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ABOUT COVER

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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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MINIREVIEWS

Enhanced recovery after surgery: Current research insights and future direction

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Abstract

Since the concept of enhanced recovery after surgery (ERAS) was introduced in the late 1990s the idea of implementing specific interventions throughout the peri-operative period to improve patient recovery has been proven to be beneficial. Minimally invasive surgery is an integral component to ERAS and has dramatically improved post-operative outcomes. ERAS can be applicable to all surgical specialties with the core generic principles used together with added specialty specific interventions to allow for a comprehensive protocol, leading to improved clinical outcomes. Diffusion of ERAS into mainstream practice has been hindered due to minimal evidence to support individual facets and lack of method for monitoring and encouraging compliance. No single outcome measure fully captures recovery after surgery, rather multiple measures are necessary at each stage. More recently the pre-operative period has been the target of a number of strategies to improve clinical outcomes, described as prehabilitation. Innovation of technology in the surgical setting is also providing opportunities to overcome the challenges within ERAS, *e.g.*, the use of wearable activity monitors to record information and provide feedback and motivation to patients peri-operatively. Both modernising ERAS and providing evidence for key strategies across specialties will ultimately lead to better, more reliable patient outcomes.

Key words: Enhanced recovery after surgery; Laparoscopic surgery; Prehabilitation; Outcome measures; Technology

Core tip: Enhanced recovery after surgery (ERAS) together with laparoscopic surgery improves clinical outcomes in patients post-operatively. Prehabilitation is gaining evidence as a further method of enhancing post-operative recovery. Pre-operative programmes to improve physical function have been used and we review this early literature as well as some current issues within ERAS. Technology, which is already in use in the peri-operative period for interventions and

monitoring could be used to further complement ERAS. Small, non-invasive devices which can monitor activity levels could help monitor compliance and post-operative patient activity levels as well as act as an intervention to encourage patients to increase their physical activity and thereby their post-operative outcomes.

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INTRODUCTION

The concept of enhanced recovery after surgery (ERAS) was initially proposed by Kehlet[1] who explored the possible determinants of post-operative morbidity in the late 1990s. He identified potential risk factors that needed to be recognised and treated peri-operatively to minimise the effects of surgical stress on the patient. He also championed the idea of working within a multi-disciplinary framework. Together these have led to a series of interventions which have been formulated into standardised protocols to span a patient's entire journey through the surgical process with distinct elements in the pre-operative, intra-operative and post-operative phase (Table 1).

Colorectal surgery was the first specialty to implement ERAS in the early 2000s. Early studies proved feasibility and demonstrated that patients benefited from shorter length of hospital stay and reduced post-operative ileus and cardiopulmonary complications, compared with standard care[2-4]. ERAS has also been shown to be feasible and safe in the emergency colorectal setting, leading to shorter length of stay and faster recovery of bowel function[5].

A 2012 consensus review of ERAS guidelines for colonic surgery examined the evidence base for each ERAS intervention and provided graded recommendations[6]. Though given strong recommendation grading, not all the interventions have high levels of evidence for their efficacy (Table 2).

Minimally invasive surgery is one element that has been strongly recommended with a high level of evidence for oncological outcomes and moderate evidence in terms of patient recovery.

ERAS and laparoscopic surgery

Minimally invasive surgery has been shown to reduce post-operative pain, length of hospital stay and complications[7-9]. Recent studies have examined the use of laparoscopic techniques within an enhanced recovery programme. For example, the LAFA-study[10] showed that laparoscopic surgery, as part of an enhanced recovery programme, significantly shortened length of hospital stay compared with open surgery. Other outcomes including morbidity, readmission rates and quality of life were similar between the groups. The EnROL Trial[11] found a statistically significant difference between length of hospital stay and 30 d readmissions favouring the laparoscopic group compared with the open surgery group, but no differences between groups for physical fatigue or other secondary outcomes.

Newer minimally invasive techniques in the form of single incision laparoscopic surgery (SILS), robotic surgery and natural orifice transluminal endoscopic surgery have recently emerged. Although still in the early stages with ongoing research in progress, SILS has been shown to reduce conversion rate to laparotomy and reduce length of hospital stay[12]. Robotic surgery has advantages over purely laparoscopic surgery including the ability for seven degrees of freedom and tremor filtration which could benefit more demanding surgery, *e.g.,* rectal resections. Robotic surgery has been shown to be both safe and feasible with short term outcomes comparable to conventional laparoscopic surgery but longer operative time and higher costs[13,14]. ROLARR (Robotic *vs* Laparoscopic Resection for Rectal cancer) is an RCT which aims to compare the benefits of robotic *vs* laparoscopic surgery, the results of which have not yet been published.

The ultimate benefits of laparoscopic surgery and ERAS are essentially the same; improved outcomes and faster recovery. Given that laparoscopic surgery has been shown to improve outcomes both separately from, and as a part of ERAS, it can be seen as a significant and integral component to any ERAS protocol where minimally invasive surgery is applicable.

Specialty specific ERAS

The principles of ERAS have been adopted by most specialties, each formulating their own specific protocols and guidelines. The generic overarching ideas of pre-operative, intra-operative and post-operative elements are included, but the actual interventions and evidence base are specialty specific. Specialties with similar operative procedures, *i.e.*, those within the lower abdominal/pelvic cavity, tend to have similar elements within their protocols, for example colonic surgery[6] and gynaecological oncology surgery[15,16] recommend no pre-operative bowel preparation, avoidance of nasogastric tube insertion and use of minimally invasive surgical techniques when expertise is available. Similar recommendations exist for urological surgery[17], however long-term oncological results following use of minimally invasive techniques are still awaited.

A review of enhanced recovery in pancreatic surgery highlighted placement of intraperitoneal drains as a controversial and highly debated element within ERAS protocols for pancreatectomy[18]. Intraperitoneal drains have been used historically to help in the recognition of a pancreatic fistula or anastomotic leak. This leak of pancreatic fluid can cause erosion of vessels, haemorrhage and sepsis. A recent meta-analysis concluded that those patients without drains had higher mortality

Table 1 An example of a generic enhanced recovery after surgery protocol

Pre-operative	Intra-operative	Post-operative
Pre-admission counselling	Short acting anaesthetic agents	Mid-thoracic epidural anaesthesia
Fluid and carbohydrate loading	Mid thoracic epidural anaesthesia	No Nasogastric tubes
No prolonged fasting	No drains	Prevention of nausea and vomiting
No/selective bowel preparation	Avoidance of salt and water overload	Avoidance of salt and water overload
Antibiotic prophylaxis	Maintenance of normothermia	Early removal of catheter
Thromboprophylaxis		Early oral nutrition
No Premedication		Early mobilisation
		Non-opioid oral analgesia
		Stimulation of gut motility
		Audit of compliance and outcomes

Table 2 Enhanced recovery after surgery society recommendations for colonic surgery and their evidence level[6]

ERAS element with high/moderate level evidence	ERAS element with low level evidence
Stopping smoking 4 wk prior to surgery	Pre-operative information and counselling
No routine use of bowel preparation	Stopping drinking alcohol 4 wk prior to surgery
Allowing clear fluids up until 2 h before and solids 6 h before anaesthetic induction	Peri-operative oral nutritional supplements and carbohydrate loading
No routine use of sedative premedication	Standard anaesthetic that allows rapid awakening
Routine thromboprophylaxis	Post-operative nausea and vomiting prophylaxis
Antimicrobial prophylaxis and skin preparation	Routine urinary drainage
Balanced intravenous fluids guided by flow measurements	Using stress reducing elements of ERAS to minimise hyperglycaemia
Use of mid thoracic epidural blocks in open surgery	Early mobilisation
Us of spinal analgesia or PCA in laparoscopic surgery	
Laparoscopic surgery	
No routine use of nasogastric tubes	
Maintenance of normothermia	
No routine intra-abdominal drains	
Early post-operative enteral feeding	
Insulin treatment of severe hyperglycaemia in ICU	
Use of chewing gum to prevent post-operative ileus	

ERAS: Enhanced recovery after surgery; PCA: Patient controlled analgesia; ICU: Intensive care unit.

but lower overall complications[19]. Current ERAS guidelines recommend systemic post-operative drainage with early removal in patients at low risk of pancreatic fistula, but these recommendations could change as further evidence is highlighted in future studies[20]. Within bariatric surgery pre-operative factors have been suggested to have important post-operative benefits, these include pre-operative weight loss, pre-operative exercise and adequate nutritional supplementation[21]. Studies have shown that pre-operative weight loss is a positive predictor of post-operative weight loss[22]. Together with adequately improving known nutritional deficiencies, which are common in obese patients, these elements seem essential additions to any bariatric ERAS protocol.

Other specialty specific elements include pre-operative respiratory physiotherapy prior to thoracic surgery[23]. This improves exercise capacity and lung function in patients who will lose lung volume after surgery. Use of pre-emptive analgesia and local anaesthetics infiltration within orthopaedic surgery is thought to allow early mobilisation and increased limb movement secondary to decreased somatic sensation[24,25].

Using generic elements as a basis for specialty guidelines with added specific interventions allows for a more comprehensive ERAS protocol with improved outcomes and recovery for each specialty.

CURRENT RESEARCH INSIGHTS AND CHALLENGES

Barriers to the implementation of ERAS

Despite the evidence of improved post-operative outcomes and recovery, ERAS implementation varies in different centres. McLeod *et al*[26] reported that of the 18 specific ERAS guideline recommendations, only two reached a compliance rate of greater than 75%. Pędziwiatr *et al*[27] implemented an ERAS protocol over a period of time and found that although only 65% compliance was reached for the first cohort, compliance rose to 89.6% by the third cohort, *i.e.*, a gradual improvement was shown over time. Recently the ERAS Compliance Group found that ERAS protocol compliance in elective colorectal cancer resections were around 75%, but there was variation between centres and elements[28]. Compliance with ERAS protocols was associated with better outcomes and exhibited a form of "dose-dependency" whereby, as compliance increased, complications decreased. Laparoscopic surgery and balanced intravenous fluid therapy were

specifically shown to be associated with a reduced risk of complications.

Certain elements are easier to implement than others, for example if they already form part of routine practice, *e.g.,* prophylactic antibiotics, thromboprophylaxis and using minimally-invasive techniques. Some elements are more difficult to implement despite increased efforts[27], including: No bowel preparation, early urinary catheter removal, no opioids and restrictive fluid therapy. An early study into ERAS protocol compliance indicates that compliance with post-operative factors significantly influenced outcomes[29], but it was difficult to determine which specific elements had an independent influence on outcomes. Conversely, a review by Ahmed *et al*[30] found that studies achieved similar outcomes despite not including all components of recommended ERAS protocols. Furthermore, a systematic review[31] looking at RCTs of ERAS *vs* standard care was unable to show that ERAS protocols with more elements were more successful than those with fewer elements.

Given the barriers to implementation and the difficulty in determining the relative importance of each individual component within the ERAS protocol the idea of a flexible and individualised method rather than a rigid protocol has been postulated, with each centre and hospital determining which elements to include for their specific protocols[29,31,32]. Factors thought to encourage the implementation of ERAS and improve compliance include; appointment of specific ERAS coordinators, use of engaged multidisciplinary teams, specific ERAS units/wards, specific teaching sessions about the benefits of ERAS and regular auditing[27,29,30].

Whichever elements are included, auditing compliance with the ERAS protocol, as well as measuring patient outcomes, form an essential part of the ERAS audit cycle[6].

Outcome measures

The impetus behind ERAS is improving post-operative recovery therefore it is necessary to measure recovery objectively. Many outcome measures have been used, yet the most frequently reported is length of hospital stay[33]. However, this surrogate measure of recovery can be influenced by external circumstances, for example patients' expectations of discharge date, social or support networks not being in place or even hospital administration issues with inability to process discharge summaries or dispense necessary medications. Furthermore, despite meeting the necessary clinical markers required for discharge, *e.g.,* blood tests and physiological observations, the patient is unlikely to be back to their functional baseline, since hospital discharge is based on the patient being safe to convalesce in the community. Other clinical outcomes studied include thirty-day mortality, thirty-day re-admission and post-operative complications[34,35]. These outcomes are often recorded as part of the clinical notes and can be used in conjunction with length of hospital stay. However, they only offer insight into the major complications or post-operative issues in patients who are readmitted or treated. There is little information to represent how patients are recovering at home in the long term.

Since 2009 the NHS in the United Kingdom has invited patients to fill in a patient reported outcomes questionnaire after hip replacement, knee replacement, groin hernia and varicose vein surgery. Such questionnaires measure a patient's health status and health related quality of life at a single point in time is collected before and after the procedure. This has been introduced to provide an indication of the quality of care being delivered. These outcome measures are more patient-focused, relating to daily living within their own environment and their return to normal function. King *et al*[33] assessed the influence of an ERAS protocol on quality of life. A validated QOL questionnaire (EORTC QLQ-C30) was used by patients undergoing surgery with an ERAS protocol compared to a historic control group. No statistically significant difference between the two groups in terms of quality of life was found. Another study measured post-operative fatigue as a long-term outcome to compare ERAS *vs* conventional care[36]. It was shown that post-operative fatigue levels increased in both groups significantly, which reached a maximum level just before discharge. However, the peak level reached was significantly smaller in the ERAS group. They also exhibited a significantly smaller Fatigue Consequence Score during the first thirty post-operative days. More recently proponents of ERAS have started to focus research on the theme of patient experience[37], and qualitative studies undertaken have highlighted areas for improvement including post-discharge support and follow-up[38].

Another consideration is the economic potential of ERAS. Studies have shown that implementing an ERAS protocol is cost effective[39]. Recent systematic reviews by Lemanu *et al*[40] and Lee *et al*[41] note however, that there are few RCTs documenting cost data, there are inconsistencies in the reporting of cost data, and suggest the need for well-designed trials in order to fully determine the true cost-effectiveness of ERAS.

A recent systematic review by Neville *et al*[42] aimed to identify useful recovery parameters within ERAS, noting that validated outcome measures were lacking for this complex recovery process. It was found that multiple different outcome measures are in use and that they tend to reflect short term recovery focusing on biological and physiological outcomes. The paucity of outcomes in the longer term was highlighted, for example few studies actually report any outcomes after thirty days post-surgery. A suggestion has been made for longer-term follow-up for post-surgical patients with a focus on patients' functional status including physical activity measurement and exercise capacity to help quantify recovery more fully. Another review by Feldman *et al*[43] postulates that phases of recovery overlap and cannot be defined as a single event within a specific time frame. This means that different outcome

measures are relevant at different time periods, but that no single outcome measure is perfect to quantify total recovery. Instead, a core set of outcome measures for each stage of recovery is proposed which reflect the perspectives of each member of the multi-disciplinary team as well as the patient.

It is now clear that different outcomes are relevant at different stages of the recovery process. One measure of recovery that is poorly represented by current outcome measures is physical activity. This is an important indicator of functional recovery both in hospital and back at home whilst convalescing. There is a potential to fill this gap by providing means of continual measurement in a non-invasive and objective manner.

Prehabilitation

Physiotherapy and mobilisation recommendations are frequently given in the post-operative period with a view to improving recovery and function. However, physical "conditioning" prior to operative stresses have been considered with the idea of enhancing patients' functional capacity and thus improving outcomes post-operatively[44,45]. For example, studies have implemented pre-operative exercise regimens and assessed subsequent post-operative functional activity and outcomes[46].

However, the benefit of prehabilitation is uncertain with systematic reviews reporting contradictory evidence. The review by Valkenet *et al*[47] included twelve studies [orthopaedic surgery, cardiac surgery and open abdominal aortic aneurysm (AAA) repair]. The risk of developing post-operative pulmonary complications was lower in those patients receiving inspiratory muscle training prior to cardiac and AAA surgery (RR = 0.40, 95%CI: 0.23-0.72). Conversely, there was no significant difference between post-operative complication rates or length of stay in joint replacement surgery. Lemanu *et al*[48] included eight studies in their review (cardiothoracic surgery, abdominal surgery and orthopaedic surgery), which found that there was poor adherence with the prehabilitation interventions with little evidence of physiological and clinical outcome improvements. One review focused more specifically on total body exercise as a prehabilitation intervention[49]. In this review of twenty one studies, improvements were seen in post-operative pain, length of stay and physical function in those undergoing the prehabilitation intervention. These differing conclusions may be due to the heterogeneity of the included studies with different physiological outcomes recorded and different prehabilitation interventions being used.

A tri-modal prehabilitation intervention was used in a randomised controlled trial with patients undergoing colorectal resection[44]. The intervention consisted of fifty minutes' total body exercise, alternating between aerobic and resistance training three times a week, nutrition counselling with protein supplementation and provision of stress reducing strategies. The trial found that the prehabilitation group had increased functional walking capacity both pre-operatively and at eight weeks post-operatively compared with the rehabilitation group. There was no difference in self-reported physical activity, health related quality of life, thirty day complications, anxiety or depression between groups.

The evidence for prehabilitation is in its preliminary stages, with mainly low powered, observational studies. It is difficult to quantify or characterise the benefits of a prehabilitation programme, or indeed which interventions should be included. Randomised controlled trials looking at prehabilitation in colorectal cancer patients[50] and in vascular patients undergoing elective abdominal aortic aneurysm repair[51] are currently underway, which will help towards informing the decision of whether or not prehabilitation should become part of the ERAS protocol.

FUTURE DIRECTIONS

Use of technology

A variety of technologies have been used within the peri-operative period as helpful adjuncts within ERAS, for example oesophageal Doppler for monitoring fluid balance[52], pneumatic calf compression to provide thromboprophylaxis[53] and the use of forced air warming units to maintain normothermia[54]. Furthermore, recent advances in technology have led to the emergence of small, wearable sensors that can measure, store and transmit large amounts of patient and environmental data[55,56]. These sensors have been used to objectively and continuously monitor physical activity in the home environment following discharge from hospital[57] and within the hospital setting[58].

Studies in the early post-operative period have offered insight on patient mobility and functional recovery[59]. Cook *et al*[60] monitored patient steps after elective cardiac surgery. An association was found between number of steps taken by a patient and their length of hospital stay and post-operative discharge destination. Wasowicz-Kemps *et al*[61] measured daily physical activity following laparoscopic cholecystectomy in a controlled study where advice was given to resume normal activity quickly following their operation. Recovery to baseline daily activity took more than one week in 64% of patients but women in the intervention group resumed normal daily activity quicker than those in the control group. One study comparing laparoscopic *vs* open distal gastrectomy used an objective physical activity monitor to evaluate post-operative recovery[62]. Recovery of activity on each post-operative day was higher in the laparoscopic group. Studies assessing longer term physical activity monitoring[63,64] have shown this is both feasible and beneficial for collecting data on longer-term outcomes.

Providing feedback on activity levels to participants has been shown to increase physical activity in a randomised controlled trial in young healthy Finnish men[65]. A randomised controlled trial assessing interventions for patients with intermittent claudication[66]

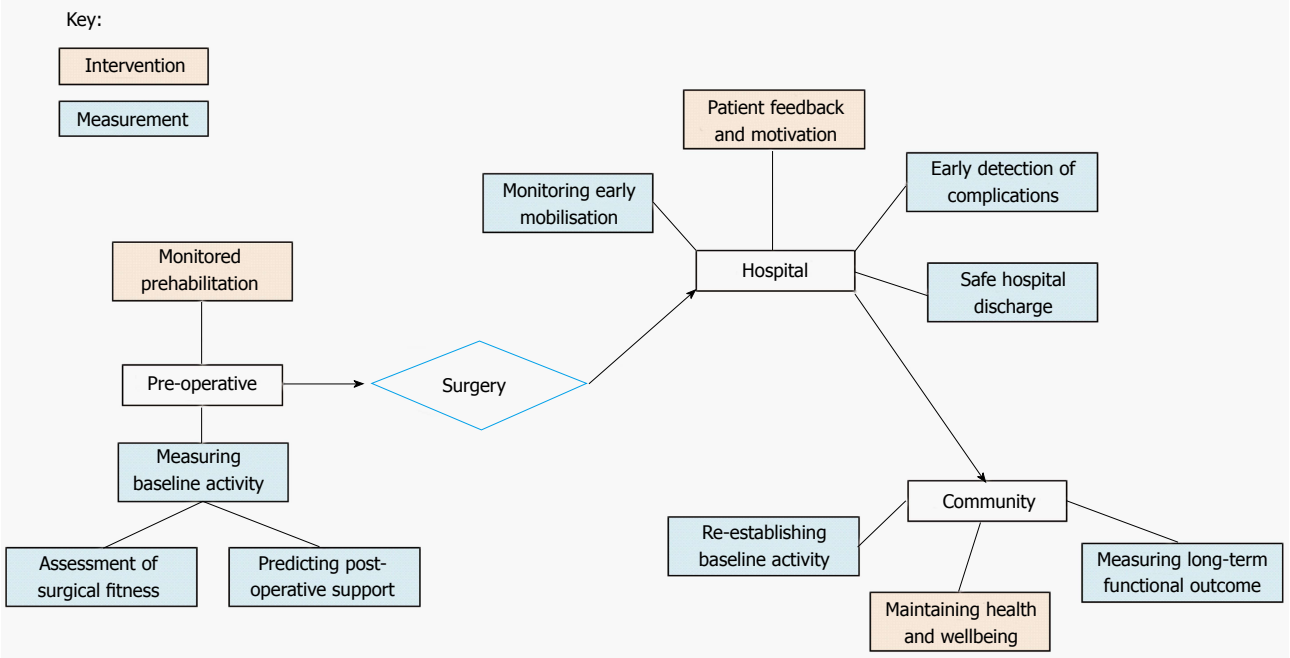

Figure 1 Uses of physical activity monitoring in the peri-operative period. Multiple opportunities exist for implementation of activity monitors in the peri-operative period. Pre-operatively, this includes the assessment of surgical fitness, and guiding a prehabilitation programme. Post-operatively there are multiple options for intervention and measurement in the hospital setting, as well as longer term assessments of functional outcome and encouraging an active lifestyle for overall physical and mental wellbeing.

Table 3 Additional enhanced recovery after surgery elements using sensor technology

Additional ERAS element	What this adds
Pre-operative physical activity monitoring	Measuring patient's baseline function to assess for surgical fitness and to predict support required post operatively
Prehabilitation	Exercise training prescribed to patients to improve their baseline functional capacity, together with nutritional advice and psychological support
Post-operative physical activity monitoring	Providing feedback to clinicians of patient recovery, monitoring compliance with mobilisation recommendations and picking up complications/allowing safer hospital discharge
Activity feedback	Providing motivation to patient to encourage them to mobilise in the initial post-operative phase, thereby reducing complications and enhancing recovery

ERAS: Enhanced recovery after surgery.

showed that wearing a feedback-enabled physical activity monitor improved claudication and walking distance as well as quality of life scores at three months.

There is therefore the potential to use sensor technology to complement and augment ERAS, leading to improved patient experience and outcomes. Knowing patients' pre-operative activity levels might correlate to their baseline function and wellbeing, which could provide an indication of anticipated support the patient may require post-operatively. Monitoring physical activity in the hospital post-operatively can help monitor compliance with post-operative mobilisation recommendations as well as measure inpatient activity providing an indication of functional recovery and screening for complications. Over time, monitoring physical activity unobtrusively can give useful long-term outcome measures that truly reflects a patient's recovery in the community[67]. Activity feedback to patients both in hospital and in the community may help to encourage an increase in their activity levels, as well as motivate them to be more engaged in their own recovery and care (Figure 1).

Sensor technology could, therefore, help overcome the current barriers to ERAS and help assess and improve patient outcomes and experience throughout the surgical period, in keeping with Kehlet's initial ERAS concept. Additional elements to add to specialty specific protocols could include pre-operative activity monitoring, prehabilitation and post-operative activity monitoring with feedback (Table 3).

CONCLUSION

Enhanced recovery after surgery is an evolving principle that aims to improve patient outcomes following surgery, with minimally-invasive surgery as an integral core. Current problems that are being discussed by ERAS proponents include barriers of implementation

of ERAS protocols and the difficulty of measuring post-operative outcomes and improvements. Evidence for prehabilitation is being explored in randomised controlled trials, as initial studies are contradictory and based on observational studies with few participants. Technological advances have enabled wearable devices to continuously and objectively collect data about the wearer's well-being. This could provide an opportunity to assess ERAS compliance, monitor patient outcomes and offer a variety of promising therapeutic interventions.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Perinatal risk factors in newborns with gastrointestinal perforation

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Abstract

AIM

To investigate correlation of perinatal risk factors in newborns with gastrointestinal perforation (GIP).

METHODS

Single-center retrospective cohort study was conducted between January 1990 and December 2012. Medical records on all newborns with GIP were reviewed (n = 35). Surgical records and histopathologic examination of all perforated intestine samples were also reviewed.

RESULTS

The most common cause of GIP was necrotizing enterocolitis (51.4%). The most common site of perforation was large intestine. Mortality rate was 31%. Infants with GIP more frequently had very low birth weight (< 1500 g), especially birth weight below 10th percentile

according to gestational age. Ponderal index was not differing between infants with GIP and control subjects. In infants with GIP anemia was more frequently found than in control group.

CONCLUSION

GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia.

Key words: Gastrointestinal perforation; Newborn; Necrotizing enterocolitis; Ponderal index

Core tip: Gastrointestinal perforation (GIP) in newborns is a severe and life threatening condition associated with high mortality. GIP usually occurs in prematures with necrotizing enterocolitis. GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia. The most common site of perforation was large intestine Mortality rate was 31%. Infants with GIP more frequently had very low birth weight (< 1500 g), especially birth weight below 10th percentile according to gestational age.

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INTRODUCTION

Gastrointestinal perforation (GIP) in newborns is a severe and life threatening condition associated with high mortality of 17%-60%[1-4]. GIP usually occurs in prematures with necrotizing enterocolitis[1-11]. The major causes of GIP are low gestational age, low birth weight, feeding with adapted formulas instead of breastfeeding, early and fast increase in meal volume, bacterial colonization and intestinal ischemia[5,6].

Although most frequently observed in prematures, necrotizing enterocolitis also occurs in term newborns. In the latter, it is clearly associated with perinatal factors, *i.e.,* intrauterine drug exposure, in particular cocaine, in mothers drug addicts; intestinal anomalies (aganglionosis or atresia); congenital heart disease; sepsis; polycythemia; asphyxia; respiratory distress syndrome; presence of umbilical catheter; and exsanguinotransfusion. These factors can affect blood flow through the mesenteric blood vessels of the newborn and lead to hypoperfusion and consequential intestinal hypoxia[7,8]. In prematures, necrotizing enterocolitis mostly develops in the second week of life, whereas in term newborns it usually occurs earlier, *i.e.,* in the first week of life[7,9,10].

Spontaneous intestinal perforation is a specific clinical entity that should be differentiated from necrotizing enterocolitis. Spontaneous intestinal perforation is a multifactorial disease of very low birth weight infants (< 1000 g), which is not related to the mode of feeding. Local intestinal ischemia is considered to be the major risk factor for the occurrence of spontaneous intestinal perforation. In addition, the following risk factors have hitherto been associated with spontaneous intestinal perforation: Neonatal hypotension, umbilical arterial catheter, dehydration, indomethacin and steroids[11,12]. The less frequent causes of perforation include intestinal obstruction, idiopathic gastric perforation and iatrogenic perforation[12-15].

To the best of our knowledge, ponderal index has not yet been assessed relative to the occurrence of GIP. Studies suggest low ponderal index or lean neonates to have been exposed to hypoxic-ischemic events during gestation, which then results in increased perinatal mortality and morbidity, in particular a higher prevalence of perinatal infection[16].

The aim of the study was to assess the correlation of ponderal index and other risk factors with GIP; the prevalence of GIP (according to causative disorder and site of perforation); and GIP mortality (according to causative disorder and site of perforation).

MATERIALS AND METHODS

Medical records of infants born at the niversity Hospital of Split from January 1, 1990 till December 31, 2012 were reviewed. There were 103852 live births, 5193 (13%) of them were prematures. Study group included 35 newborns (19 males, 16 females) with confirmed GIP, gestational age 25-40 wk. Control group comprised of all newborns admitted immediately before or immediately after study group subjects, matched by no more than plus or minus one gestational week (n = 76), free from neonatal intestinal perforation. Study group was compared to control group matched by gestational age (case-control study).

The following perinatal risk factors were observed: maternal age and parity; maternal edema, proteinuria, hypertension (EPH) gestosis-preeclampsia; prolonged amniotic sac rupture; fetus presentation; method of delivery termination; neonate sex; Apgar score at 1 min; birth weight (BW); birth length (BL); and ponderal index.

Considering particular population specificities for birth weight determination according to gestational age, sex and maternal parity, percentile curves developed for our population at the Department of Gynecology and Obstetrics, University Hospital of Split in 2005 were used[17,18]. Ponderal index (PI) was determined for each study subject using the following formula: PI (g/cm^3) = 100 × BW (g)/BL (cm^3).

The following postnatal risk factors were also ob-

Table 1 Perinatal risk factors *n* (%)

Perinatal risk factor	GIP *n* = 35	Control group *n* = 76
Maternal age (years, min-max)	26 (18-44)	28 (18-41)
Maternal parity		
Primipara	20 (58.8)	35 (46.7)
Secundipara	10 (29.4)	27 (36.0)
Multipara	4 (11.7)	13 (17.4)
EPH gestosis-preeclampsia	5 (15.2)	2 (2.6)
Prolonged membrane rupture	5 (15.2)	13 (17.1)
Breech presentation	5 (15.2)	7 (9.2)
Cesarean section	11 (32.4)	17 (22.4)
Sex (male)	19 (54.3)	38 (50.0)
Apgar score at 1 min		
0-3 (severe hypoxia)	2 (5.9)	1 (1.3)
4-7 (moderate hypoxia)	13 (38.2)	23 (30.3)
8-10 (normal vitality)	19 (55.9)	52 (68.4)
Birth weight (BW)		
< 1500 g (very low BW)	8 (22.9)	7 (9.2)[a]
1500-2499 g (low BW)	4 (11.4)	24 (31.6)
⩾ 2500 g (normal BW)	23 (65.7)	45 (59.2)
Birth lenght (cm)	47 (34-53)	48 (32-55)

[a]$P < 0.05$ (χ^2-test). GIP: Gastrointestinal perforation; EPH gestosis: Edema, proteinuria, hypertension (EPH) gestosis.

served: Respiratory distress syndrome; presence of central venous umbilical catheter; sepsis; polycythemia; and anemia. GIP was demonstrated radiologically by visualizing free air intraperitoneally.

The risk factors for GIP were divided into perinatal and postnatal variables. Ponderal index was analyzed by *t* test; qualitative variables and maternal parity were analyzed by use of χ^2 test; and maternal age was analyzed by Mann-Whitney *U* test. Epidemiological measures of correlation or measures of relations, *i.e.*, odds ratio, was employed on assessing the power of statistical relationship between a particular risk factor and the disease (GIP) and on drawing conclusions on the potential causative relationship. An approximate risk for the occurrence of GIP was obtained by calculating the probability of a particular risk factor exposure in study subjects and control group. Then the 95%CI was calculated. All data were interpreted at the level of significance of $P < 0.05$.

The prevalence of GIP was calculated using the following formulas: (1) number of children with GIP/total number of live births × 1000; (2) number of children with GIP/number of children treated at clinical department × 1000; and (3) number of prematures with GIP/number of prematures × 1000.

Mortality following GIP shows the ratio of newborns with GIP that died during the neonatal period (28 d) and total number of newborns with GIP. Neonatal mortality due to GIP was determined according to the cause and site of GIP.

RESULTS

During the 22-year study period, there were 103852 live births at the University Hospital of Split, and 5193 of them were preterm infants. During the study period 35 patients with GIP were identified, yielding a 0.34‰ GIP incidence and 3.66‰ incidence of prematures in overall live births. The matched control group consisted of 76 infants. The study and control infants were matched for gestational age.

Table 2 Number (%) of newborns according to ponderal index mean value: arithmetic mean ± SD, birth weight and birth length percentiles

Variable	GIP *n* = 35	Control group *n* = 76
PI, mean ± SD, g/cm^3	2.53 ± 0.3	2.52 ± 0.3
BW, %		
SGA (< 10th percentile)	31.4	13.2[a]
AGA (10th-90th percentile)	51.4	77.6
LGA (> 90th percentile)	17.1	9.2
BL, %		
< 10th percentile	18.2	9.2
10th-90th percentile	66.7	84.2
> 90th percentile	15.2	6.6

[a]$P < 0.05$ (χ^2-test). SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age.

Perinatal risk factors of 35 infants with GIP compared with control subjects are shown in Table 1. There were trends toward a higher incidence of male infants in the study group compared with control subjects. There were no differences between groups in prolonged rupture of membranes, method of delivery, presentation at delivery and Apgar score. Mothers were young in both groups (mean age 26 and 28 years in study group and control group, respectively) and tended to be primiparae. Mothers of infants suffering from GIP showed a trend toward increased pregnancy-induced hypertension, but the number of mothers with pregnancy-induced hypertension was too small for statistical analysis.

The mean values of ponderal index, and number and percentage of newborns according to birth weight and birth length percentiles *per* gestational age are shown in Table 2.

Infants suffering from GIP were significantly more likely to have birth weight less than 1500 g (22.9% *vs* 9.2%, $P < 0.05$) and birth weight below 10th percentile according to gestational age (31.4% *vs* 13.2%, $P < 0.05$). There was no statistically significant difference between groups in the mean value of ponderal index.

Table 3 shows postnatal risk factors in the both groups. More infants in the study group had anemia (25.7% *vs* 3.9%), yielding a statistically significant difference ($P < 0.05$).

Additional statistical tests of logistic regression and multiple logistic regressions were employed to confirm birth weight less than 10th percentile and anemia as risk factors for GIP. The results obtained by logistic regression are shown in Table 4.

The likelihood of GIP development was threefold greater in the group of hypotrophic for gestational age infants as compared with the group of eutrophic and

Table 3 Postnatal risk factors *n* (%)

Variable	GIP (*n* = 35)	Control group (*n* = 76)
RDS	13 (38.2)	29 (38.1)
RDS + mechanical ventilation	12 (35.3)	14 (18.4)
CVUC	5 (14.7)	9 (11.8)
Positive blood culture	4 (11.8)	11 (14.5)
Polycythemia[1]	5 (14.3)	6 (7.9)
Anemia[2]	9 (25.7)	3 (3.9)[a]

[1]Polycythemia was defined as hematocrit > 0.60; [2]Anemia was defined as hemoglobin level < 140 g/L in venous blood; [a]$P < 0.05$ (χ^2-test). RDS: Respiratory distress syndrome; CVUC: Central venous umbilical catheter.

Table 4 Logistic regression results *n* (%)

Risk factor	GIP *n* = 35	Control group *n* = 76	OR (95%CI)
Hypotrophy	11 (31.4)	10 (13.2)	3 (1.14-8)[a]
Eutrophy and hypertrophy	24 (68.5)	66 (86.8)	
With anemia	9 (25.7)	3 (3.9)	8.4 (2.1-33)[a]
Without anemia	26 (74.3)	73 (96.1)	

[a]$P < 0.05$.

Table 5 Multiple logistic regression results

Risk factor	OR	95%CI
Birth weight < 10th percentile for gestational age (hypotrophy)	4.01[a]	1.45-11.2
Anemia	10.9[a]	2.6-45

[a]$P < 0.05$.

hypertrophic for gestational age infants, with 95%CI. The probability of GIP was 8.4-fold greater in infants suffering from anemia as compared to those without anemia, with 95%CI. Multiple logistic regression confirmed both risk factors, *i.e.*, birth weight below 10th percentile for gestational age (hypotrophy) and anemia to be statistically significant for GIP development (Table 5).

The infants suffering from GIP were diagnosed mostly during the first 7 d (60%), and the age at diagnosis ranged from 1 to 25 d of life. Enteral feeding was started in 57.1% of case patients and in all matched control subjects.

All case patients underwent exploratory laparotomy, except one patient who underwent thoracotomy because of esophageal perforation. Stoma was established in 80% of patients. Direct suture was performed in five infants. The most common location of perforation was large intestine (45.7%), followed by ileum (20.0%), jejunum (11.4%), multiple perforation of both small and large intestine (11.4%), duodenum (5.7%) and esophagus in one patient (2.9%).

The causes of perforation were divided into four categories according to pathological and intraoperative reports. Necrotizing enterocolitis was the predominant cause of perforation (*n* = 18; 51.4%), followed by intestinal obstruction (22.9%), meconium plug (14.3%), spontaneous perforation (8.6%) and iatrogenic perforation of the esophagus (2.8%).

The overall mortality rate was 31.4% (during the neonatal period of 28 d). In the early study period (1990-2000), seven of 17 (41.2%) infants with GIP died, but later a considerably lower mortality rate was recorded, *i.e.*, four of 18 (22.2%) infants with GIP died in the 2001-2011 period. Most of these deaths were due to perforated necrotizing enterocolitis (63.6%), and the most common site among the expired was small bowel (36.4%).

DISCUSSION

According to available data, the prevalence of GIP is low. There are few studies addressing and assessing all causes of GIP and their interplay leading to this severe disorder. Asabe *et al*[3] found 34 cases of GIP during a 30-year period[3]. Khan *et al*[19] report on 89 cases of GIP that accounted for 16.5% of all newborns admitted to the Department of Pediatric Surgery. In their multicenter study, Calisti *et al*[4] recorded 85 cases of neonatal GIP in the region of Lazio, Italy, during a ten-year period. The authors estimate the prevalence of GIP in newborns treated at neonatal intensive care units to range between 1% and 3%.

In our study, necrotizing enterocolitis was the most common causative entity leading to GIP (51.4%), followed by intestinal obstruction (22.9%). This is consistent with literature data, where necrotizing enterocolitis is also reported as the most common cause of GIP[1-4,19,20]. A low prevalence of necrotizing enterocolitis (0.2%) has only rarely been reported[21]. According to the literature, spontaneous or idiopathic intestinal perforation has been postulated as the second leading cause of GIP, and less frequently meconium peritonitis[2-4,14]. Gastrointestinal obstruction as the cause of GIP is more common in term newborns. In our study, the rate of intestinal obstruction was high, as expected considering the high proportion of term newborns.

In our study, the most common site of GIP was large intestine (45.7%), whereas small intestine perforation was recorded in 37.1% of cases. In the literature, the most common site of GIP is small intestine, in particular distal ileum[22-24]. Colon perforation is considered a rare event; however, in a recent study, Sakellaris *et al*[25] found colon perforation in 18.5% of newborns. According to literature reports, colon perforation is more common in high birth weight newborns (> 2500 g), which predominated in our study sample (65.7%)[26].

Considering maternal characteristics, we found no statistically significant between-group difference in maternal age and parity. However, there are literature reports on the newborns with GIP to be born to young mothers (22 to 28 years on average) with a lower number of previous deliveries In our study, mothers in both case and control groups were young (26 and 28 years on average, respectively) and most of mothers in

both groups were primiparae[22,27].

In all previous studies, GIP was more common among male newborns, with a rate ranging from 59% to 89% of cases[5,6,19,22,24,27]. In our study, the rate of male newborns with GIP was 54.3%.

The group of newborns with GIP included a significantly higher proportion (22.9%) of very low birth weight (< 1500 g) infants. Literature reports reveal GIP to occur more frequently in very low birth weight newborns[4-6,10,20,22-24]. In our study, the group of newborns with GIP also included a high proportion of hypotrophic infants (31.4%). Thus, the likelihood of GIP was threefold greater in the group of hypotrophic infants as compared to other study subjects.

According to literature reports, intrauterine growth retardation (IUGR) leads to hypotrophy but has been rarely tackled specifically as a risk factor for GIP. Some studies dealing with IUGR failed to confirm its association with necrotizing enterocolitis or spontaneous intestinal perforation, whereas others compared case and control groups matched by gestational age and found IUGR to be a potential clinical risk factor for necrotizing enterocolitis as the most common cause of GIP[22,27,28]. Recently, however, there are ever more studies observing IUGR by fetal and neonatal blood flow Doppler monitoring. These studies recorded a higher prevalence of necrotizing enterocolitis in infants with impaired umbilical artery or superior mesenteric artery blood flow[29].

In our study, anemia was the major risk factor for GIP. The likelihood of GIP was 8.4-fold greater in neonates with anemia as compared with those without anemia. In the literature, anemia is sporadically associated with individual cases of GIP. Pelizzo *et al*[30] describe intrauterine anemia with consequential fetal hydrops and signs of meconium peritonitis caused by distal ileum perforation. On the other hand, others report on anemia detected by laboratory testing, along with thrombocytopenia and elevated C-reactive protein, in infants with GIP caused by necrotizing enterocolitis[31,32].

Recent studies confirm the association of deplasmatized red blood cell transfusion for anemia and necrotizing enterocolitis[33-35]. Other studies assessing the effect of administering erythropoietin and iron agents for anemia found a lower incidence of necrotizing enterocolitis[33]. In our study, anemia was an important risk factor for GIP; the more so, it also proved important for the prognosis after GIP. In more than half of the study subjects (54.5%) that died from GIP, anemia had been diagnosed even before the clinical signs of the diseases that caused GIP. In their recent study, Bracho-Blanchet *et al*[35] also identified anemia as a prognostic factor associated with mortality in newborns with necrotizing enterocolitis.

In our study, 57.1% of infants were fed per oral, as a rule with adapted formulas, until GIP onset. In necrotizing enterocolitis, perforation generally occurs upon switching to oral feeding[6]. It is considered that there is no causative relationship between oral feeding and spontaneous intestinal perforation. Ragouilliaux *et al*[22] report on enteral nutrition to have been introduced before the onset of GIP in 69% of newborns. As necrotizing enterocolitis was the most common cause of GIP in our study, the proportion of newborns on oral feeding before GIP occurrence was high, as expected.

Our study results showed that 31.4% of the newborns died from GIP. However, in the last 11 study years, the mortality was nearly half that recorded in the first 11 study years (22% *vs* 41%). Search of the literature yielded a mortality following GIP to range from 17% to 60%[2,4,19]. A 31.6% mortality rate has been reported for newborns with GIP in Japan in 2003. However, the same authors report on 50% mortality among 34 newborns during a 30-year period[3]. These figures correspond to the trend observed in our study on the mortality decline in the past decades. Advances in operative techniques, anesthesiology procedures and intensive care measures probably have contributed to the GIP mortality decline.

In our study, necrotizing enterocolitis was the most common cause of GIP in deceased infants (63.6%). Other studies also report on the highest mortality following GIP to be associated with necrotizing enterocolitis[2,19,25]. Although colon was the most frequent site of perforation, small intestine perforation was found in the majority of deceased neonates (36.4%). According to literature reports, the small intestine perforation mortality is also higher than colon perforation mortality[26]. Exploratory laparotomy is considered as the surgical method of choice in newborns with intestinal perforation, in particular the one caused by necrotizing enterocolitis. Most studies report on laparotomy with intestinal segment resection to be performed in all or nearly all infants with GIP[4,25]. Primary management with peritoneal drainage instead of laparotomy is less frequently described[19]. However, definite recommendations in favor of either laparotomy or peritoneal drainage are still lacking. In our study, percutaneous stoma after intestinal segment resection was established in 80% of newborns with GIP. According to literature data, stoma formation following resection is associated with better survival than primary anastomosis after resection[4,35].

In conclusion, Based on our study results, newborns with anemia and hypotrophic newborns, along with all very low birth weight newborns should be considered at high risk of GIP. The pattern of fetal growth (neonatal proportions, *i.e.*, birth weight to birth length ratio) as determined by ponderal index is not a risk factor for GIP development.

COMMENTS

Background

Gastrointestinal perforation (GIP) in newborns is mostly associated with necrotizing enterocolitis. Congenital anomalies with obstruction can also be the cause of GIP. There are little informations in literature about perinatal risk factors,

and ponderal index in infants with GIP has not been reported.

Research frontiers

A single institutional retrospective study of patients undergoing surgery because of GIP from 1990 to 2012 was performed.

Innovations and breakthroughs

GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia.

Applications

Newborns with very low birth weight and anemia should be monitored carefully for GIP.

Terminology

Ponderal Index is a measure of leanness of a person calculated as a relationship between mass and height.

Peer-review

The manuscript is well written and important in its field.

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ORIGINAL ARTICLE

Retrospective Study

Critical analysis of feeding jejunostomy following resection of upper gastrointestinal malignancies

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Abstract

AIM

To assess nutritional recovery, particularly regarding feeding jejunostomy tube (FJT) utilization, following upper gastrointestinal resection for malignancy.

METHODS

A retrospective review was performed of a prospectively-maintained database of adult patients who underwent esophagectomy or gastrectomy (subtotal or total) for cancer with curative intent, from January 2001 to June 2014. Patient demographics, the approach to esophagectomy, the extent of gastrectomy, FJT placement and utilization at discharge, administration of parenteral nutrition (PN), and complications were evaluated. All patients were followed for at least ninety days or until death.

RESULTS

The 287 patients underwent upper GI resection, comprised of 182 esophagectomy (n = 107 transhiatal, 58.7%; n = 56 Ivor-Lewis, 30.7%) and 105 gastrectomy [n = 63 subtotal (SG), 60.0%; n = 42 total (TG), 40.0%]. 181 of 182 esophagectomy patients underwent FJT, compared with 47 of 105 gastrectomy patients (99.5% *vs* 44.8%, $P < 0.0001$), of whom most had undergone TG (n = 39, 92.9% *vs* n = 8 SG, 12.9%, $P < 0.0001$). Median length of stay was similar between esophagectomy and gastrectomy groups (14.7 d *vs* 17.1 d, $P = 0.076$). Upon discharge, 87 esophagectomy patients (48.1%) were taking enteral

feeds, with 53 (29.3%) fully and 34 (18.8%) partially dependent. Meanwhile, 20 of 39 TG patients (51.3%) were either fully (n = 3, 7.7%) or partially (n = 17, 43.6%) dependent on tube feeds, compared with 5 of 8 SG patients (10.6%), all of whom were partially dependent. Gastrectomy patients were significantly less likely to be fully dependent on tube feeds at discharge compared to esophagectomy patients (6.4% *vs* 29.3%, P = 0.0006). PN was administered despite FJT placement more often following gastrectomy than esophagectomy (n = 11, 23.4% *vs* n = 7, 3.9%, P = 0.0001). FJT-specific complications requiring reoperation within 30 d of resection occurred more commonly in the gastrectomy group (n = 6), all after TG, compared to 1 esophagectomy patient (12.8% *vs* 0.6%, P = 0.0003). Six of 7 patients (85.7%) who experienced tube-related complications required PN.

CONCLUSION

Nutritional recovery following esophagectomy and gastrectomy is distinct. Operations are associated with unique complication profiles. Nutritional supplementation alternative to jejunostomy should be considered in particular scenarios.

Key words: Feeding jejunostomy; Esophagectomy; Gastrectomy; Nutritional recovery; Outcomes

Core tip: Adequate nutrition following major upper gastrointestinal cancer resection is critical in order to achieve optimal recovery. However, feeding jejunostomy tube placement should not be considered obligatory as part of upper gastrointestinal resection. Alternative methods of nutritional supplementation are available and perhaps better-tolerated.

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INTRODUCTION

Upper gastrointestinal malignancy, comprised of esophageal and gastric cancer, represents nearly 42000 new diagnoses per year in the United States. These diagnoses carry a high disease-related mortality, causing an estimated 26000 deaths annually[1]. Patients with esophageal and gastric malignancies often present in a malnourished state, with significant unintentional weight loss a common sign of disease. Such weight loss has been associated with worse outcomes following resection[2]. Adequate nutrition for patients undergoing resection is critical in order to recover from the operation and to successfully undergo adjuvant therapy.

Nutritional support modalities include enteral nutrition *via* feeding tubes and parenteral nutrition (PN) *via* central venous catheters. Enteral feeding is preferred as it has been shown to maintain the epithelial lining of the gut in animals, with limited evidence of the same in humans[3,4]. However, enterally-fed patients are often unable to meet prescribed caloric goals due to postoperative dysmotility, tube malfunctions, missed feedings, or other reasons[5,6]. Parenteral nutrition has been used postoperatively when patients demonstrate that they are unable to orally or enterally achieve adequate caloric intake, with the benefit of consistent nutritional support. However, parenteral nutrition has been associated with a higher incidence of infectious complications[7]. Regarding oncology patients, Bozzetti *et al*[8] randomized 317 patients undergoing major gastrointestinal cancer resection to either enteral or parenteral nutritional support immediately postoperatively, finding lower overall, and specifically infectious, complication rates in enterally-supported patients.

Options for nutritional support following upper gastrointestinal resection include needle catheter jejunostomy, Stamm or Witzel jejunostomy, or nasojejunal feeding tube placement[9-14]. In some centers, feeding jejunostomy (FJT) is routinely performed following esophagectomy or total gastrectomy, with more selective utilization with subtotal gastrectomy. However, other groups advocate selective use of FJT to minimize tube-related complications[15]. This study examined parenteral nutrition administration and feeding tube utilization rates at the time of discharge in order to better assess the need for enteral support following upper gastrointestinal resection.

MATERIALS AND METHODS

The medical records for all patients who underwent esophagectomy and total or subtotal gastrectomy with curative intent from January 2001 to December 2014 were identified from a prospectively-maintained database. Patients' demographic information, procedure performed, utilization of nutritional support, post-operative length of stay, and post-operative complications were obtained from the medical record. Surgical complications within 30 d after the operation were graded using a surgical secondary events grading system, as described elsewhere, in which grade 1 complications required local or bedside care; grade 2 complications required invasive monitoring or intravenous medication; grade 3 complications required an operation, interventional radiology procedure, intubation, or therapeutic endoscopy; grade 4 complications resulted in a persistent disability or required major organ resection; and grade 5 complications resulted in death[16].

Nutritional support was considered to have been utilized if the patient was not able to achieve adequate oral intake during hospital admission and therefore (1)

received PN post-operatively while an inpatient and/or home PN at time of discharge or (2) required tube feeds to meet caloric goals at the time of discharge. PN was administered *via* triple-lumen subclavian or internal jugular venous lines or peripherally-inserted central catheters. Of note, all PN in our institution is managed by a physician-led multi-disciplinary team in conjunction with the primary service. All of the surgeons performing upper GI resections were observed by a second attending for a minimum of five cases to ensure technical uniformity and quality of feeding jejunostomy placement in order to confirm that the complications were not technical in nature. Jejunostomy was performed in conjunction with upper gastrointestinal resection in order to gain enteral access to (1) provide nutritional support in the immediate post-operative phase or (2) supplement caloric intake in the event that the patient could not meet nutritional goals with oral intake. Feeding jejunostomy-related complications were considered as such when an invasive intervention was required, such as interventional radiology procedure or reoperation; improper tube function such as clogging was not considered a complication.

Our institutional esophagectomy protocol is to keep the patient *nil per os* for seven days after resection, with nasogastric tube decompression of the conduit until post-operative day six. Trophic tube feeds are started on post-operative day two and slowly advanced to goal. Patients undergo thin barium swallow to evaluate for anastomotic leak on post-operative day seven, and if negative they are advanced first to clear liquids, then full liquids, and finally post-esophagectomy diet. If calorie counts demonstrate adequate intake, the patients are discharged without tube feeds. Tube feeds are continued on discharge if patients are unable to take oral diet or do not meet caloric requirements by mouth.

Our institutional subtotal gastrectomy protocol is to keep the patient *nil per os* with nasogastric tube decompression until the patient has return of bowel function. The tube is removed and the patient's diet is advanced as tolerated from clear liquids to post-gastrectomy diet. The total gastrectomy protocol is to keep the patient *nil per os* with nasogastric tube decompression until they undergo diatrizoic acid swallow to evaluate for anastomotic leak, on post-operative day seven. If the study is negative, the nasogastric tube is removed and the patient is advanced first to clear liquids, then full liquids, and finally post-gastrectomy diet. Enteral feeds are started in patients who are unable to tolerate oral feedings within the seven to ten days following operations. If calorie counts demonstrate adequate intake, the patients are discharged without tube feeds. Tube feeds are continued on discharge if patients are unable to take oral diet or do not meet caloric requirements by mouth.

All patients meeting inclusion criteria were identified and followed up for a minimum of 180 d or until death. Data were analyzed using SAS statistical software, version 5.0 (SAS Institute, Inc., Cary, NC). Data were expressed as percentages in the case of categorical variables. Frequencies were compared by the χ^2 test. Means of continuous variables were analyzed using *t* test or ANOVA. All reported *P* values were two-tailed and for all tests values less than 0.05 were considered significant. This study was approved by the institutional review board at Rhode Island Hospital.

RESULTS

Resection of an upper gastrointestinal malignancy was performed in 287 patients. The median patient age and proportion of males were similar between the esophagectomy and gastrectomy groups. There was no significant difference in mean length of stay groups (14.7 d *vs* 17.1 d, $P = 0.076$). Within the gastrectomy group, the median length of stay was significantly longer for the TG group compared to the SG group (16 d *vs* 10 d, $P = 0.0002$). Patients were more likely to be fully dependent on tube feeds at discharge following esophagectomy than gastrectomy ($n = 53$, 29.3% *vs* $n = 3$, 6.4%; $P = 0.0006$). Within 30 d of operation, 52.4% of TG and 29.6% of SG patients experienced complications, compared to 91 patients (50.0%) from the esophagectomy group. Major complications (grade 3-5) occurred in 59 esophagectomy patients and 26 gastrectomy patients (32.6% *vs* 24.8%, $P = 0.18$). Feeding tube-specific complications requiring reoperation within 30 d of operation occurred in 6 of 47 gastrectomy patients (12.8%), all within the TG group ($P = 0.23$). Complications were comprised of closed-loop obstruction around the feeding tube ($n = 2$), feeding tube leak ($n = 2$), small bowel perforation ($n = 1$), and multi-organ failure after initiation of tube feeds ($n = 1$). Conversely, within the esophagectomy group, only one jejunostomy tube-related major complication presented in follow-up, a small bowel obstruction at the jejunostomy site in a patient who had undergone transhiatal esophagectomy who required reoperation (Table 1).

Between January 2001 and June 2014, 182 patients underwent esophagectomy for esophageal malignancy with curative intent (Figure 1). Patients' median age was 64.0 years and 145 were male (79.7%). The predominant tumor type consisted of adenocarcinoma ($n = 158$, 86.8%), followed by squamous cell carcinoma ($n = 15$, 8.2%), high grade dysplasia ($n = 8$, 4.3%), and neuroendocrine tumor ($n = 1$, 0.5%). The primary tumor was located in the middle third of the esophagus in 11 patients (6.0%), lower third in 144 patients (79.1%), and at the gastroesophageal junction in 27 patients (14.8%). One hundred and seven patients (58.7%) underwent transhiatal esophagectomy, 56 patients (30.7%) had Ivor-Lewis esophagectomy, 10 patients (5.4%) underwent three-incision esophagectomy, and 9 patients (4.9%) had thoracoabdominal esophagectomy. Endoscopic ultrasound was used during pre-operative staging in 70 patients (38.4%). Neo-adjuvant induction therapy was administered to 114 patients (62.6%).

Between January 2004 and December 2013,

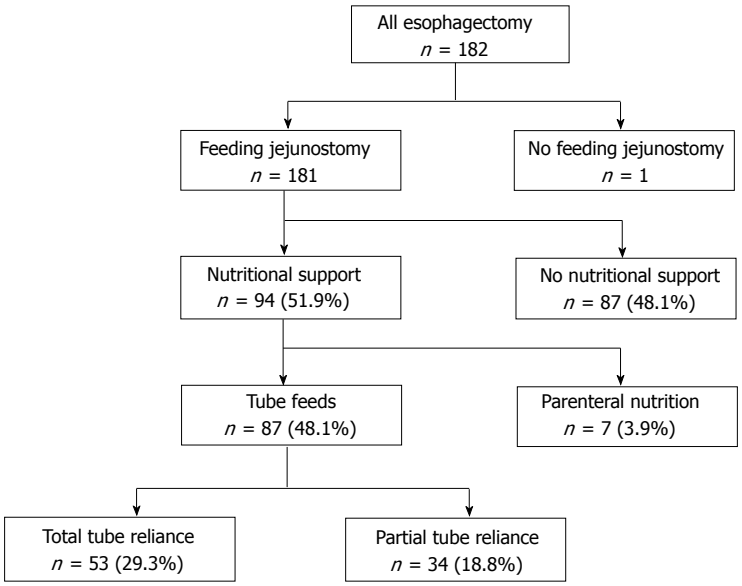

Figure 1 Flow chart of nutritional support for esophagectomy patients.

Table 1 Comparison of complications within thirty days by grade *n* (%)

Complication	Subtotal gastrectomy (*n* = 63)	Total gastrectomy (*n* = 42)	Esophagectomy (*n* = 182)
None	45 (71.4)	20 (47.6)	91 (50.0)
Low-grade	10 (15.9)	4 (9.5)	32 (17.6)
High-grade	8 (12.7)	15 (35.7)	54 (29.7)
Overall mortality	0 (0.0)	3 (7.1)	5 (2.7)
Tube-related complications	0	6	1

Low-grade denotes grade 1-2; high-grade denotes grade 3-4.

Table 2 Clinical characteristics of esophagectomy in relation to tube feed requirement *n* (%)

Characteristic	Total (*n* = 182)	Tube feeds used	Tube feeds not used	*P* value
Age > 65 yr	93	40 (43.0)	53 (57.0)	0.24
Male sex	145	69 (47.6)	76 (52.4)	0.91
Tumor type				
Adenocarcinoma	158	76 (48.1)	82 (51.9)	
Squamous cell carcinoma	15	7 (46.7)	8 (53.3)	0.99
High-grade dysplasia	8	4 (50.0)	4 (50.0)	
Neo-adjuvant therapy	114	52 (45.6)	62 (54.4)	0.54
Post-operative complication	91	66 (72.5)	25 (27.5)	< 0.0001
Esophagectomy approach				
Transhiatal	107	64 (59.8)	43 (40.2)	< 0.0001
Ivor-Lewis	56	14 (25.0)	42 (75.0)	

105 patients underwent total gastrectomy (TG) (*n* = 42, 40%) or subtotal gastrectomy (SG) (*n* = 63, 60%) (Figure 2). The TG and SG groups had similar proportions of males (66.7% each), however, the TG group was younger compared to the SG group (66.6 years *vs* 72.7 years, respectively, *P* = 0.018). Pre-operative albumin was obtained from the medical record in 36 TG patients (85.7%) and 41 SG patients (65.1%); mean albumin was higher in the TG group compared to the SG group (3.5 *vs* 3.2, *P* = 0.024).

A feeding jejunostomy tube was placed in 181 of the 182 esophagectomy patients (99.5%). At the time of discharge, 87 esophagectomy patients (48.1%) required tube feeds for nutritional supplementation, of whom 53 (29.3%) were fully and 34 (18.8%) were partially reliant (Table 2). There was no association between tube feed requirement and age, gender, tumor type, or administration of induction therapy. Patients who had undergone transhiatal esophagectomy were more likely to require tube feeds at discharge than patients who underwent Ivor-Lewis esophagectomy (64 of 107 transhiatal, 59.8% *vs* 14 of 56 Ivor-Lewis, 25.0%; *P* < 0.0001) (Table 3). Meanwhile, seven patients (3.9%) were discharged on parenteral nutrition, four for chylothorax and three having had the feeding tube removed on reoperation (for hemoperitoneum, evisceration, and anastomotic leak). Of the patients with transhiatal esophagectomy, 56 of 107 patients (52.3%) had a complication, of which 34 were cervical anastomotic leak (31.8%). Fifteen of 56 patients (26.8%) with Ivor-Lewis esophagectomy experienced complications, of which four were anastomotic leaks (7.1%). The difference in anastomotic leak rate between the two approaches was statistically significant (*P* = 0.0003).

A feeding jejunostomy tube was placed for 47 of the 105 gastrectomy patients (44.8%), of which significantly more were performed for the TG than the SG group (92.9% *vs* 12.9%, *P* < 0.0001). After TG with feeding tube, 20 of 39 patients (51.3%) were fully (*n* = 3, 7.7%) or partially (*n* = 17, 43.6%) dependent on tube feeds at the time of discharge, whereas after SG with feeding tube, 5 of 8 (62.5%) were partially dependent and no patients were fully dependent on tube feeds (Table 4). Need for tube feed-based nutritional support in gastrectomy patients was not associated with extent of resection (51.3% TG *vs* 62.5% SG, *P* = 0.56). During

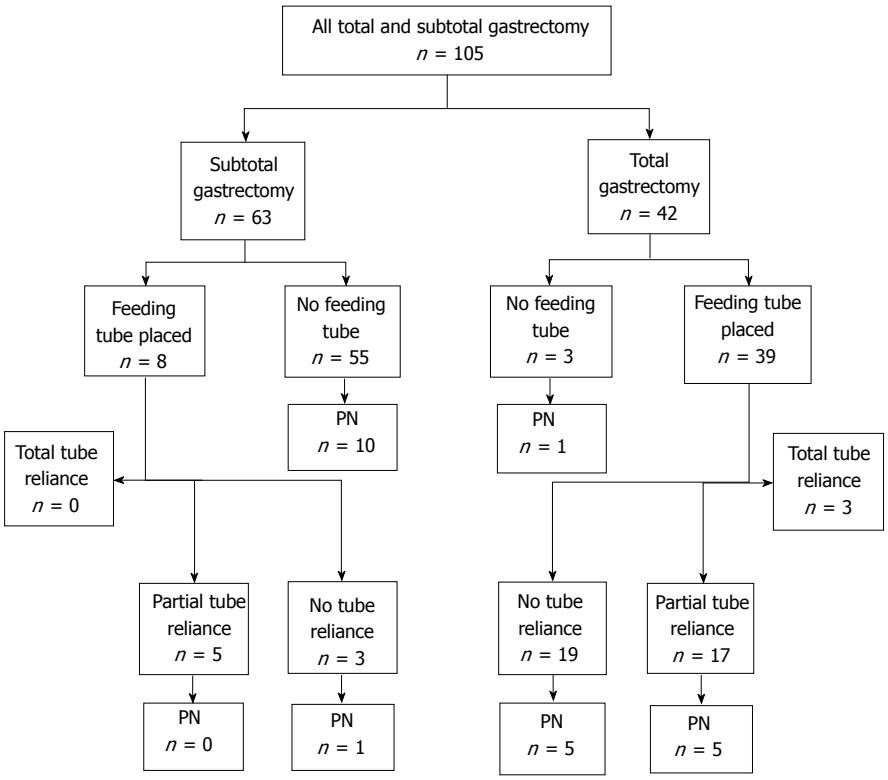

Figure 2 Flow chart of feeding tube placement, tube utilization and parenteral nutrition administration for gastrectomy patients. PN: Parenteral nutrition.

Table 3 Tube feed reliance by esophagectomy approach *n* (%)

Tube feed reliance	Transhiatal (*n* = 107)	Ivor-lewis (*n* = 56)	Other (*n* = 19)
None	43 (40.2)	42 (75.0)	10 (52.6)
Partial	20 (18.7)	10 (17.6)	4 (21.1)
Total	44 (41.1)	4 (7.1)	5 (26.3)

admission, 11 TG and 11 SG patients (26.2% *vs* 17.4%, respectively) required PN as a bridge to adequate oral or enteral intake. Following TG with feeding tube placement, 10 of the 39 patients (25.6%) required PN, whereas one of the SG with feeding tube placement patients required PN. Three patients (2.9%) required home parenteral nutrition, of whom two had had tube-related complications and one had persistent feeding intolerance. For TG and SG patients, PN administration was not associated with extent of resection (11 of 42 TG, 26.2%, *vs* 11 of 63 SG, 17.5%; $P = 0.28$), feeding tube placement (11 of 47 with tube, 23.4% *vs* 11 of 58 without tube, 19.0%; $P = 0.58$), or feeding tube utilization (5 of 25 with tube utilization, 20.0% *vs* 6 of 22 without tube utilization, 27.3%; $P = 0.56$).

DISCUSSION

Although both esophageal and gastric malignancies are classified as being upper gastrointestinal, nutritional recovery after resection of each is significantly different. The surgeon must consider not just the patient's pre-operative nutritional status but the planned resection, the potential complications, and the various methods of nutritional support available. This study illustrates those tenets, with variable reliance on enteral supplementation between transhiatal and Ivor-Lewis esophagectomy and between subtotal and total gastrectomy, as well as a substantial feeding-tube related major complication rate. Older literature has suggested that feeding jejunostomy placement is a well-tolerated, low-risk additional procedure that secures enteral access following esophagectomy and total gastrectomy[9].

The operative approach to esophagectomy has its attendant risks and complication profiles. The transhiatal esophagectomy is thought to accept a higher rate of lower-grade morbidity in that a cervical anastomosis is more likely to leak but is less detrimental to the patient. Meanwhile, the Ivor-Lewis approach is believed to provide a lower likelihood of anastomotic leak with the understanding that such a leak is more devastating given the resultant mediastinitis. Of note, randomized controlled trials have not borne out such beliefs[17]. In our series, the Ivor-Lewis approach to esophagectomy was associated with lower feeding tube utilization rates at discharge compared to the transhiatal approach (25.0% *vs* 59.8%, respectively; $P < 0.0001$). As the inability to use the reconstructed conduit is the most likely reason for need for nutritional support following esophagectomy, the difference in tube utilization rates was most likely related to lower leak rates of intrathoracic anastomoses (7.1%) *vs* cervical anastomoses (31.7%).

The extent of gastric resection determines the reconstruction approach, typically either Billroth II

Table 4 Feeding tube placement and utilization and overall need for nutritional support in relation to extent of gastric resection *n* (%)

Variable	Overall (*n* = 105)	Subtotal (*n* = 63)	Total (*n* = 42)	*P* value
Feeding tube placed	47 (44.8)	8 (12.7)	39 (92.9)	< 0.0001
Tube placed, utilized	25 (53.2)	5 (62.5)	20 (51.3)	0.71
Tube placed, utilized, PN utilized	5 (10.6)	-	5 (12.8)	0.57
Tube placed, not utilized	22 (46.8)	3 (37.5)	19 (48.7)	0.71
Tube placed, not utilized, PN utilized	6 (12.8)	1 (12.5)	5 (12.8)	1.0
PN utilized	22 (21.0)	11 (17.5)	11 (26.2)	0.28
PN utilized with feeding tube	11 (10.5)	1 (9.1)	10 (90.9)	0.42
PN utilized without feeding tube	11 (10.5)	10 (90.9)	1 (9.1)	0.51
No nutritional support used regardless of feeding tube placement	63 (60.0)	47 (74.6)	16 (38.1)	0.0004

PN: Parenteral nutrition.

gastrojejunostomy following subtotal gastrectomy or Roux-en-Y esophagojejunostomy following total gastrectomy. The lack of a gastric remnant eliminates the accommodating reservoir function of the stomach and requires a second anastomosis involving the small bowel. For these and other reasons, feeding jejunostomy placement is often routinely performed in conjunction with total gastrectomy and more selectively done with subtotal gastrectomy. In our series, feeding jejunostomy tube placement was more frequently placed during total than subtotal gastrectomy (92.9% *vs* 12.7%, $P < 0.0001$). Despite the significant difference in the frequency of feeding tube placement, tube utilization rates at the time of discharge were similar (51.3% *vs* 62.5%, respectively; $P = 0.56$). While the majority of patients who undergo subtotal gastrectomy will recover without requiring nutritional support, the relatively high tube utilization rate likely reflects a preference for enteral nutritional support instead of parenteral support when enteral access has already been established. This is evidenced in that no patient who underwent subtotal gastrectomy with feeding tube placement also received parenteral nutrition.

Our traditional institutional practice has been to routinely place FJT at the time of esophagectomy, while tube placement at the time of gastric resection has been more selective, with a higher rate of feeding jejunostomy following total gastrectomy than subtotal resection. Intra-operative feeding jejunostomy placement does not guarantee consistent enteral access or obviate the need for parenteral nutrition for post-operative supplementation. In the esophagectomy group, seven patients (3.9%) received parenteral nutrition to meet caloric goals since four patients developed chylothorax and three patients had their feeding jejunostomy removed at reoperation for intra-abdominal complications. Following gastrectomy, eleven of forty-seven patients (23.4%) who underwent feeding tube placement required parenteral nutrition. Six of these patients were given parenteral nutrition as a direct result of having developed tube-related major complications requiring reoperation. Of the remaining five patients, three had other intra-abdominal complications precluding tube feed administration and two demonstrated tube feed intolerance. Meanwhile, eleven of fifty-eight patients (19.0%) who underwent gastric resection without feeding jejunostomy placement required parenteral nutrition as a bridge to adequate oral caloric intake.

Feeding tube-specific complication rates within 30 d were identified in seven of 228 patients (3.1%), which is consistent with rates published in other series. However, nearly all tube-related complications occurred following gastrectomy, for a complication rate of 12.8% (6 of 47), all of whom had undergone total gastrectomy. All tube-related complications were major, requiring invasive procedure or reoperation for indications such as bowel ischemia, bowel perforation, or acute obstruction. This tube complication rate might be considered higher than expected, but it is consistent with the study by Llaguna *et al*[18] in which 18 of 73 patients (24.7%) experienced a jejunostomy tube-related complication, with 10 patients (13.7%) experiencing a complication requiring reoperation or interventional radiology procedure. In addition, Patel *et al*[19] demonstrated that in a population of 132 patients who underwent total or subtotal gastrectomy, feeding jejunostomy placement was associated with a greater frequency of any grade complication (59% *vs* 41%, $P = 0.04$) and specifically any infectious complication (36% *vs* 17%, $P = 0.01$). Of note, the rate of major complications was not significantly different, and the authors did not separately identify tube-related complications. Only tube placement was associated with post-operative complications on multivariate analysis, whereas age, functional status, T stage, N stage, and extent of resection were not. The higher rate of tube-specific complications following total gastrectomy compared to subtotal gastrectomy or esophagectomy in the absence of technical error suggests an inherent difference in post-operative recovery. The combination of the lack of a gastric remnant with the performance of D2 lymphadenectomy and Roux-en-Y reconstruction may place the small bowel at greater risk of impaired recovery and therefore greater likelihood of tube-related complications.

Overall tube utilization rates at discharge were on the order of fifty percent for both esophageal and gastric resection. While the optimal time for placing a feeding jejunostomy tube is at the time of resection, this does not mean that it should be done solely for sake of ease or potential prophylaxis, as half of patients will recover to discharge without the need for prolonged

tube feeds. Specific resections were associated with need for tube feed supplementation, as patients who underwent transhiatal esophagectomy more frequently required nutritional supplementation at that time of discharge compared to Ivor-Lewis esophagectomy (59.8% *vs* 25.0%, respectively; $P < 0.0001$). A similar distinction was also seen when comparing total and subtotal gastrectomy patients (61.9% *vs* 25.4% respectively, $P = 0.0004$).

Parenteral nutrition has its own risks, such as central line sepsis, but has an advantage in that the decision to administer nutritional support may be postponed until the postoperative phase of recovery, when patients' early postoperative courses can better indicate a need for such support. An alternative method of enteral access that is receiving more attention is nasojejunal tube placement at operation[13,14]. This modality is less invasive than jejunostomy tubes or central lines with fewer associated complications, but is more aimed towards supplemental nutrition while the patient is in-house as opposed to long-term. Since the placement of a nasojejunal tube adds essentially no morbidity to the operation, our practice has shifted to routinely place these tubes at the time of total or subtotal gastrectomy in order to provide nutritional support.

Given suboptimal tube utilization rates, significant feeding tube-related complication rates, and the presence of alternative methods of nutritional supplementation, we would argue that feeding jejunostomy placement should not be considered an obligatory component of any upper gastrointestinal resection. Although this study is prospective in nature, it is limited in its generalizability to patients with upper gastrointestinal malignancy. Despite that, our data suggest that the majority of patients who undergo Ivor-Lewis esophagectomy or subtotal gastrectomy will recover adequate oral caloric intake in the short term. In addition, enteral supplementation *via* nasojejunal tube placement may be a preferable method of nutritional delivery following total gastrectomy. By reducing the frequency of feeding jejunostomy placement, tube-related complications would be minimized and tube utilization rates would be improved. How best to predict the need and optimal route for post-operative nutritional support would be optimally assessed in a randomized, prospective manner.

In conclusion, nutritional recovery following upper gastrointestinal resection for malignancy must be assessed according to the specific pathology being treated. Esophagectomy and gastrectomy have different risks based on operative approach and complication profiles. Feeding jejunostomy was associated with significant tube-related complications, particularly following total gastrectomy. This study suggests that jejunostomy tube placement is not obligatory following upper gastrointestinal resection for malignancy and that alternative methods of nutritional supplementation such as parenteral nutrition or nasojejunal tube placement are potentially better tolerated and allow enhanced patient selection for nutritional support.

COMMENTS

Background

Adequate nutrition has been demonstrated to be critical to the recovery process after major resection. Various methods of nutritional support may be employed, including but not limited to parenteral nutrition, nasojejunal tube feeds, or jejunostomy tube feeds. At many institutions, feeding jejunostomy tubes (FJT) are often placed as a matter of routine in conjunction with resection of upper gastrointestinal malignancy in order to gain enteral access for support during the immediate post-operative phase as well as in anticipation of adjuvant chemotherapy. This study evaluated the actual utilization rates of such feeding tubes upon discharge as well as to assess tube-related complication rates.

Research frontiers

Feeding jejunostomy has been widely studied in esophageal resection, but limited literature has evaluated them in major gastric resection. Although both esophageal and gastric malignancy are in the upper gastrointestinal tract, they are unique neoplasms and comparing utilization rates in each patient population has not been done to date.

Innovations and breakthroughs

In this study, tube utilization rates at discharge for both patient populations were on the order of 50%. However, utilization rates were higher in the subpopulations of total gastrectomy and transhiatal esophagectomy. Major tube-related complications were 3.1%; these were predominantly experienced by patients who underwent total gastrectomy. Meanwhile, Ivor-Lewis esophagectomy and subtotal gastrectomy patients were more likely to achieve adequate oral nutritional intake prior to discharge home.

Applications

This study suggests that nasojejunal feeding tube placement may be a preferred route of nutritional support over feeding jejunostomy following Ivor-Lewis esophagectomy and subtotal gastrectomy. This method of nutritional delivery has potential benefit as well for transhiatal esophagectomy and total gastrectomy patients, while avoiding the complications related to feeding jejunostomy placement, with consideration of parenteral nutrition as an alternative route if nasojejunal tube feeds are not able to be administered.

Peer-review

The authors of this paper evaluated feeding jejunostomy utilization for esophagectomy and gastrectomy for malignancy. Suboptimal utilization rates and significant tube-related major complications suggest that alternative methods of nutritional support to routine feeding jejunostomy placement allow enhanced patient selection.

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ORIGINAL ARTICLE

Retrospective Study

Clinicopathological features and surgical outcome of patients with fibrolamellar hepatocellular carcinoma (experience with 22 patients over a 15-year period)

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Author contributions: Wahab MA and El Hanafy E contributed to study concept; Wahab MA, El Hanafy E and El Nakeeb A contributed to data collection; El Hanafy E and El Nakeeb A contributed to data analysis; Wahab MA and Ali MA contributed to writing the draft; all authors have approved the manuscript in its final form and approving the manuscript in its final form.

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Abstract

AIM

To evaluate the clinicopathological features and the surgical outcomes of patients with fibrolamellar hepatocellular carcinoma (FL-HCC) over a 15-year period.

METHODS

This is a retrospective study including 22 patients with a pathologic diagnosis of FL-HCC who underwent hepatectomy over a 15-year period. Tumor characteristics, survival and recurrence were evaluated.

RESULTS

There were 11 male and 11 female with a median age of 29 years (range from 21 to 58 years). Two (9%) patients had hepatitis C viral infection and only 2 (9%) patients had alpha-fetoprotein level > 200 ng/mL. The median size of the tumors was 12 cm (range from 5-20 cm). Vascular invasion was detected in 5 (23%) patients. Four (18%) patients had lymph node metastases. The median follow up period was 42 mo and the 5-year survival was 65%. Five (23%) patients had a recurrent disease, 4 of them had a second surgery with 36 mo median time interval. Vascular invasion is the only significant negative prognostic factor

CONCLUSION

FL-HCC has a favorable prognosis than common HCC

and should be suspected in young patients with non cirrhotic liver. Aggressive surgical resection should be done for all patients. Repeated hepatectomy should be considered for these patients as it has a relatively indolent course.

Key words: Fibrolamellar hepatocellular carcinoma; Common hepatocellular carcinoma; Recurrence after resection fibrolamellar hepatocellular carcinoma; Pathology of fibrolamellar hepatocellular carcinoma; Survivalefter resection fibrolamellar hepatocellular carcinoma

Core tip: Fibrolamellar hepatocellular carcinoma (FL-HCC) has conventionally been considered to be a histologic variant of HCC, with distinct clinicopathologic features. Many series have mentioned that FL-HCC is less aggressive than conventional HCC. However, other studies have failed to confirm the observation of a better outcome in FL-HCC. Our study shows that FL-HCC has a favorable prognosis than common HCC and should be suspected in young patients with non cirrhotic liver. Aggressive surgical resection should be done for all patients. Repeated hepatectomy or excision of recurrent disease should be considered for these patients as it has a relatively indolent course.

Wahab MA, El Hanafy E, El Nakeeb A, Ali MA. Clinicopathological features and surgical outcome of patients with fibrolamellar hepatocellular carcinoma (experience with 22 patients over a 15-year period). *World J Gastrointest Surg* 2017; 9(2): 61-67 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i2/61.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i2.61

INTRODUCTION

Fibrolamellar hepatocellular carcinoma (FL-HCC) has conventionally been considered to be a histologic variant of hepatocellular carcinoma (HCC), with distinct clinicopathologic features. It is a rare primary hepatic malignancy that was first described as a pathological variant of HCC by Edmondson[1] in 1956.

FL-HCC is usually well circumscribed masses characterized by polygonal hepatic cells with deeply eosinophilic cytoplasm and abundant fibrous stroma arranged in thin parallel bands. On gross examination, there is a central scar which resulted from coalesced lamellar bands of fibrosis[2].

The etiology of FL-HCC remains unclear. It typically occurs in normal livers without underlying liver fibrosis or cirrhosis[3]. In contrast to HCC which usually found in the presence of cirrhosis or chronic hepatitis[4]. FL-HCC has been reported to occur in association with focal nodular hyperplasia a type of benign liver lesion[5,6]. Some suggest that FHN may be a benign precursor lesion to FL-HCC as both diseases share several features: They tend to present in younger patients, and in the setting of normal liver parenchyma. Pathologically both have as a stellate central scar on imaging studies and copper accumulation on histological examination[6,7].

Many series have mentioned that FL-HCC is less aggressive than conventional HCC[8-10]. However, other studies have failed to confirm the observation of a better outcome in FL-HCC[11-13]. Other studies reported that the survival was similar between common HCC and FL-HCC, and that may be related to the higher resectability rate which improve the survival of patients with FL-HCC[12,14].

The aim of this study was to evaluate the clinicopathological features and the surgical outcomes of patients with FL-HCC who were referred to our tertiary referral center over a 15-year period.

MATERIALS AND METHODS

This is a retrospective study of patients underwent hepatectomy for a pathologic diagnosis of FL-HCC over an 15-year period between February 1999 to February 2014, in gastroenterology surgical center, Mansoura University, Egypt. A total of 22 patients was diagnosed and underwent hepatectomy during this period. The diagnosis of FL-HCC was made depending on its histological and pathological characteristics by an independent pathologic team.

All patients were subjected to clinical assessment; laboratory investigation and imaging work up including: Ultrasonography, Enhanced computed tomography and MRI imaging study to evaluate the extent of the tumor, vascular involvement and lymph node affection. Clinicopathological parameters, including gender and age of patients; location, size and number of the tumor; safety margins; vascular invasion; lymph node metastasis status; operative details; morbidity and mortality; and survival and recurrence were collected. The parenchymal disease of the liver is defined as hepatitis C antibody and/or hepatitis B surface antigen was present. Safety margin is defined as complete tumor excision after surgical treatment proved by pathologic examination of the resected margins. Patients with synchronous malignancies were excluded from the study. Non of our patients underwent preoperative portal vein embolization or chemoembolization and they did not received adjuvant treatment.

Clinical staging of the tumor was performed using the American Joint Committee on Cancer staging criteria[15]. The extent of hepatic resection was defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections[16]: Right hepatectomy involves resection of segments V-VIII, whereas left hepatectomy involves resection of segments (II-IV). Extended right hepatectomy involves resection of segments IV-VIII, whereas extended left hepatectomy involves resection of segments (II-IV, V, VIII). All these resection may or may not involve segment I. Most of liver resections were performed with selective vascular inflow occlusion. However, intermittent clamping was used in selected

Table 1 Patient demographics

	FL-HCC (n = 22)
Median age, years (range)	29 yr (21 to 58)
Male/female	11/11 (50%:50%)
Hepatitis or cirrhosis	2 (9%)
Elevated AFP (> 200 ng/mL)	2 (9%)

FL-HCC: Fibrolamellar hepatocellular carcinoma; AFP: Alpha-fetaprotein.

Table 2 Tumor characteristics' and treatment features n (%)

	FL-HCC (n = 22)
Number	
Single	19 (86)
Multiple	3 (14)
Size (cm)	Median 12 cm (range, 5-20)
Location	9 right, 10 left, 3 bilateral
Hepatic resection	
Hepatectomy	16 (73)
Extended hepatectomy	4 (18)
Localized resection	2 (9)
Stage	
I	10 (45)
II	5 (23)
III	7 (32)
IV	0
Nodal metastases	4 (18)
Vascular invasion	5 (23)
Positive safety margin	2 (9)
Repeated hepatectomy	4 (18)

FL-HCC: Fibrolamellar hepatocellular carcinoma.

patients to avoid ischemia of the remnant liver. Liver transsection was performed using harmonic scalpel, ultrasonic dissector. Follow-up was obtained in the out-patient clinic by personal contact with the patients.

Survival analysis

Log-rank test and Kaplan-Meier curves were used for survival analysis. For continuous variables, descriptive statistics were calculated and were reported as median. Categorical variables were described using frequency distributions. Mortality was defined as death occurring in the hospital or within 30 d. Significance was defined as $P < 0.05$.

RESULTS

Twenty two patients with FL-HCC were diagnosed in our retrospective data base. All our patients underwent partial hepatectomy over a 15-year period. There were 11 male and 11 female with a median age of 29 years (range from 21 to 58 years). Two patients (9%) had liver cirrhosis due to hepatitis C viral infection while the remaining patients had a normal liver, and only 2(9%) patients had high AFP levels (> 200 ng/mL) (Table 1). In comparison to HCC, patients with common HCC were evaluated at our center[17], it was predominantly in male, the mean age was 54.8 ± 9.2 years, 100% had cirrhotic liver and AFP levels were elevated in all

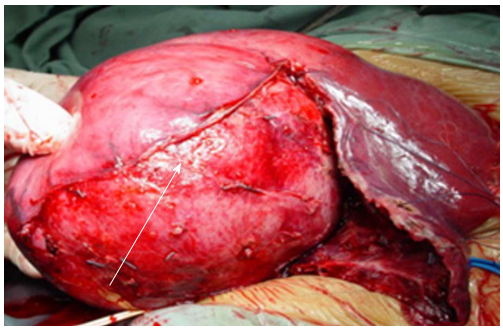

Figure 1 Large right lobe fibrolamellar hepatocellular carcinoma.

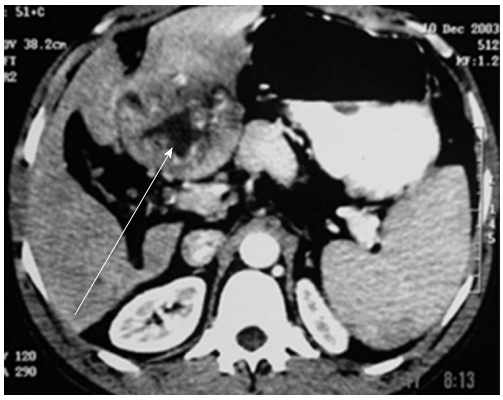

Figure 2 Fibrolamellar hepatocellular carcinoma left lobe.

patients. FL-HCC represents about 3% of patients with hepatic malignancies (1260 patients) during the study period.

Vague abdominal pain was the most common presentation, other were asymptomatic and discovered incidentally during physical examination or routine imaging work up. These tumors are well circumscribed, large and often have areas of hypervascularitywith a central scar Figure 1. Figure 2 shows FL-HCC at left liver lobe while Figure 3 demonstrates a different CT scans for FL-HCC in the right liver lobe.

Surgery and pathology

The type of hepatic resection for our 22 patients is shown in Table 2. Seventy three percent of cases required hepatectomy and 18% needed extended hepatectomy to excise their tumors. Multiple primary tumors were present in 3 patients. The median size of the tumors was 12 cm (range from 5-20 cm). Vascular invasion was detected in 5 (23%) patients. Four of those patients had microscopic vascular invasion, and one had microscopic invasion of the right hepatic vein. The safety margin was invaded in 2 (9%) patients who might be due to presence of the tumor closer tovascular structures which couldn't be resectable. Four (18%) patients had lymph node metastases.

In this study, 5 patients had a recurrent disease.Four patients had a second surgery with 36 mo median time interval. Three patients had a repeated liver resection (including both patients with microscopic invasion of

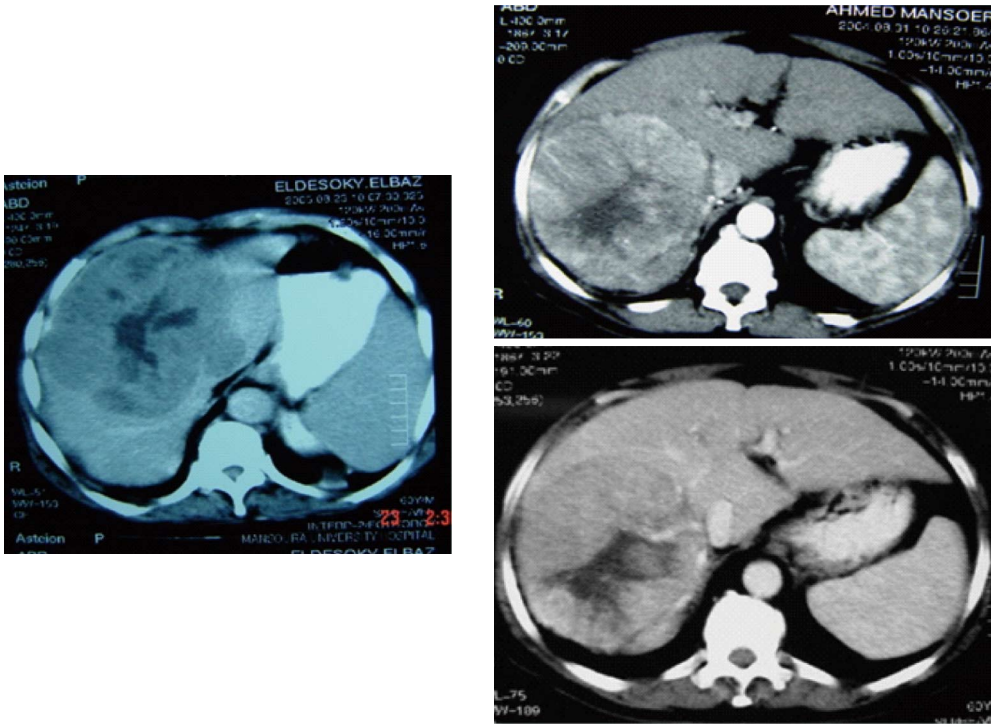

Figure 3 Fibrolamellar hepatocellular carcinoma right lobe.

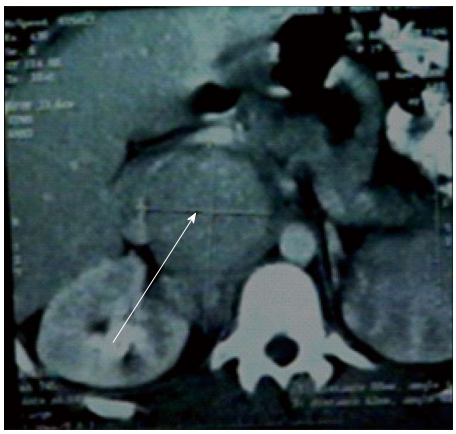

Figure 4 Large retro-caval lynph node 2-year after resection fibrolamellar hepatocellular carcinoma.

resection margins and 1 patient with vascular invasion) and one patient underwent resection of large retro-caval lymph node (Figure 4). The last patient had peritoneum dissemination and nothing was done for him. The median survival was 28 mo after the second operation in these patients. There was no hospital mortality.

Overall survival

The median overall survival in our 22 patients was 88 mo and the 5-year survival was 65%. The median follow up period was 42 mo. In our experience of hepatic resection for HCC in cirrhotic liver (n = 175), the median survival after surgical resection was 24 mo while 5-year survival was 10.7%[17].

The univariate analysis for overall survival was performed and includes the following variables: Age, gender, size and number of tumors, type of hepatic resection, vascular invasion, nodal metastases, and resection margins (Table 3). The two patients with positive microscopic margins developed a recurrent disease. Although radically resected patients have a

Table 3 Clinicopathologic features and survival in fibrolamellar carcinoma (figures in parenthesis reflect percentages)

Factor	*n* (%)	Overall survival (mo)	*P* value
Age (yr)			
< 40	16 (73)	86	
⩾ 40	6 (27)	72	0.4
Gender			
Female	11 (50)	84	
Male	11 (50)	79	0.6
Tumor size (cm)			
< 10	8 (36)	82	
⩾ 10	14 (64)	76	0.3
Number			
1	19 (86)	89	
> 1	3 (14)	77	0.2
Hepatic resection			
Hepatectomy	16 (73)	86	
Extended hepatectomy	4 (18)	77	
Localized resection	2 (9)	79	0.62
Nodal metastases			
Negative	18 (82)	88	
Positive	4 (18)	78	0.09
Vascular invasion			
Absent	17 (77)	92	
Present	5 (23)	58	0.03
Safety margin			
Negative	20 (91)	87	
Positive	2 (9)	72	0.08

Table 4 Published series on fibrolamellar hepatocellular carcinoma

Ref.	*n*	Age	Male: female	Cirrhosis/ hepatitis	AFP elevated	Median size (cm)	> 1 tumor	Positive node	Vascular invasion	Initial operation	Repeat operation	Median f/u	5 yr survival	Prognostic factor
Hemming *et al*[18], 1997	10	31	50:50	NR	10%	8	20%	20%	NR	Phx 100%	50%	101	70%	NR
El-Gazzaz *et al*[19], 2000	20	27	65:35	0% hep B	0%	14	20%	30%	55%	Phx 55% OLT 45%	NR	25	50%	NONE
Kakar *et al*[20], 2005	20	27	53:27	0%	3/13 (23%)	< 10 31% ⩾ 10 69%	10%	35%	NR	Phx 100%	NR	NR	62%	Metastasis at presentation
Stipa *et al*[21], 2006	28	28	43:57	0%	7%	9	11%	50%	36%	Phx 100%	61%	34	76%	Positive LN
Present study	22	29	50:50	9%/hepc	9%	12	13%	18%	23%	Phx 100%	18%	42	65%	Vascular invasiom

Hep: Hepatitis; AFP: Alpha-fetoprotein elevated (> 200 ng/mL); Phx: Partial hepatectomy; NR: Not reported; f/u: Follow up.

prolonged survival (87 mo *vs* 72 mo) it is not reach a statistical significance. Only vascular invasion was significant.

In our study, we have 8 patients with greater than 5-years follow up. Of these patients, 4 died of disease at 63, 67, 74 and 88 mo. Four patients were alive at 65-92 mo after surgery with no evidence of a recurrent disease.

DISCUSSION

FL-HCC has been considered to be a histologic variant of HCC, with distinctive morphological and clinical setting. This study confirms the distinctive clinicopathological finding of other studies that FL-HCC were larger in size than conventional HCC, affects young patients with no sex predilection and occurs in the healthy liver in absence of parenchymal disease or cirrhosis and without elevation of AFP level (Table 4)[18-21]. Elevations in AFP levels are uncommon with less than 10% of patients have AFP levels greater than 200 ng/mL[21]. In this study, only 2 patients (9%) had high AFP level (> 200 ng/mL).

FL-HCC occurs in normal livers without underlying liver fibrosis or cirrhosis[3]. Pinna 1997, reported that 6% of his patients were hepatitis C positive and 7% had cirrhotic liver[10]. In our study, 2 patients (9%) were hepatitis C antibody positive, this may be attributed to high prevalence of hepatitis C virus in our community.

Preoperatively, FL-HCC can be diagnosed by CT scan and MRI imagingcharacteristicas these tumors are usually heterogenous with areas of hypervascularity. Preoperative biopsy was avoided and our patients underwent surgery without biopsy which was reserved for patients who are unresectable. Ichikawa *et al*[22] 1999 reported that FL-HCC had 68% calcification, 65% abdominal lymphadenopathy and 71% central scar.

Surgical resection is the only hope for these patients which should be done whenever possible. Our patients had 73% hepatectomy, 18% extended hepatectomy, while only 9% needed localized resection. The 5-year survival was 65% after resection, which was comparable to the 50%-70% 5-year survival rates in other reported studies (Table 4)[18-21].

Several factors have been identified in the surgical studies of FL-HCC that can predict worse prognosis. More than one tumor, metastasis at presentation, vascular invasion and positive lymph nodes[10,12,20,21] have been identified to be a negative prognostic factors. In this study, vascular invasion is the only significant negative prognostic factor after resection.

Our patients have a low rate of lymph node metastasis (18%) compared to other series which range from 20%-50% (Table 4). This may be related to different tumor biology and the presence of liver cirrhosis in 9% of patients which may delay lymphatic metastases due to inhibition lymphatic outflow from the liver. On our published study on common HCC[17], lymph node metastases were found on only 8 from 175 patients (8%) this may confirm the previous data.

Despite the relatively indolent tumor biology of FL-HCC, it recurs after surgical resection. The site of recurrences includes the liver, regional lymph nodes, peritoneum, and lung[23]. Some authors recommend resection of a recurrent disease due to its indolent course and absence of alternative treatment option[2]. Four patients (18%) underwent a second surgery for a recurrent disease. Three patients underwent hepatic resection while one patient underwent resection of large retro-caval lymph node. This rate is lower than the reports 50%-61% in the other series[18,21]. However, the median survival was 28 mo after the second operation.

The aggressiveness and outcomes of FL-HCC vary significantly between previously published series. Some studies reported that FL-HCC is less aggressive than conventional HCC[8-10,24,25]. Other series reported that survival of FL-HCC was similar with common HCC[12,14] while other pathology and hepatology texts mention that it is associated with favorable prognosis[26-29]. Kakar *et al*[20], 2005 reported that FL-HCC is an aggressive tumor and nearly that half of patients develops lymph node or distant metastasis. In our study, the FL-HCC

has an indolent course than common HCC, better 5-year survival can be reached in absence of vascular invasion and positive safety margins.

In conclusion, FL-HCC has a favorable prognosis than common HCC and should be suspected in young patients with non cirrhotic liver. Aggressive surgical resection should be done for all patients. Repeated hepatectomy or excision of recurrent disease should be considered for these patients as it has a relatively indolent course.

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COMMENTS

Background

Fibrolamellar hepatocellular carcinoma (FL-HCC) has conventionally been considered to be a histologic variant of hepatocellular carcinoma (HCC), with distinct clinicopathologic features. It is a rare primary hepatic malignancy. The etiology of FL-HCC remains unclear. It typically occurs in normal livers without underlying liver fibrosis or cirrhosis. In contrast to HCC which usually found in the presence of cirrhosis or chronic hepatitis. Some suggest that FHN may be a benign precursor lesion to FL-HCC as both diseases share several features: they tend to present in younger patients, and in the setting of normal liver parenchyma. The prognosis of FL-HCC is differ from common HCC.

Research frontiers

Many series have mentioned that FL-HCC is less aggressive than conventional HCC. However, other studies have failed to confirm the observation of a better outcome in FL-HCC. Other studies reported that the survival was similar between common HCC and FL-HCC, and that may be related to the higher resectability rate which improve the survival of patients with FL-HCC. The aim of this study was to evaluate the clinicopathological features and the surgical outcomes of patients with FL-HCC who were referred to their tertiary referral center over a 15-year period.

Innovations and breakthroughs

The epidemiology, surgical management and outcomes for patients with FL-HCC differs from one area of the world to another. The authors have a published data and experience from Western, Eastern and European countries. However, The authors have a little data from Middle East countries, and here they represent their work from a large gastroenterology and transplantation center in Egypt in dealing with patients with FL- HCC over a 15 years period.

Applications

The surgery of FL-HCC is differs from HCC as it occurs in non-cirrhotic liver, so aggressive surgery was adopted for more radical surgery even for a recurrent disease.

Terminology

Clinical staging of the tumor was performed using the American Joint Committee on Cancer (AJCC) staging criteria. The extent of hepatic resection was defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections: Right hepatectomy involves resection of segments V-VIII, whereas left hepatectomy involves resection of segments (II-IV). Extended right hepatectomy involves resection of segments IV-VIII, whereas extended left hepatectomy involves resection of segments (II-IV, V, VIII).

Peer-review

This manuscript seems worth to be reported, because clinicopathological features of FL-HCC are clearly written.

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CASE REPORT

Giant abdominal osteosarcoma causing intestinal obstruction treated with resection and adjuvant chemotherapy

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Abstract

Extraskeletal osteosarcoma (ESOS) is an uncommon tumor that accounts for 1% of all soft tissue sarcomas and 4% of all osteosarcomas. Its presentation may be atypical, while pain has been described as the most common symptom. Radiological findings include a large mass in the soft-tissues with massive calcifications, but no attachment to the adjacent bone or periosteum. We present the case of a 73-year-old gentle man who presented with a palpable, tender abdominal mass and symptoms of bowel obstruction. Computer tomography images revealed a large space-occupying heterogeneous, hyper dense soft tissue mass involving the small intestine. Explorative laparotomy revealed a large mass in the upper mesenteric root of the small intestine, measuring 22 cm × 12 cm × 10 cm in close proximity with the cecum, which was the cause of the bowel obstruction. Pathology confirmed the diagnosis of an ESOS. ESOS is an uncommon malignant soft tissue tumor with poor prognosis and a 5-year survival rate of less than 37%. Regional recurrence and distant metastasis to lungs, regional lymph nodes and liver can occur within the first three years of diagnosis in a high rate (45% and 65% respectively). Wide surgical resection of the mass followed by adjuvant chemotherapy or radiotherapy has been the treatment of choice.

Key words: Osteosarcoma; Sarcoma; Extraskeletal;

Intestinal obstruction; Abdominal mass; Soft tissue

Core tip: We present the case of an elderly man who presented with a palpable abdominal mass and signs of intestinal obstruction. Intra-operative findings revealed a mass in the right abdomen involving the small intestine, which was widely resected. A diagnosis of soft tissue osteosarcoma was confirmed by pathology; further treatment with chemotherapy followed. To our knowledge it has never been reported a case of abdominal obstruction due to soft tissue sarcoma in the literature. Due to its rarity, we strongly believe that the presentation of this case would contribute to further understanding of the biology and management of this tumor.

Diamantis A, Christodoulidis G, Vasdeki D, Karasavvidou F, Margonis E, Tepetes K. Giant abdominal osteosarcoma causing intestinal obstruction treated with resection and adjuvant chemotherapy. *World J Gastrointest Surg* 2017; 9(2): 68-72 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i2/68.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i2.68

INTRODUCTION

Extraskeletal osteosarcoma (ESOS) is a rare mesenchymal malignant soft tissue neoplasm. It constitutes 1%-2% of all soft-tissue sarcomas and 4%-5% of all osteosarcomas, while it is considered to be an aggressive tumor with an overall 5 year mortality rate up to 60%[1-3]. Patients are usually affected in the 6th decade of life and men are affected with a slightly higher frequency than women[4,5]. Their exact pathogenesis is not clear; even though there is some evidence that ESOS can be associated with trauma, radiation and radiotherapy[2,4]. The most common location includes the deep soft tissue of the thigh (47%), the upper extremity (20%) and the peritoneum (17%)[4].

We present a unique case of intestinal obstruction due to a giant abdominal osteosarcoma treated with resection and adjuvant chemotherapy.

CASE REPORT

A 73-year-old male patient presented to the emergency department with a two-week history of abdominal pain, progressive appetite loss, vomiting and constipation, with no reported weight loss. There was no history of pathological fractures. Physical examination revealed a palpable, tender mass in the central abdomen without any signs of acute abdomen or ascites.

Standard blood tests showed a mild increase in inflammatory markers (white blood cells, C-reactive protein), while tumor markers (CEA, CA19-9, AFP, PSA) were within normal limits.

Abdominal radiograph revealed air-fluid levels, as well as a rounded, densely calcified mass mainly occupying the right abdomen. Computed tomography (CT) revealed a large space occupying, heterogeneous soft tissue mass with cystic spaces involving the small intestine, surrounded by multiple massively enlarged lymph nodes (Figure 1).

The patient underwent an exploratory laparotomy. The intraoperative findings included a large mass in the upper mesenteric root of the small intestine, measuring 22 cm × 12 cm × 10 cm, occupying the right abdomen (Figure 2A). The tumor was in close proximity with the cecum, the right kidney and the urinary bladder and there were no signs of invasion to the surrounding organs or distant metastasis. There were also enlarged lymph nodes in proximity to the lesion. The tumor was excised en bloc with a 40 cm part of the ileum and lymph nodes of the mesenteric (Figure 2B).

Microscopic examination, with the use of Haematoxylin and Eosin stain, confirmed the diagnosis of soft tissue osteosarcoma (Figure 3).

In the multidisciplinary team meeting was decided that the oncologists should follow up the patient. The patient was furthermore treated with adjuvant chemotherapy (Adriamycin and Ifosfamide) and three years after surgery he remained disease free.

DISCUSSION

ESOS is an uncommon tumor that accounts for 1% of all soft tissue sarcomas and 4% of all osteosarcomas. It affects most commonly individuals older than 30 years. It has a mesenchymal origin that produces osseous components such as bone, osteoid and chondroid without being attached to the bone or the periosteum. History of trauma is related with soft tissue osteosarcoma as well as former radiotherapy especially in the breast region[1,6,7]. The most common sites where the soft-tissue osteosarcoma may arise are the deep tissue of the thigh, the upper and lower extremity and the retroperitoneum. However, few cases of ESOS have been reported arising in unusual sites, such as the larynx, kidney, esophagus, small intestine, liver, heart, urinary bladder, parotid, and breast[8].

The main symptoms include a slowly enlarging and painful mass while in some cases ulceration of the mass has been reported. To our knowledge a case report of intestinal obstruction due to a giant ESOS has never been reported in literature before.

These tumors are usually large at the time of diagnosis, with an average diameter of 9 cm. The size of the tumor constitutes a significant prognostic factor. Patients with a tumor size > 5 cm have usually a worse outcome despite the radical treatment. However, in some studies, the small size of the tumor did not result in a better prognosis or a long-term survival[7].

According to Allan *et al*[1], the diagnostic criteria of

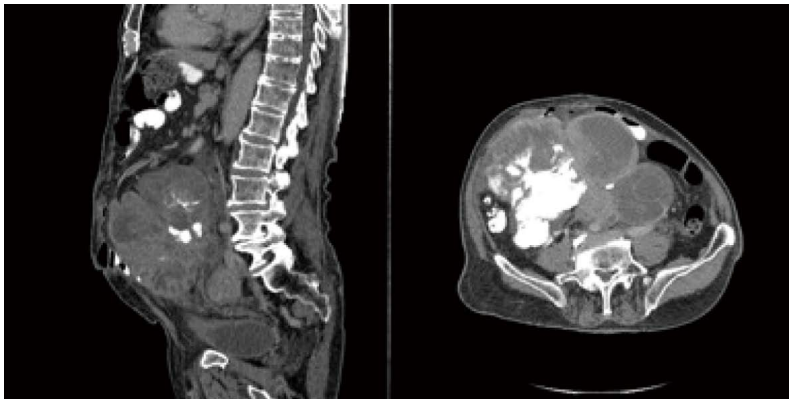

Figure 1 A giant heterogeneous, partially hyper dense soft tissue mass containing cystic spaces located in the right abdomen.

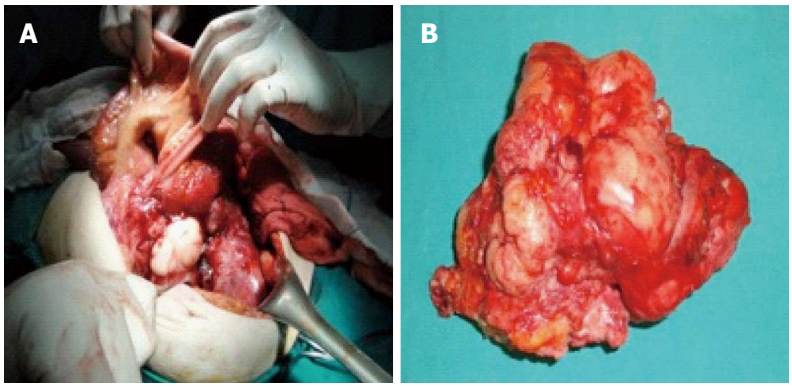

Figure 2 Intra-operative findings: A 22 cm × 12 cm × 10 cm mass occupying the right abdomen in close proximity with the cecum, the right kidney and the urinary bladder (A and B).

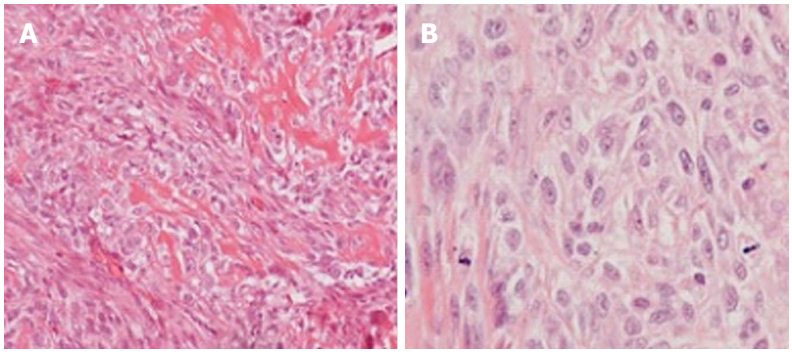

Figure 3 The tumor. A: The tumor consisted of atypical spindle or polyhedral cells that were intimately associated to neoplastic bone deposited in a lacy pattern (haematoxylin and eosin stain, original magnification × 20); B: The tumor cells were mitotically active and frequently demonstrated atypical mitotic figures (haematoxylin and eosin stain, original magnification × 40).

ESOS are the presence of a major morphological pattern of sarcomatous tissue and the production of malignant bone or osteoid, whose origin is not osseous. The microscopic examination reveals atypical spindled and epithelioid mesenchymal cells that produce a lace-like, abnormal osteoid. There is an increase of mitoses with pleomorphic cells, with or without deposition of hyaline cartilage. The tumor osteoid and bone is centrally located with a lucent edge, which is the reverse zonation from that seen in myositis ossificans[1]. Various types of soft-tissue osteosarcoma are reported, each of which follows a different histological pattern. The usual patterns include the chondroblastic, fibroblastic, telangiectatic, and small cell. Although a tumor can include more than 2 histological patterns, in case the major histological pattern represents 75% or more of the tumor, this specific type characterizes the lesion.

The immunohistochemical search usually shows that the neoplastic cells are positive for vimentin, alpha smooth muscle actin and osteonectin, CD99, S100 but are negative for c-kit, CD34, cytokeratin, epithelial membrane antigen, and desmin.

The radiological images of ESOS often present similarities with the images of parosteal osteosarcoma, however the parosteal osteosarcoma has a broad attachment to thickened cortical bone. The radiographs and the CT present ESOS as a large mass in the soft-tissues with massive calcifications, with no attachment to the adjacent bone or periosteum. The MRI images present a nonspecific intermediate signal on T1-weighted imaging and high signal intensity on T2-weighted imaging, which is enhanced by the administration of gadolinium. The presence of a pseudocapsule has also been reported. The tumor presents an increased radiotracer uptake in scintigraphy. Finally, the ESOS is presented as a multilobulated large mass with mineralized components and abnormal uptake on F-18-FDG PET/CT fusion images.

The diagnosis of ESOS should be made using the combination of the atypical clinical manifestations, the radiographical findings and the pathological verification. The differential diagnosis of the soft-tissue osteosarcoma includes various malignant and benign entities of soft-tissue origin[5], such as myositis ossificans, liposarcoma and histiocytoma.

ESOS has a high rate of regional recurrence (45%) and distant metastasis (65%). Common sites of involvement are the lungs (80%), the regional lymph nodes and the liver. Recurrence and/or metastasis usually occur within the first three years of the diagnosis[5].

Treatment of ESOS consists of wide surgical resection of the tumor or amputation combined with adjuvant chemotherapy or radiation. Even though ESOS is considered to be of low responsiveness to radiotherapy and/or to chemotherapy, with a response rate to chemotherapy up to 45%, the survival and recurrence rate may be reduced by postoperative adjuvant chemotherapy, while radiotherapy is still questioned for its results[9-11]. Goldstein-Jackson *et al*[12] recommend that all ESOS should be treated like conventional osteosarcoma with a combination of multiagent chemotherapy and surgery.

Finally, the prognosis is quite poor and a large percentage of the cases succumb to metastatic disease or recurrence within 2-3 years of the diagnosis with an overall 5-year mortality up to 60%.

In conclusion, ESOS is an unusual high-grade malignant soft tissue neoplasm with a poor prognosis and a 5-year survival rate less than 37%. Multiagent chemotherapy following radical surgery seems to be the best choice to treat these patients while radiation may also contribute in some cases. A careful follow-up of patients with soft-tissue osteosarcoma is required because of the high rates of local recurrence and distant metastasis despite the radical treatment.

COMMENTS

Case characteristics

A 73-year-old man presented to the emergency department with a two-week history of abdominal pain, progressive appetite loss, vomiting and constipation, with no reported weight loss.

Clinical diagnosis

Physical examination revealed a palpable, tender mass in the central abdomen without any signs of acute abdomen or ascites.

Differential diagnosis

The diagnosis of extraskeletal osteosarcoma (ESOS) should be made using the combination of the atypical clinical manifestations, the radiographical findings and the pathological verification.

Laboratory diagnosis

Standard blood tests showed a mild increase in inflammatory markers (white blood cells, C-reactive protein), while tumor markers (CEA, CA19-9, AFP, PSA) were within normal limits.

Imaging diagnosis

An abdominal radiograph and a computed tomography of the abdomen were performed with the findings discussed in the text.

Pathological diagnosis

Microscopic examination, with the use of haematoxylin and eosin stain, confirmed the diagnosis of soft tissue osteosarcoma.

Treatment

Wide surgical excision of the lesion and the involved intestine.

Term explanation

ESOS is an uncommon mesenchymal tumor that produces osseous components such as bone, osteoid and chondroid without being attached to the bone or the periosteum and accounts for 1% of all soft tissue sarcomas and 4% of all osteosarcomas.

Experiences and lessons

Multiagent chemotherapy following radical surgery seems to be the best choice to treat these patients while radiation also may contribute in some cases. A careful follow-up of patients with soft-tissue osteosarcoma is required because of the high rates of local recurrence.

Peer-review

This is a well written case report.

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