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AN OVERVIEW OF THE CURRENT STATUS OF LAPAROSCOPIC MANAGEMENT OF OESOPHAGO-GASTRIC JUNCTION TUMORS

Oncology

Dr. Subbiah Shanmugham Professor & HOD, MCh., Department of Surgical Oncology, Government Royapettah Hospital, Kilpauk Medical College and Hospital, Chennai. Tamil Nadu, India.

Dr. A. Jagadish Singh.* Department of Surgical Oncology, Government Royapettah Hospital, Kilpauk Medical College and Hospital, Chennai. Tamil Nadu, India. *Correspobding Author

ABSTRACT

OBJECTIVE: To assess the outcome of surgical therapy based on a topographic/anatomical classification of esophagogastric junction tumours including squamous cell carcinoma and adeonocarcinoma after neoadjuvant chemo-radiotherapy.

BACKGROUND: This study analyses the clinicopathological characteristics , surgical methods and response after neoadjuvant chemo-radiotherapy in oesophagogastric junction tumours.

METHODS: The study reviewed the data of the major histological types of tumours involving oesophago-gastric junction in Tertiary cancer care centre from 2016-2018. Surgical patients were defined and classified according to AJCC 8TH manual . The data of 37 total patients diagnosed as involving oesophago-gastric junction were analysed. The collected data was recorded with emphasis on clinical features,pathological, endoscopic/imaging findings before neoadjuvant therapy. The study compared and analyzed the clinicopathological characteristics and the median survival rates of the tumor involving oesophago-gastric junction. Response after neoadjuvant chemo-radiotherapy was classified according to RECIST criteria. Among the surgery modes involving laparoscopic versus open methods the groups were subcategorised based on response assessement, nodal harvest and complications

RESULTS: Among the 25 patients 23 patients were selected for surgery due to presence of residual disease by endoscopy/biopsy and imaging,17 were adenocarcinoma and 6 were squamous cell carcinoma. There were 4 patients with adenocarcinoma of the distal esophagus (Type I); 5 patients with true carcinoma of cardia (Type II); and 8 patients with subcardial carcinoma (Type III). Obvious differences were found in the clinicopathological characteristics of the three types of adenocarcinoma and squamous cell carcinomas, but no significant difference of the 1-year survival rates was found among the patients with curative resection adenocarcinoma and squamous cell carcinoma. Laparoscopic group of patients (total seven) experienced less complications in terms of lung complications and early start of oral feeds.

CONCLUSION: On the data, the distribution of the three locations of adenocarcinoma was found to be different from that reported in Western countries(Type III being commonthan Type I). The squamous cell carcinoma prevalence was 26% as per our data. All oesophago-gastric junction tumours who had undergone curative resection were found to have similar 1-year survival rates. Laparoscopic surgery definitely improves post-operatively morbidity and less hospital stay with similar 1-year survival rate on comparison to open surgery methods.

KEYWORDS

SCC - Squamous Cell Carcinoma, ADC – Adenocarcinoma, OGJ – Oesophago-Gastric Junction Tumors, MIS – Minimally Invasive Surgery

INTRODUCTION

Worldwide oesophago-gastric junction tumours received a great importance not only because of its increased incidence in specific histological type but also because its anatomy continues to be a great challenge to the treating surgeons. Lying in the junction between two anatomical chambers of the body, chest and abdominal cavity its complete resection holds the most important determinant in the patients survival. Hence comes the concept of neoadjuvant therapy to make the tumour amendable to R0 resection by surgery. When numerous trials like Cancer and Leukemia Group B(CALGB) 9781 study, CROSS trial and MAGIC trial suggested the preoperative therapy either chemotherapy or chemo-radiotherapy are a essential component in treatment of oesophago-gastric junction tumors now the trend is to operate upon minimally invasive methods at the hiatus balancing the R0 resection on one hand with less morbidity associated on the another. This paper attempts how far are we balancing as we are walking on the tight rope between the highest mountains. Adding to the problem is the management of the squamous cell carcinoma at the oesophago-gastric junction which still are accountable to approximately 50% of the tumours at OG junction in a country like India. As most of the SCC OG junction tumours are treated by radical chemo-radiotherapy, the presence of residue should be treated by surgery with higher morbidity. Recent literature lists surgery even in complete response of SCC at OG junction after chemo-radiotherapy as SCC at this site has worser prognosis than ADC of OG junction.

Barrett oesophagus has been singled out as the most important risk factor for OAC. Chronic gastro-oesophageal reflux disease predisposes to Barrett oesophagus. Adenocarcinomas of the OGJ share many characteristics with those of the distal oesophagus in countries where distal oesophageal adenocarcinomas are more common. However there appear to be geographical variations whereby in some Asian countries OGJ cancers have more similarities with proximal cardiac cancers than distal oesophageal cancers.

MATERIALS AND METHODS

All patients of OG junction who underwent surgery either by open or minimally invasive routes after pre-op therapy were analysed from 2014-2018. Only the patients who were found to have OG junction involved at final resected specimen by histology were included. (See Flow Chart 1) Surgically fit patients who underwent definitive surgery were included irrespective of histology. Preoperative workup included oesophago-gastro-duodenoscopy, CECT/MRI and diagnostic laparoscopy in almost all cases before starting preoperative therapy. Patients with poor ECOG performance score and undergoing palliative procedures with distant metastases were excluded from the study. Preoperatively patients were classified as Siewerts types I/II/III were correlated with final histopathology report as most the tumours were totally occlusive and not allowing endoscopy to pass beyond the distal limit of the growth, rendering us to rely on radiological imaging to define the epicenter of the tumour. For SCC the tumour should involved OG junction 5 cm above and below. AJCC 8th Edition has been used to re-stage and analyse the tumours. The changes have been the usage of epicenter instead of upper limit of tumour (figure). At surgery the tumour confirmation involving the OGJ was done and decision to remove the entire oesophagus was taken is more than 3 cm above the junction is involved and the decision to remove the entire stomach with D2 lymphadenectomy was taken if involving more than 2 cm below the junction.

The type of surgery used to treat the OGJ tumours with respect to histology and morbidity patterns were analysed using univariate analysis and if significant multivariant analysis using Log-Rank and Chi-Square test were used for comparison.

RESULTS

Total number of patients enrolled were 25, surgery was done in 23. Male and female ratio was 15:8. Adenocarcinoma in 17 and squamous cell carcinoma in 6 patients. SIEWERTS Type I in 4,SIEWERT Type II in 5 and SIEWERTS Type III in 8. Pre-op chemotherapy was given in 15/23 (65%) , Chemo-radiotherapy to 8/23 (35%). Transthoracic

oesophagectomy (2-field lymphadenectomy) 8/23(34.7%), Trans-hiatal oesophagectomy (mediastinal lymphadenectomy) 5/23(21.7%), total gastrectomy D2-lymphadenectomy with hiatal resection of distal oesophagus 10/23 (43.5%). Minimally invasive surgery was done in 7/23 (30.4%) patients.

Adenocarcinoma was 74%, Squamous cell carcinoma was 26%. SIEWERTS Type-III was common in our study. All patients had a ycT+ tumor with majority having ycN+disease. A radical resection (R0) was achieved in 95%. All oesophago-gastric junction tumours who had undergone curative resection were found to have similar 1-year survival rates. There is no survival difference between laparoscopic and open methods, differences in only being morbidity.

DISCUSSION

Molecular genetics of OGJ tumours:Her 2 over expression is reported in approximately 15- 25% of gastric/gastro-oesophageal junction (OGJ) adenocarcinomas in Western countries.Over expression of EGFR -1 is found in 1/3 to 2/3 of oesophageal adenocarcinoma and squamous cell carcinoma (SCC).VEGF is over expressed in 30 – 60% of oesophageal adenocarcinoma. Over expression is associated with higher tumour stage and poorer survival. Other include cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), heat shock protein 90 (Hsp90), and PI3K/Akt, matrix metalloproteinases, insulinlike growth factor receptor (IGFR) and regulators of the cell cycle e.g. cyclins and nuclear factor κβ.

Most data exists for oesophageal adenocarcinoma and has found that expression or identification of the following markers to predict survival - Epidermal growth factor receptors (1 and 2 - Her2/neu): Transforming growth factor (TGF α and β1); P53, Ki-67, Cyclin dependent kinase inhibitor 1 (p21); B-cell lymphoma 2 (bcl-2); Cyclooxygenase-2 (COX-2); Nuclear factor-κB (NF-κB); Vascular endothelial growth factor (VEGF); Tissue inhibitor of metalloproteinase (TIMP) and microsatellite instability (MSI). At present, routine testing for all or any of these markers is not warranted.

Disparity of preoperative staging versus postoperative HPE:

Endoscopy (Highest level)	Mucosal colour transition with Z-line identification
Radiology	Diaphragm crura attachment
Surgical landmark (Lowest level)	Angle of transition from oesophagus to cardia

Type I tumors clearly constitute a distinct entity that requires a specific therapeutic approach as distal esophageal cancer. Most if not all of these tumors arise from areas of intestinal metaplasia in the distal esophagus (Barrett esophagus, which develops as a consequence of chronic gastroesophageal reflux). (TABLE 2) Because of effective endoscopic surveillance programs, such tumors are increasingly diagnosed at an early stage and may be amenable to limited surgical or endoscopic treatment. Similarly, type III tumors clearly represent a special form of proximal gastric cancer and require treatment according to the well-established gastric cancer guidelines. The relation of Type II tumors to distal esophageal or proximal gastric cancer, however, remains controversial.

Anatomical constraints of oesophago-gastric hiatus in diaphragm: The thoracic case varies in its anteroposterior and transverse diameters in obese and non obese patients and hence in patients with SCC and ADC. Due to the poor built and malnourishment in particularly patients with SCC early thoracic aorta infiltration and mediastinal structures can be anticipated.

FIGURE 1

Histology determines prognosis in OGJ tumours:

Both adenocarcinoma and squamous cell carcinoma at the OG junction behave more aggressively with early potential for distant metastasis. Both tumour staging and patients performance determined the prognosis after surgery then the histology per se. The more mortality and morbidity associated with SCC at OGJ may be due to late effects of radiotherapy after surgery. Surgical complications after radiotherapy are more oftenly seen in SCC than ADC due to the perceived assumptions of achieving pCR in SCC. This is underlined by the fact that most common genetic abnormality in both SCC and ADC at OGJ is TP53 mutations.

TABLE 1

Effect of preoperative chemotherapy on patient and tumour: The cause of death from carcinoma esophagus is mainly due to distant Metastasis. Chemotherapy decreases locoregional Recurrences and also dowwnstages tumors and improve R0 Resection rates. There is no convincing role for adjuvant chemotherapy.MRC trial at United Kingdom was done for adenocarcinomas of the distal esophagus and proximal stomach in which preoperative neo adjuvant 5-fluorouracil (5-FU) and cisplatin chemotherapy showed a survival advantage over surgery alone. MAGIC trial at UK done for distal esophageal and proximal gastric adenocarcinomas where they used epirubicin in combination with cisplatin and 5FU .They also demonstrated a survival advantage for the induction chemotherapy.

CHEMOTHERAPY REGIMENS

- Carboplatin and paclitaxel (which may be combined with radiation)
- Cisplatin and 5-fluorouracil (5-FU) (often combined with radiation)
- CF: epirubicin , cisplatin, and 5-FU (especially for gastroesophageal junction tumors)
- DCF: docetaxel, cisplatin, and 5-FU
- Cisplatin with capecitabine
- Oxaliplatin and either 5-FU or capecitabine
- Irinotecan

Effect of preoperative radiotherapy on patient and tumour: Preoperative chemoradiotherapy using cisplatin and 5-FU with radiotherapy beneficial in both adenocarcinoma and squamous cell carcinoma. Addition of radiation may improve local response of the tumor (greater opportunity for R0 resection). Most of the radiation oncologists prefer giving pre-operative chemoradiation than adjuvant radiotherapy as it is interferes with newly created enteric conduit and anastomosis at the oesophageal hiatus. Further the dose of radiotherapy given pre-operatively is higher than the post operative dose, the tumour shrinkage is better and R0 resection can be achieved. In SCC at OGJ radical chemoradiation given compounds the morbidity of surgery particularly MIS. Hence comes the argument of dose with appropriate tumours shrinkage with less morbidity, as even the complete pCR patients of SCC at OGJ need definitive surgery.

CROSS Trial done at Dutch evaluated Chemoradiation and surgery v/s Surgery alone. Most convincing benefit for survival in SCC.

Minimally invasive surgery- balancing the rope: Our study though low volume has broughtout the insight in to the management of OG junction tumours encompassing both SCC and ADC. Numerous studies have evaluated the management of ADC of OGJ into Siewerts classification and manage it correspondingly. In a country like India were SCC at OGJ occurring in low socio economic group continuous to occupy a major proportion, its management carries a significant impact on both patients survival and overall cancer burden. Although recent guidelines envisage the use of chemo-radiotherapy for both ADC and SCC at OGJ, we used chemo-radiotherapy preferably for SCC and pre-op chemotherapy for ADC assuming to achieve complete pCR for SCC and doing surgery for ADC for residual disease. The reason being the most of the patients with SCC at OGJ are surgically unfit than the patients with ADC at OGJ. According to LNT theory of radio biology tumour shrinkage starts at 40 Gy peaks at around 50 to 52 Gy. But our patients tolerate around 45 Gy ± 4 Gy. Also the ill effects of radiotherapy starts increasing after 45 Gy, doing surgery compounds the complications. Minimally invasive surgery aggravates the complications of radiotherapy more than the open surgery.

LIMITATIONS OF OUR STUDY

- Our study has very low volume of patients involving OGJ and is retrospective in nature.
- Although the complications are more in open surgeries done MIS, the radiation compounded the beneficial effects of MIS. Hence implying that patients with SCC at OGJ can be treated by pre operative chemo-radiotherapy (uptill the unto ward effects of both surgery and RT starts compounding till 45Gy), as even complete remission after radical RT need to be followed by surgery. The ultimate aim of pre-opertive therapy is to make tumour amendable for R0 resection with less effects of late RT toxicity.

CONCLUSION

Although adenocarcinoma occupied a major proportion of OGJ the prognosis of SCC continues to be grim because of additive effects of radiotherapy and MIS.

All oesophago-gastric junction tumours who had undergone curative resection were found to have similar 1-year survival rates. There is no survival difference between laparoscopic and open methods, differences in only being morbidity. Also the concept of less radical pre-operative chemoradiation can be applied to the SCC at OGJ so that surgery can be done with less 30 day morbidity.

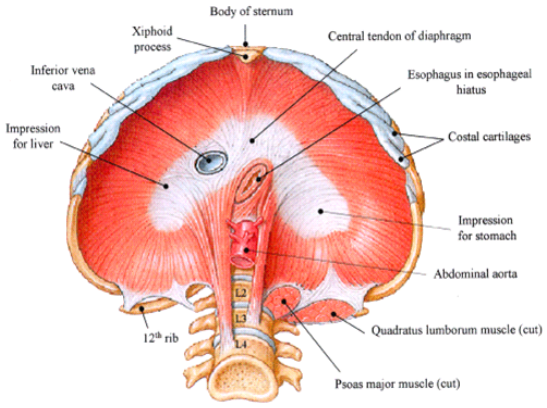
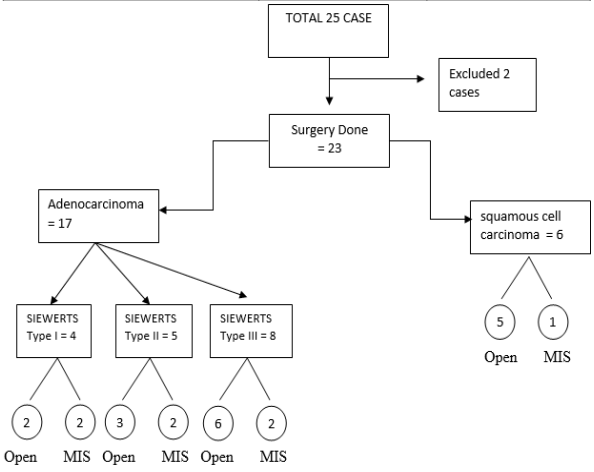


TABLE 1: Morbidity patterns of open thoraco-laparotomy surgeries:

	Type-I	Type-II	Type-III	SCC	MIS	P-value	HR
Pulmonary complications	1:0	1:0	2:0	1:0		0.01	
Pneumonia	1:0		1:0				
Pleural effusion requiring intervention		1:0	1:0				
Therapeutic bronchoscopy				1:0			
Pulmonary embolism	Nil	Nil	Nil	Nil	Nil	Nil	
Reintubation/respiratory failure							
Tracheostomy	Nil	Nil	Nil	Nil	Nil	Nil	
RLN injury	1	Nil	1	Nil			
Anastomotic leak	Nil	Nil	Nil	Nil			
Median length of stay (days)					10±2 days		
30-day mortality	Nil	Nil	Nil	Nil	Nil	Nil	
1 year mortality							

TABLE 2

Type - I	Type - II	Type - III
Adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett esophagus) and may infiltrate the esophagogastric junction from above;	True carcinoma of the cardia arising immediately at the esophagogastric junction;	Subcardial gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below.



FLOW CHART 1

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