases predispose to the development of venous thrombosis. Prolonged immobilisation, inflammation or underlying neoplasm may precipitate the emergence of deep venous thrombosis, associated with ischemic brain attacks [7]. In our case of a 34-year-old healthy woman, with normal prior medical history and initial coagulation studies, the diagnosis of a TIA is deemed not likely. Furthermore, preoperative measures with prophylactic anticoagulants and compression socks were employed and no signs of deep vein thrombosis observed pre- or postoperatively.

Laparoscopic surgery can be associated with increased neurological adverse outcomes owing to possible CO2 systemic absorption and subsequent effect on cerebral vessels [7,8]. This is more likely in prone patients with multiple comorbidities, extended operative time and high CO2 pressure. In this instance, surgery was completed in under 50 minutes of pneumoperitoneum with maintenance of "low-pressure" (10-11mmHg) throughout the operation. Furthermore, CO2 values based on intraoperative capnometry and postoperative arterial blood gas analysis was within normal range. Extreme positioning of the patient during the operation may be associated with postoperative deficits. Such cases have been reported after gynecological surgery, with extensive time in the Trendelenburg position [7-10]. This can be attributed to venous congestion and subsequent cerebral oedema [7-10]. However, in our case, as in the majority of laparoscopic cholecystectomy procedures, only a slight reverse Trendelenburg position was employed.

Anaesthesia drug effect is a possible cause of neurological deficit in the immediate postoperative period. Unreversed neuromuscular blockade can lead to muscle weakness, including vocal cord paralysis [11]. In addition to that, possible trauma during intubation or extubation may cause inability to talk normally [12]. In our case, however, muscle tone was uninfluenced and postoperative laryngoscopy excluded structural or functional damage to the vocal cords.

Psychogenic disorders may present postoperatively in various forms. Surgery, especially in the emergency setting, has been described as a major stressogenic event. Postoperative delirium may not be uncommon and can be expressed as speaking disability. Certain anaesthesia and muscle relaxation agents, including midazolam and scopolamine, have been proven to elicit such attacks, although they were not used in our case [10].

Regarding the management of a patient who develops aphonia immediately postoperatively, the investigation should be immediate. The primary goal should be to secure the patient's airway. This will be done by assessing the patient's level of consciousness and pO2. Immediate laryngoscopy to rule out injury or oedema of the vocal cords and other laryngeal structures is essential. At the same time, the patient's ability to breathe should be checked. This will be done by listening to the chest to check the patient's ventilation, as well as the reversal of anaesthetic drugs. Next, a check for neurological deficits, other than aphonia, will be performed. A CT scan of the brain at two to six hours is necessary to rule out a stroke and, if it does not reveal pathology, repeat it at 24 to 48 hours. The patient should remain under monitor observation to ensure respiratory and haemodynamic stability. Performing MRI and carotid triplex is optional after the patient's discharge, as is rechecking by a neurologist. Aphonia most often returns in the first postoperative hours, however, this may take longer. Despite the earlier belief that if there is no immediate reversal of the aphonia, it may be permanent, this is not documented [16,17]. Table 1 lists possible modes of potential causes of postoperative transient aphonia and associated pathophysiological mechanisms.

CONCLUSION

Transient aphonia is an extremely rare complication after surgery under general anaesthesia. Emergence of such symptoms should prompt appropriate measures in order to ensure appropriate patient support while assessing the possibility of reversible causes. Immediate supportive management according to standard protocols should prioritise assessing and securing airway patency, sufficient ventilation and haemodynamic stability. After initial assessment and support, detailed neurological, psychiatric and ENT assessment is mandatory in order to promptly identify possibly reversible causes, including ischaemic brain injury, in the acute phase.

In our case, following immediate supportive measures, urgent clinical assessment , imaging studies and labora-

TABLE 1. Potential causes of postoperative transient aphonia and associated pathophysiological mechanisms.

CAUSES	MECHANISM
Endotracheal intubation factors [14,15,16]	Vocal cord injury/oedema Improper endotracheal tube position
Anaesthesia-related factors [11]	Muscle relaxants related voice volume reduction Drug-induced vocal cord irritation
Postoperative allergic reaction [14,16]	Laryngeal oedema
Psychogenic aphonia [17]	Hyperfunctional type: characterised by a significant contraction of the vocal cords (less common) Hypofunctional type: vocal folds come close together but do not fully close (more common)

tory workup failed to reveal any abnormal findings that would explain the patient's symptoms. Following detailed neurological and psychiatric evaluation and laboratory follow-up, psychogenic disorder is considered the most likely cause of the symptoms exhibited by our patient [12]. The full recovery of voice function, the absence of other symptoms or abnormal findings of postoperative workup support this diagnosis.

Conflict of interest: *None*

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155 Years from the birth of professor of anatomy Georgios Sclavounos: His contribution to the greek surgical anatomy

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ABSTRACT

Georgios Sclavounos (1869 - 1954) was a 20th-century Greek physician and university professor. He reformed the field of Anatomy in Greece, at a time when it began to be qualitatively compared with its progress in other countries.

Key Words: *Georgios Sclavounos; professor of Anatomy; National and Kapodistrian University of Athens*

Georgios Sclavounos was born in Tithorea in the province of Lokris, Fthiotides, Greece, on October 16, 1869. He graduated from Thebes School and in the academic year 1884-1885 he enrolled in the Philosophy School of the University of Athens. He then transferred to the Law School. A year later, the University was closed due to conscription and Sclavounos went to Zurich for eight months and later to Würzburg in Bavaria where he studied Medicine. He graduated in 1891 with a doctorate with the thesis "On elaidin and the keratogenic process of the cardiac fate of the stomach of mammals" [1] (Figures 1-4).

In 1891, he passed practical examinations and worked for two years as an assistant in the anatomical institute of the famous Swiss great anatomist, physiologist and histologist Albert von Köliker (1817-1905) in Würzburg. Kölliker made contributions to the study of zoology. Köliker's earlier efforts were directed to the invertebrates, and his memoir on the development of cephalopods (which appeared in 1844) is considered a classical work [1].

G. Sclavounos collaborated with the great anatomists Max Schultze (1825-1874), Hermann Braus (1868-1924) and Johannes Sobotta (1869-1945), who are the authors of well-known contemporary anatomical textbooks and atlases.

In 1892, he returned to Greece for family reasons. Upon his return to Athens, he was appointed assistant professor of Anatomy and curator of the Anatomy under the supervision of Professor Rigas Nikolaidis (1856-1928). In 1893 he was appointed lecturer of anatomy, in 1895 curator of the anatomy laboratory and in 1899-1900 he was elected professor and director of the Institute of Anatomy [2].

Sclavounos introduced anatomical research and many anatomical terms into Greek medical literature. Greek anatomical science began to be comparable to its Western counterpart.

In 1906, Sclavounos published the first volume of his three-volume monumental scientific work about Human Anatomy. To illustrate his book, he borrowed anatomical paintings from Werner Spalteholz (1861-1940), professor of the University of Leipzig, and histological and anatomical images from Johannes Sobotta (1869-1945), professor

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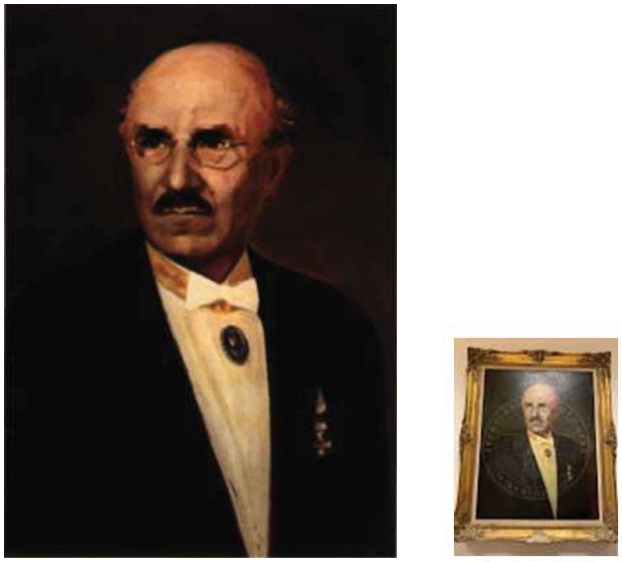

FIGURE 1. Georgios Sclavounos. Oil painting of Georgios Sclavounos by an unknown artist. Adapted from the Department of Anatomy of the National and Kapodistrian University of Athens.

of the University of Würzburg and later professor of the University of Königsberg and University of Bonn, and Otto Schultze, also professor of the University of Bonn. The 48 illustrations in Sclavounos' book were illustrations of his own preparations and they are astonishing in their accuracy of detail [3-5].

In 1899, G. Sclavounos became full professor in the chair of Anatomy and Physiology. From the academic year 1933-1934 he was director of the Dental School. He retreated, due to retirement, from the University of Athens in 1938. During his presence at the University, he ordered new anatomical casts from abroad while he inaugurated the new Anatomy Department in Goudi, Athens [1,2].

Georgios Sclavounos used the technique of pyrography to describe the adhesion of muscles to bones by representing the cauterised points which were the points of attachment of the muscles. At that time, the use of the Teichmann technique for injecting a colored substance into corpses was introduced and this technique was applied in Greece before it was applied in Europe. This achievement is considered important for the progress of surgical anatomy and anatomical research.

G. Sclavounos taught Anatomical and Physiological Histology and gave a demonstration with microscopic presentations of embryological preparations, Anatomical and Histological exercises, as well as dealing with Osteology and Syndesmology and taught Anatomy courses at the School of Fine Arts.

In 1897, he was elected a life member of the International Anatomical Society, the German Anatomical Society and since 1926 a member of the Academy of Athens. He died on May 13, 1954 in Athens.

He was married to Victoria Kyriazis, daughter of the mayor of Drymia, Fthiotides, Themistocles Kyriazis and great-granddaughter of the famous fighter in the Revolution of 1821 Komnas (Komninos) Trakas (1786-1840). They had four children including Themistocles Sclavounos, professor of Histology-Embryology at the School of Medicine of the University of Athens and Konstantinos Sclavounos, professor at the Agricultural School of the University of Thessaloniki. Themistocles Sclavounos was the first Professor -Director from 1936 when the extraordinary chair of Histology-Embryology became regular, until 1967 [1-5].

In 2010, a museum in his honor was opened in Amfikleia, Fthiotides. The museum, which bears the name of the late academician, was created jointly by the Municipality of Amfikleia and the School of Medicine of the National and Kapodistrian University of Athens [6].

G. Sclavounos wrote numerous books and scientific works on Anatomy and Physiology in Greek and German. Among them [3-5]:

- Untersuchungen über das Eleidin und den Verhornunsprozess der Pars cardiaca des Magens der Säugetiere (Investigations on eleidin and the keratinization pro-

FIGURE 2. The Anatomy Museum. Department of Anatomy-"Anatomeion", Medical School, National and Kapodistrian University of Athens, Athens, Greece.

FIGURE 3. Georgios Sclavounos of tithorea, fthiotides, academician, professor of anatomy.

cess of the pars cardiaca of the stomach of mammals), PhD thesis, 1890

- Beiträge zur feineren Anatomie des Rueckenmarks der Amphibien (Contributions to the finer anatomy of the spinal cord of amphibians), 1892
- Über Oesophagitis dissecans superficialis (About esophagitis dissecans superficialis),1893
- Über die feineren Nerven und ihre Endigungen in den männlichen Genitalorganen (On the finer nerves and their endings in the male genital organs), 1893
- On the first embryonic cell and its relation to the finished organism, opening lecture, 1899
- Some observations on the construction of the placenta of carnivores, 1904
- Über Ventricularsäcke des Kehlkopfes beim Erwachsenen und Neugeborenen Menschen sowie bei einigen Affen (On ventricular sacs of the larynx in adult and newborn humans and in some monkeys), 1904
- Über eine einfache Methode zur Feststellung und Abbildung der Umrisse der Muskelansätze (On a simple method for determining and depicting the outlines of muscle attachments), 1907
- Anatomy of man, i.e. a collection of anatomy after colored pictures and tables, 3 volumes, 1906
- On anomalous course of the vena cava through the apex of the right lung, 1918
- Zur schnellen Ablösung der Placenta (For rapid detachment of the placenta), 1920
- Über die Appendices epiploicae des Duenn, und Dickdarmes des Menschen und der Thiere und über deren Abstammung (On the Appendices epiploicae of the small and large intestine of humans and animals and on their origin), 1926
- Sur l'epiploidium de l'appendice vermiculaire de l'homme (On the mesenteriolum of the vermicular appendix of man), 1929
- Über einen Fall von Mesenteriolum ventrale beim Menschen (On a case of ventral mesenteriolum in humans), 1931

From the Greek Bibliography of the History of Medicine it is established that Georgios Sclavounos, has published three works on the History of Medicine [7]:

A. "On the color of the hair of the ancient Greeks", announced at the Academy of Athens, Session 20 May 1943, and published in the magazine Helios, vol. 136-140, 1946. Proceedings of the Academy of Athens, vol. 18, 1943, p. 92.
B. "On the stomach and its constriction according to Galen", Hellenic Medicine, vol. 16, 1947, p. 505.
C. "On Galenian terms and in particular on the terms "ανάδοσις, ευανάδοτος, δυσανάδοτος" after two epimeters, the first for Galen, the second for Michail Psellos (the great Byzantine physician and scholar), Proceedings of the Academy of Athens, vol. 25, 1950, pp. 298-334 [7].

Half of these references are in Galen's works: "On ana-

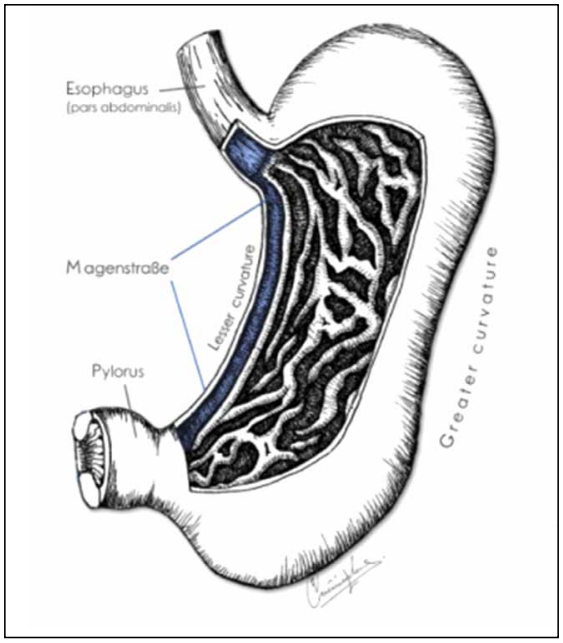

FIGURE 4. Brief explanation of Georgios Sclavounos' "sialine groove of the stomach" created by Michail Saintanis.

tomical operations", "Medical terms", "On dissection of muscles", and "On the necessity of the molecules in the human body". This is also a sample of breadth of knowledge and familiarity with the multi-volume work of Galen.

The description by the late Professor Georgios Sclavounos of the sialine groove of the stomach in a fetal stomach is considered an important contribution to the progress of surgical anatomy. According to Sclavounos' book "The Anatomy of Man", our internal gastric anatomy is very complex. In particular, the internal surface of the stomach displays folds. In an empty stomach eleven plications are created in total by the contraction of the muscularis mucosae (mucosal plications). Some disappear when the stomach is full and expands, some correspond to pachynsis or strangulation of the muscular coat and others are created by the retraction of the entire gastric wall (total folds) [3].

The eminent Professor Georgios Sclavounos described the gastric tract at the same time as Wilhelm von Waldayer (1836-1921) did in adults, but Sclavounos did it alone in infants. Sclavounos called it the salivary groove of the stomach, while Waldayer called it gastric road or Magenstrasse.[8].

The term magenstrasse refers to a tubular portion of the stomach adjacent to the lesser curve of the stomach. It is a favored route by food, fluids and drugs as they flow from the cardia/fundus to the gastric outlet [9].

Magenstrasse is an old German anatomical term that has come back into common medical usage in view of the commonly performed Magenstrasse and Mill procedure, a form of bariatric surgery [10].

Magenstrasse is a compound word from the German for "Magen" meaning stomach and "Strasse" meaning road or street. Therefore, "magenstrasse" means stomach road [11].

To conclude, Georgios Sclavounos was undoubtedly a great Greek physician and professor of his time, whose work contributed to the gradual formation of the foundations of modern anatomy science. His field of interest was extensive and among others, he described the "stomach road", a tubular portion of the stomach, which is a route favored by fluids.

He reformed the branch of Anatomy in Greece, at a time when it began to compare qualitatively with its progress in other countries. The imprint that Georgios Sclavounos left on the science of anatomy and medicine in general during these years was very strong for two main reasons. One was the competence and scientific rigor that was installed in all the functions of the Department of Anatomy without exception. The other was his three-volume, many thousand-page monumental work about Anatomy of the Human Body, which influenced doctors in Greece for many decades.

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