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Total meso-esophagogastrectomy in surgically resectable Siewert type II-III junctional gastric cancer: Safety and long term oncologic outcome

Luca Maria Siani[1,*]

[1] Department of General Surgery, Unit of General Surgery, Azienda Ospedaliera "Carlo Poma", Mantua, Italy

Abstract

Aim: To analyze our experience confronting meso-esophagogastric resection (transhiatally extended total gastrectomy en-bloc with its inviolate primitive dorsal and ventral mesenterium) to less radical planes of surgery (intra-mesoesophagogastric and muscularis propria planes), in the multimodal management of junctional Siewert II/III resectable gastric cancer. *Methods:* 138 patients with stage I-III/C type II-III Siewert junctional cancers were enrolled. Proximal and distal marginal clearance, closest meso-esophageal resection margin (CRM), volume in mm^3 of meso-esophageal tissue around the tumor, R0 resections rate, number of lymph nodes harvested and five years overall and disease-free survival were recorded for each plane of surgery. *Results:* Mortality and morbidity were 3.6% and 22.4% respectively; operative length was 235 ± 23 min.; mean blood loss was 195 ± 53cc. Mean meso-esophageal tissue volume including tumor was 35,157 mm^3 for meso-esophagogastric resections, 25,397 mm^3 for intra-mesoesophagogastric resections and 20,531 mm^3 for "muscularis propria" resections, all statistically significant ($p < 0.05$). Mean follow-up was 40.3 months. Five years overall survival was 52.2% for meso-esophagogastric resection, 45% for intra-mesoesophagogastric and 35.2% for muscularis propria resections, all statistically significant; the difference was particularly enhanced in stage II-IIIA/B (56.2%, 47.8% and 30% for meso-esophagogastric, intra-meso-esophagogastric and muscularis propria planes respectively). On multivariate analysis, meso-esophagogastric plane of resection, pCR after neo-adjuvant chemo-radiation, R0, CRM > 1mm and pN0 were associated with increased recurrence-free survival. *Conclusions:* When compared to less extensive planes of surgery, transhiatally extended total meso-esophagogastrectomy confers a survival advantage in the intermediate stages of Siewert type II-III junctional gastric cancer, increasing R0 resection rate, decreasing CRM < 1mm and enhancing lymph node harvesting, with consequent impact on loco-regional control and survival; differently, in the extreme stages (I and IIIC N + patients), total meso-esophagogastrectomy is ineffective in altering the standard oncologic outcome. In our experience, total meso-esophagogastrectomy proved to be safe and oncologically effective, especially in stage II-IIIA/B, representing a pivotal part of multimodal management of type II/III EGJ cancers.

Keywords: meso-esophagectomy; meso-gastrectomy; Siewert II/III esophagogastric junctional cancer; safety; long term oncologic outcome

Introduction

At the end of the 19th century, Theodor Kocher firstly realized that any oncologic resection is the excision of the organ en-bloc with its lymphatic drainage; this concept was shortly after substantiated by Miles and Jemison for rectal and colonic cancer respectively [1, 2]. Yet, the real revolution in radical oncologic surgery was performed by Heald, who firstly theorized resection of the mesorectum, the primitive embryological dorsal mesentery of the rectum, reaching excellent local control and improving overall survival [3, 4].

Today, little is written about this new embryological concept in oncologic gastric surgery [5, 6], but en-bloc resection of the primitive esophagogastric dorsal and ventral mesenterium could be the new key factor for optimal local control and survival in the multimodal management of EGJ cancers: the primitive mesenterium

***Corresponding author:** Dr. Luca Maria Siani, Department of General Surgery, Unit of General Surgery, Azienda Ospedaliera "Carlo Poma", Mantua, Via Luigi Pigorini, n.16 – 00162 Rome, Italy. Tel.: 0039 - 348-4731768; Fax 0039-06-45448165; Email: lucamaria.siani@gmail.com

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is de facto the embryological "envelope" where the neuro-lymphovascular structures develop within a double-layered mesenchymal fibrofatty tissue and, consequently, the route for cancerous spread from the primitive neoplasia: its complete "en-bloc" inviolate excision is thus mandatory for extensive local clearance, minimizing residual disease in the surgical field, improving R0 resection rate and possibly impacting on the oncologic outcome.

Aim of the present study is to discuss our experience with total en-bloc meso-esophagogastric excision in treating Siewert type II/III junctional cancers, analyzing its safety and long term oncologic outcome.

Materials and methods

From January 2005 to December 2013, 138 patients with stage I/IIIC Siewert type II/III EGJ cancer (classification according to the latest TNM: Seventh Edition, 2010) were treated with total meso-esophagogastrectomy; all patients were staged by thoraco-abdominal PET-CT scan and subsequently EUS in M0 patients; patients clinically staged T3-4 and/or N positive were considered locally advanced and thus planned for staging laparoscopy and neo-adjuvant chemo-radiation.

Pathology protocol and tissue morphometry

All cancer specimens were left intact, photographed both anterior and posterior aspect for morphometric measurement, and fixed in 10% formalin for subsequent serial slicing with 3-5mm intervals through the tumor segment. Proximal and distal marginal clearance, the closest meso-esophageal resection margin (CRM), volume in mm^3 of meso-esophageal tissue around the tumor and number of lymph nodes harvested were recorded.

Accordingly to the plane of resection achieved, quality of the specimen was categorized as "meso-esophagogastric" (primitive dorsal and ventral meso-esophagus and mesogastrium intact), "intra-mesoesophagogastric" (meso-esophagus and mesogastrium slightly violated with scattered areas of mucolaris propria visible) and "muscularis propria" (meso-esophagus and mesogastrium with wide areas of mucolaris propria exposed).

Operative technique

The abdominal cavity is explored with intra-operative US of the liver, peritoneal washing and wide Kocher maneuver to assess station 13 and 16A2/B1 nodes. The greater omentum is progressively dissected off the transverse colon up to the gastrosplenic ligament which is completely removed; the gastric fundus is entirely mobilized, taking down the gastrophrenic ligament. Lesser sac is entered and fully exposed, with downward traction of the transverse colon and upward traction on the gastro-omental block. Saline is injected at the root of the transverse mesocolon to facilitate bursectomy from the base of the mesocolon up to the superior border of the pancreas: on the left side, node dissection of group 10, 11d and 11p is progressively performed up to the left lateral aspect of the celiac trunk; on the right side, node dissection of station 14v and 6 is carried out (clearance of the primitive posterior mesogastrium).

Duodenal transection is performed by stapling device, preceded by section of the right gastric pedicle; gastro-hepatic ligament is taken down at its liver insertion. Upward traction of the stomach facilitates node dissection in station 12a, 8a, 7 and of right side of celiac trunk (clearance of the posterior portion of the primitive ventral mesogastrium).

Diaphragmatic ventral incision of the hiatus and excision of right and left paracardial nodes in continuity with the iuxta-diaphragmatic meso-esophagus and a 0.5cm cuff of crus is then carried out until the anterior surface of the aorta is reached; development of the avascular plane of the anterolateral surface of the meso-esophagus from the posterior pericardial fat-pad up to the carina, and of the pre-aortic fascia from the hiatus up to the tracheal bifurcation is thus performed. At this point, the meso-esophagus is prepared both anteriorly and posteriorly, and dissection proceeds with rightward traction of the meso-esophageal complex: the left border of the meso-esophagus along the pulmonary ligament and left mediastinal pleura up to the inferior pulmonary vein and left main bronchus are dissected free, with lymphadenectomy of left bronchial and subcarinal nodes; analogous dissection is carried out on the right side.

Esophageal transection is carried out 10cm from the superior border of the tumor with "en-bloc" removal of the specimen. Single stapled end to end esophagojejunal anastomosis according to Roux, and side to side jejunojejunal anastomosis are fashioned. The resected hiatus is repaired with nylon suture. Two drainages are left near the duodenal stump and the esophagojejunal anastomosis.

Data are expressed as a mean ± Standard deviation. The Student's t test was used to analyze quantitative variables, while the chi-squared test was used for the qualitative ones. Survival curves were calculated according to the Kaplan-Mayer method and the statistic differences were confronted by the log-rank test. Multivariate analyses using Cox's proportional hazards model were performed to identify independent prognostic factors in relation to age, sex, pT, pN, CRM, pCR, plane of surgery achieved, neo-adjuvant chemo-radiation, type of junctional tumor, differentiation of tumor, and surgical complication. A $p < 0.05$ was considered statistically significant.

All statistical analysis was performed using dedicated software (Med-Calc®) on Windows Vista®.

Results

Mean age of patients was 66 ± 1.2, with 78 males and 60 females. There were 85 type II and 53 type III Siewert esophagogastric junctional cancer. Stage of disease was in accordance to the latest TNM edition (Seventh Edition, 2010): 5 cases of stage IA (3.7%), 10 cases of stage IB (7.4%), 21 cases of stage II (15.5%), 38 cases of stage IIIA (28.1%), 39 cases of stage IIIB (28.8%) and 25 cases of stage III/C (18.1%).

Mean operative length was 235 ± 23 minutes. Intra-operative blood loss was 195 ± 53 cc. Mortality at 90 days was 3.6% (5 patients): 2 for sepsis due to esophagojejunal failure (1.4%), 2 for pneumonia (1.4%) and 1 for pulmonary embolism (0.7%). Morbidity was 22.4% (31 cases: 8 patients with anastomotic leakage, 12 pancreatic fistulas, 6 patients with pneumonia, 3 pleural effusions, 2 deep venous thromboses of the lower limb). Flatus passage and hospital stay were respectively 3.5 ± 0.9 days and 13.5 ± 2.5 days (Table 1).

Table 1 Safety parameters.

Parameters	
Mortality (90 days)	3.6% (5 patients)
Morbidity (90days)	22.4% (31 patients)
Operative length	235 ± 23 minutes
Blood loss	195 ± 53 cc
Passage of flatus	5.3 ± 1.5 days
Oral intake	8.3 ± 0.5 days
Hospital Stay	11.5 ± 5.9 days

Mean lymph nodes harvested was 39 ± 16. Resection planes were classified as “muscularis propria” in 24.6% (34 cases), “intra-mesoesophagogastric” in 43.4% (60 cases) and “meso-esophagogastric” in 31.8% (44 cases).

Mean meso-esophageal tissue volume including tumor was 35,157 mm^3 for meso-esophagogastric resections, 25,397 mm^3 for intra-mesoesophagogastric resections and 20,531 mm^3 for “muscularis propria” resections, all statistically significant ($p < 0.05$). Pathological Complete Response (pCR) after neo-adjuvant chemo-radiation (108 patients) was recorded in 14.8% of cases (16 patients).

Pathologically R0 resection (absence of macro-microscopic residual disease) in the specimen at proximal, distal and radial margins was achieved in 95.7% of meso-esophagogastric specimens, in 80.9% of intra-mesoesophagogastric resections and in 64.2% of muscularis propria resections, all statistically significant ($p < 0.05$). Circumferential resection margin (CRM) < 1mm was present in 12.7% of meso-esophagogastric, 31.7% of intra-mesoesophagogastric and 46.4% of muscularis propria resections, being statistically significant; CRM < 1mm was present in all loco-regional recurrence. Mean esophageal length was 9.5 ± 0.7 cm and the proximal margins of the specimens were all free of microscopic disease (Table 2).

Mean follow-up was 40.3 months. Five years overall survival was 52.2% for meso-esophagogastric resection, 45% for intra-mesoesophagogastric and 35.2% for muscularis propria resections, being all statistically significant (Figure 1); the difference was clearly enhanced in stage II-IIIA/B (56.2%, 47.8% and 30% respectively; $p < 0.05$; Figure 2).

Table 2 Oncologic outcome and morphometric parameters.

Parameters	*Mesoresection*	*Intra-mesoresection*	*Muscolaris-propria*	*p-value*
Mean follow-up	39.7 months	39.9 months	41.3 months	> 0.05
Lymph nodes harvested	48 ± 18	40 ± 16	36 ± 13	< 0.05
Mean meso-esophageal tissue volume including tumor (mm3)	35,157	25,397	20,531	< 0.05
Mean esophageal length (cm)	10.1	9.9	10.7	> 0.05
R0 resection	95.7%	80.9%	64.2%	< 0.05
CRM <1mm	12.7%	31.7%	46.4%	< 0.05
5-years overall survival	52.2%	45%	35.2%	< 0.05
5-years disease-free survival	43.1%	33.3%	20.6%	< 0.05

Differently, survival of stage IIIC N3 nodes positive patients was 12.5%, 10% and 0% respectively for meso-esophagogastric, intra-mesoesophagogastric and muscularis propria surgery, not reaching statistical difference for plane of resection achieved ($p = 0.935$; Figure 3). No statistical difference in survival was also noted for stage I, being 100%, 100% and 85.7% for previous stated planes, respectively ($p = 0.993$).

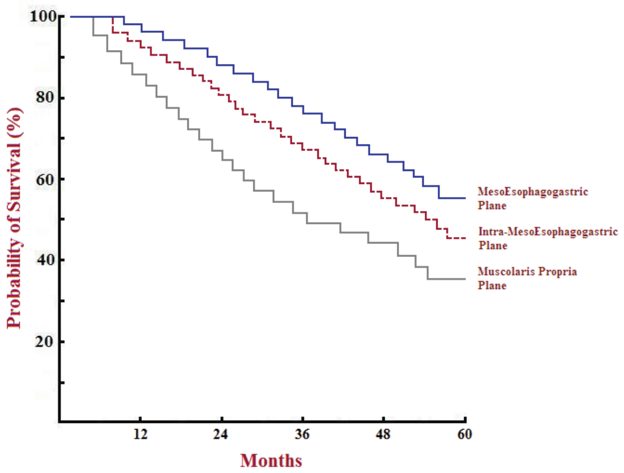

Figure 1 Not stratified 5-years survival curves. Survival was 52.2% for meso-esophagogastric (in blue), 45% for intra-mesoesophagogastric (in dotted red) and 35.2% for muscularis propria (in gray) resections, all statistically significant.

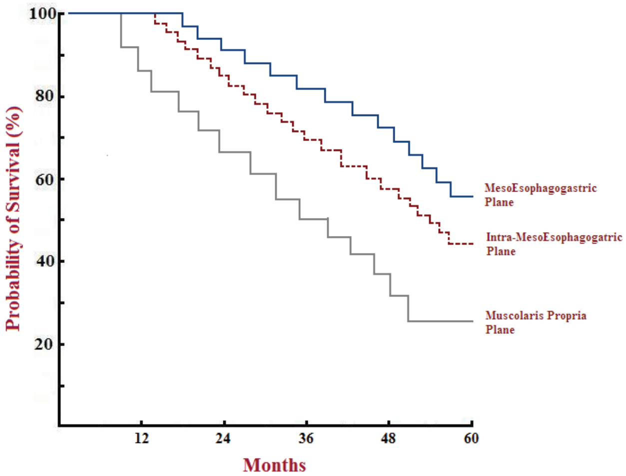

Figure 2 Stratified stage II-IIIA/B 5-years survival curves. Survival was 56.2% for meso-esophagogastric (in blue), 47.8% for intra-mesoesophagogastric (in dotted red) and 30% for muscularis propria (in gray) resections, all statistically significant.

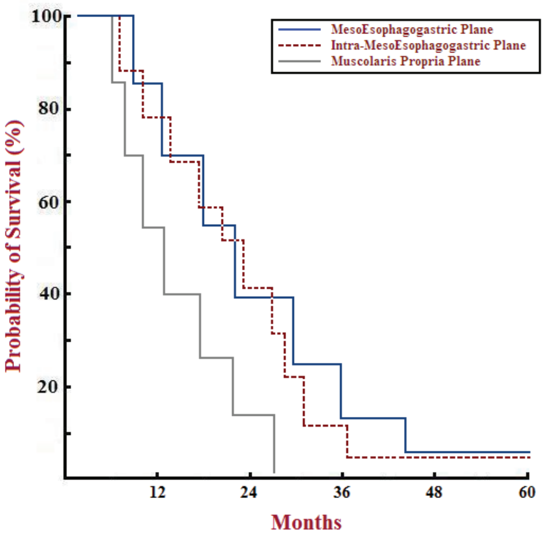

Figure 3 Stratified stage IIIC 5-years survival curves. Survival was 12.5% for meso-esophagogastric (in blue), 10% for intra-mesoesophagogastric (in dotted red) and 0% for muscularis propria (in gray) resections, not statistically significant (p = 0.993).

Disease-free survival at 5-years was 43.1% for meso-esophagogastric resection, 33.3% for intra-mesoesophagogastric and 20.6% for muscularis propria resections, being all statistically significant (Table 2). Multivariable Cox regression analysis revealed pCR, R0 resection, pN0, CRM > 1mm and surgical meso-esophagogastric plane of surgery to be independent predictor of recurrence-free survival, as shown in Table 3.

Table 3 Results of multivariate Cox regression analysis for recurrence-free survival.

Parameters	*Hazard-ratio*	*95% Confidence interval*	*p-value*
pCR	0.371	0.157 – 0.593	< 0.05
R0 resection	0.357	0.197 – 0.715	< 0.05
pN0	0.395	0.215 – 0.759	< 0.05
CRM >1mm	0.439	0.175 – 0.593	< 0.05
Meso-esophagogastric resection	0.457	0.195 – 0.739	< 0.05

Discussion

Complete excision of the primitive mesenterium along the anatomo-embryological surgical planes is today considered crucial for rectal and colonic cancers, according to TME [3, 4] and Complete Mesocolic Excision [8-10] principles respectively. In the opinion of the author, the same concepts should be extended to the surgical management of Siewert type II-III gastric cancer, in the view of cancerous spread along the primitive dorsal and ventral mesenteria of the embryological fore-gut.

In the 8mm embryo, the esophagus develops a dorsal mesentery along with its intra-thoracic course, and a brief ventral mesentery in its terminal part. On the other hand, the stomach is connected to the posterior primitive abdominal wall by its dorsal mesenterium, inside which the future spleen and distal pancreas develop; the ventral mesenterium, in which the anterior pancreas will rotate posteriorly to fuse with the dorsal pancreas and the primitive liver bud will expand in the septum trasversum, stretches to the anterior abdominal wall [11].

90^0 clockwise rotation of the stomach determines the primitive dorsal and ventral mesenteric folding, giving rise to the future lesser (posterior part of the ventral mesentery) and grater omentum, gastrohepatic ligament, hepatoduodenal ligament, hepatopancreatic folds, splenopancreatic folds, gastrophrenic ligament and gastrosplenic ligament (dorsal mesentery) [12, 13]. The esophagogastric junction grows within a mesodermal envelope which forms a "compartment" that Matsubara defines as distal mesoesophagus [5], analogous to the mesorectum, but different in the lack of a mesothelial fascia propria, hence, Botha defines its borders anteriorly with the post-pericardial fat-pad, posteriorly with the pre-arotic fascia, and states its excision as total adventitial resection of the cardia or TARC [14].

The en-bloc resection of all components of both dorsal and ventral primitive mesenteria along the anatomo-embryological avascular cleavage planes is therefore fundamental for a true radical R0 resection, as lymphovascular and neuro-perineural cancerous spread takes place essentially along these structures.

According to several trials regarding the most appropriate surgical approach for Siewert type II and III cancers, transhiatally extended excision (THE) can be considered a valid and oncologically adequate resection, while trans-thoracic approach appears to confer a survival advantage in type I with 1 to 8 lymph nodes involved [16-17]. The author believes that THE approach is absolutely adequate to achieve a complete total meso-esophagogastrectomy in Siewert type II/III junctional cancers.

The first surgical step is based on a "complete total meso-gastrectomy", thus on removal of the primitive dorsal and ventral gastric mesentery. The primitive dorsal mesogastrium consists of an anterior part between the greater curvature and the primitive splenic bud which gives rise to the greater omentum distally, the omental bursa posteriorly and the gastrosplenic ligament cranially. The posterior part stretches between the splenic bud and the posterior abdominal wall which gives rise to the lienorenal ligament caudally and the gastrophrenic ligament cranially. The primitive ventral mesogastrium is involved in meso-gastrectomy only in its posterior component between the lesser curvature and the liver bud, which gives rise to the geastrohepatic ligament and hepatoduodenal ligament.

Thus, greater omentectomy (st. 4sb, 4sd and 6), bursectomy, removal of the gastrosplenic ligament (st. 4sa) and lymphadenectomy along the splenic artery (st. 11p and 11d), splenic hilum (st. 10) and left portion of the celiac trunk removes the entire dorsal mesogastrium. Lesser omentectomy (st. 3 and 5), lymphadenectomy of the proper and common hepatic artery (st. 12a and 8a), left gastric artery (st. 7) and right portion of the celiac trunk excise the posterior part of the ventral mesogastrium; lympho vascular and neuro-perineural tissues around the common bile duct (st. 12b), portal vein (st. 12p) and posterior aspect of the common hepatic artery (st. 8p) are not components of the primitive ventral mesogastrium, but elements of the primitive dorsal meso-duodenum and thus not included in a formal meso-gastrectomy [18].

Usually, station 14v, even if not developing into the primitive mesogastrium, is dissected free, as the right gastroepiploic veins drains into the common trunk of Henle (branching off the superior mesenteric vein), being potentially involved in metastatic process if subpyloric nodes are pathologic [19].

Left and right paracardial nodes appears between 12th and 20th week in the mesenchymal region between the esophagus and the gastric fundus, and part of the left paracardial nodes appear in front of the aorta and in continuity with those from the left renal hilum (st. 16A2lat): these lymph nodes should be excised because potentially involved in up to 18% of cases [20-22].

In 6- to 7-week embryo, caudally to the diaphragm, the esophagus is wrapped in a mesenchymal tissue forming its anterior and posterior mesentery [18] and thus its definitive meso-esophagus [13, 14]. This "distal meso-esophagus"[5] has its boundaries in the tracheal carina on the top, the diaphragm on the bottom, the pre-aortic plane posteriorly, the pericardial fat-pad anteriorly, and the pulmonary ligaments laterally; all the fibrofatty tissues within this compartment must be completely removed "en-bloc" with the distal esophagus for a length of 8-10cm: dissection begins with detachment of the anterolateral surface of the meso-esophagus from the posterior pericardial fat-pad, up to the carina; then, the pre-aortic fascia is separated from the diaphragmatic hiatus up to the level of tracheal bifurcation; left dissection along the pulmonary ligament and left mediastinal pleura proceeds up to the inferior pulmonary vein and left main bronchus, removing all the left bronchial and subcarinal nodes; same dissection is carried out on the right side [23].

Translating the same concepts used for TME [7], quality of the specimen is thus classified according to the amount of meso-esophageal tissue wrapping the distal esophagus and the esophagogastric junction: specimens with very little or no attached meso-esophageal tissue and large areas of visible muscularis propria are defined as ''Muscularis propria resections'', those with a moderate amount of meso-esophageal tissue and intermittent small areas of visible muscularis propria as ''Intra-mesoesophagogastric resections'', and those with meso-esophageal tissue covering totally or near-totally the muscular tube in a continuous fashion as "Meso-esophagogastric resections" [24].

The experience of the author shows that meso-esophagogastrectomy is safe, without significant increase in morbi-mortality, and oncologically effective when compared to historical standard transhiatally extended gastrectomy, improving loco-regional control. Yet, it remains a complex surgical procedure, requiring meticulous dissection along anatomo-embryological avascular surgical planes, especially in bursectomy, which is the main source of morbidity [25, 26].

Pathologically R0 resection was achieved in 95.7% of meso-esophagogastric specimens, in 80.9% of intra-mesoesophagogastric resections and in 64.2% of muscularis propria resections, all statistically significant ($p < 0.05$). Circumferential resection margin (CRM) < 1mm was very common in muscularis-prorpia resection

(46.4%), rare in meso-esophagogastric specimens (12.7%), and impacted dramatically on loco-regional recurrence. Multivariate Cox regression analysis showed that, along with pCR, R0 resection, CRM > 1mm and pN0, the plane of surgery obtaining an inviolate meso-esophagogastric specimen is independently associated with favorable oncologic outcome, increasing the recurrence-free survival.

The impact on survival is definitively evident in stage II, IIIA and IIIB, with 5-years overall survival of 56.2%, 47.8% and 30% for ''meso-esophagogastric'', ''intra-mesoesophagogastric'' and "muscularis propria" resections respectively, while overlaps the standard oncologic outcome in stage IIIC (especially N3 node positive) with only 12.5% of patients alive at 5-years for meso-esophagogastric resections and 0% for "muscularis propria" plane (not statistically significant): this could be justified by the fact that IIIC is a stage where pathologic disease has gone far beyond the original primitive mesenterial diffusion and consequently not further controllable with more extensive surgery; similarly, no survival benefit was observed in stage I node negative patients, for whom a more extended surgery over-treats a merely local disease without mesenterial spread, with excellent results independently from the plane of surgery achieved.

In our experience, the specimen obtained with meso-esophagogastric resection results in significantly increased meso-esophageal tissue volume, more R0 resection, higher rate of CRM > 1mm and more lymph node retrieved when compared to historical and less radical "standard" resections reported both in literature and in our initial experience (Table 2): our performance of 68.1% of "non-mesoesophagogastric" (intra-mesoesophagogastric and muscularis propria) resections was mainly concentrated when we started with the procedure and was virtually absent in the last 2 years.

Yet, given the study design, error and bias are likely: the relative small sample size increase the risk of type II error, while the retrospective, non-randomized setting make plausible selection bias, i.e. that patients with a "per se" better prognosis had a higher chance of being treated with a meso-esophagogastric plane; thus, prospective randomized trials are needed to recommend total meso-esophagogastrectomy as the definitive surgical treatment in resectable type II-III EGJ cancer.

Conclusion

Despite these statistical limits, it's anyhow opinion of the author that oncologic surgery should be based on anatomo-embryological concepts of loco-regional cancerous spread and, consequently, complete resection of the primitive inviolate "mesenteria" containing the organ and all the vasculo-lymphatic and neuro-perineural structures as an "intact envelope" becomes cardinal in obtaining a really extensive, radical R0 resection. Thus, meso-esophagogastrectomy can be pursued exactly the same way modern surgeons perform TME in rectal cancer: meso-resectional surgery has the potential to become the novel key factor in the multimodal management of EGJ Siewert type II/III cancers, determining a significant impact on loco-regional control in tumors without spread beyond the primitive mesostructures.

Conflict of interest

The author declares no conflict of interest or any financial support.

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