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FACTORS INFLUENCING SURVIVAL OUTCOME IN CARCINOMA ESOPHAGUS - PATIENTS TREATED WITH NEOADJUVANT CHEMORADIATION FOLLOWED BY ESOPHAGECTOMY - 10 YEAR ANALYSIS

Oncology

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ABSTRACT

To assess tumor response to neoadjuvant chemoradiotherapy in oesophageal carcinoma and to determine whether pathological assessment of tumor regression correlates with overall survival. Total of 65 patients with non metastatic, lower & mid thoracic oesophageal cancer and OG junction cancers (T2, T3/ N0, N1) that were treated with neoadjuvant chemoradiotherapy followed by esophagectomy were included in this study. Patients characteristics age, gender, histological type, grade, clinical response, method of surgery ,margin status, pathological response of primary tumor and lymph nodes were analyzed . Survival outcome were analysed using SPSS version 17.0.Total number of patients were 65 with mean age of 50.8±10 years. Median follow-up period was 40 months. 21 (35%) patients were less than 50 years. 41(63%) patients were male. Lower and OG junction tumours were 46(70%) patients. Squamous cell carcinoma-50(77%), low grade 38(58%). Complete clinical response noted in 21(32%) patients. Pathological complete response noted in 18(27.7%) patients. Overall survival were 96%,75%,71% & 32% for 1 ,2 ,3 and 5 years respectively. Univariate analysis showed that younger age, low grade tumour and no pathological residue in resected specimen were correlating with good survival outcome. Cox regression multivariate analysis showed that post treatment pathologic stage was better predictor of survival outcome (HR-37.6 ; 95%C.I 4.22-334.8%) p<0.001 even though age (HR – 3.35; 95%C.I 1.59-7.00)p=0.001 and grade (HR-1.87; 95%CI 0.96-3.65)p=0.065 had statistically significant p value. Conclusion:Most of the patients had residual cancer post neoadjuvant chemoradiotherapy hence esophagectomy is warranted to improve overall survival. Survival outcome depends on pathological residual status.

KEYWORDS

Esophagectomy ,Neoadjuvant chemoradiation,Response assessment ,Overall survival.

Introduction

Oesophageal cancer is the 6th most common cause of cancer deaths worldwide and is more common in men.[1] It is an endemic in many parts of the world, particularly in the developing nations, where it is the 4th most common cause of cancer deaths.[1] Oesophageal cancers are histologically classified as Squamous cell carcinoma (SCC) or adenocarcinoma. Both are more common in men. SCC is more common in Asia, less common in western countries. SCC is more sensitive to chemotherapy & radiotherapy than adenocarcinoma.

For patients with locally advanced cancer, lymph node involvement has been shown to be a strong independent predictor of poor survival with surgery alone, hence considered for preoperative chemoradiation followed by surgery. Combined modality therapy has been employed for the treatment of oesophageal and OG junction cancers because of poor overall survival rates in patients who have been treated with resection alone[2]. Preoperative chemoradiation plus surgery signific antly reduced 3-year mortality and loco regional recurrence, and preoperative chemoradiation therapy also down staged the tumor when compared with surgery alone[3].

Our study analyses factors influencing overall survival in patients with oesophageal and OG junction cancer who were treated with preoperative chemoradiation plus esophagectomy.

Materials and methods

Patients that were non metastatic & mid and lower thoracic oesophageal cancer and OG junction cancers (bulky tumours T2,T3 and regional lymph node enlargement (N1)on imaging) were included in this study. All patients were treated with 50Gy EBRT and 2 cycles of Cisplatin& 5-flurouracil chemotherapy. Those who were not tolerating either chemotherapy or RT & progressive disease were excluded from the study. Study period was from 2008 to 2016. Median follow up period-40 months(average 5-86 months).

Patients were evaluated with upper GI endoscopy, barium swallow if the endoscopy not passed beyond distal stricture , Contrast enhanced CT chest and abdomen. Patients were re evaluated with endoscopy and CECT chest and abdomen after 4 weeks of completion of preoperative chemo radiation. Endoscopic ultrasound and PET-CT not done for evaluation because of non availability.Open or minimally invasive esophagectomy were performed. Patients characteristics such as age, gender, pathological type, grade of tumour, clinical response, method of surgery, margin status and assessment of treatment response were analyzed. Patients with nodal residue were given adjuvant chemotherapy.All patients were followed systematically. Follow up includes a complete history and physical examination every 2 to 3 months for 1 to 2 years, then every 6 months for 3 to 5 years and annually thereafter. Survival outcome were analyzed using kaplan-meier curve. Statistical analysis was done with SPSS 17.0 version.

Results

Total number of patients were 65 with mean age of 50.8±10 years. Median follow-up period was 40 months. Table 1 summarizes patients characteristics. 21(35%) patients were less than 50 years. 44(63%) patients were more than 50 years. 41(63%) patients were male and 24(37%) were female. Mid esophageal cancers were12(18%) patients. Lower and OG junction tumours were 46(70%) patients. Squamous cell carcinoma-50(77%),and adenocarcinoma 15(23).Low grade tumors were 38(58%) and high grades tumors(G1,G2) were 27(42%). Complete clinical response noted in 21(32%) patients and reminders had clinical residual disease both endoscopically and/or radiologically.Transhiatal esophagectomy was done in 57(88%) patients. Thoracolaparoscopic esophagectomy was done in 8(12%) patients .

Table 1 Clinical and pathologic characteristics

parameters	*No (%)*
Age ≤50 yrs	*28 (43%)*
>50 yrs	*37(57%)*
Gender Male	*41 (63%)*
Female	*24 (37%)*
Tumor location Mid	*12 (18%)*
Lower	*34 (52%)*
OG junction	*19 (30%)*
Biopsy Squamous carcinoma	*50 (77%)*
Adeno carcinoma	*15 (23%)*
Nodal enlargement on CT imaging	*41 (63%)*
N1	*24(37%)*
N0	

Clinical complete response *Clinical residual tumor*	*21(32%)* *44(68%)*
Surgery *Transhiatal* *Thoraco laparoscopy*	*57(88%)* *8(12%)*

Table-2 Pathological report

Post operative Pathology report	*No .(%) Of patients*
Complete response (pCR)	*18(28%)*
Partial response	*47(72%)*
Circumferential margin positive	*3(5%)*
R0 resection *R1 resection*	*62(95%)* *3(5%)*
Pathological positive lymph node	*12(18%)*

Pathological specimen analysis:

Pathological analysis of esophagectomy specimen (Table-2) showed complete response (pCR) in 18 patients(28%) and residual tumors in 47 patients ,of them 3 (5%) patients had circumferential margin positive for tumor. Average lymph nodes harvested during surgery was 8. Tumor deposits in lymph nodes were found in 18%(12) of patients ,of them 2 patients only had no primary tumor residue(pT0,N+). pT1a-20 patients, pT1b-21 patients and pT2 were 3 patients.

Survival analysis:

Overall survival rate were calculated using Kaplan-meier curve analysis. 1 year,2 year,3 year and 5 year survival rates were 96%, 75%, 71% and 32% respectively. In CROSS study,1-,2-,3-,and 5 year survival rates were 82%,67%,58%,47%, respectively. Factors influencing survival outcome according to mono variate analysis were summarized in Table.3

Table-3 survival outcome according to monovariate analysis

variables	*Survival(%)*	*P value*
age≤50years *>50years*	*57.7* *15.3*	***<0.001***
Male *female*	*24* *47.4*	*0.106*
Squamous.carcinoma *Adeno carcinoma*	*39.6* *22.3*	*0.293*
Grade -low *-high*	*45.6* *19*	***0.016***
Lymphnodes.harvested *≤8* *>8*	*34.5* *25.9*	*0.817*
Lymphnode negative *positive*	*34.4* *22.5*	*0.187*
Residual tumor absent *Residual tumor present*	*93* *8*	***<0.001***

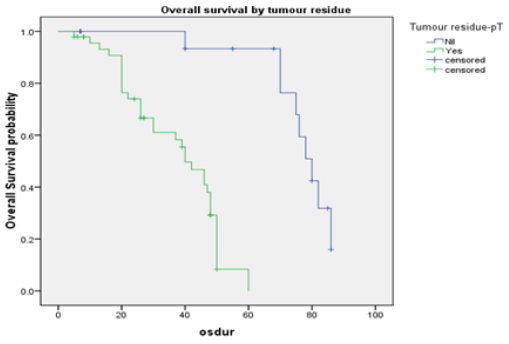
5 years Survival outcome of patients with age group ≤ 50 years were 57.7% vs 15.3% for age group more than 50 years (p<0.001). Females had better survival outcome (47.4%) compared to male(24%) (p<0.106). Female gender(47% vs24.4%,p=0.146) had no better survival outcome as compared to male.Squamous cell carcinoma patients had no statistically difference in survival outcome as compared to adenocarcinoma (39.6% vs22.3%,p value 0.293).Low grade tumors had better survival compared with high grade tumors (45.6% vs 19%, p value 0.016). Location of tumors did not affect survival whether located in mid or lower esophagus or OG junction tumors.Lymphnodes harvested in resected specimen(34.5% vs 25.9%,p value 0.817) and nodal positivity (34.4% vs22.5% ,p value 0.187) were not influencing survival outcome.Survival outcome was greatly influenced by residual tumor status. Patient with complete pathological response(pCR) had 5 year survival of 93% compared with 8% (p value 0.001)in residual tumor (Table-4).

Table-4 Multi variatiate analysis for independant prognostic factor for Overall survival

Factors	Hazards ratio	95% CI	P value
Pathological residue	*37.6*	*4.22-334.8*	*<0.001*
Age	*3.35*	*1.59-7.00*	*0.001*
Grade	*1.87*	*0.96-3.65*	*0.065*

Discussion

The prognostic significance of pathologic complete response (pCR) and histologic tumor regression after preoperative chemoradiation therapy in patients with adenocarcinoma and SCC of esophagus has been demonstrated in several studies[4,5,6]. Post treatment pathological stage was the best predictor of survival outcome in our study when analyzed using cox regression method (HR-37.6; 95% CI 4.22-334.9%,p<0.001)(figure 1). This was proved already by Chirieac LR[7] et al study.



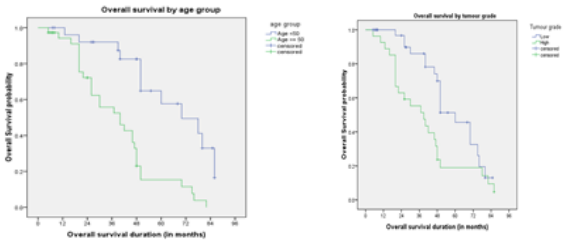
Several tumor regression grading system have been developed to assess the pathologic response to preoperative neoadjuvant therapy. In Chirieac LR et al, the overall survival was significantly better for patients with no residual carcinoma (133 months) than it was for those with more than 50% residual carcinoma (10.5 months). Although grading system for tumor response in esophageal cancer have not been uniformly adopted, the 3-tiered classification system by Wu et al[8]: P0(0% residual carcinoma), P1 (1% to 50% residual carcinoma),and P2 (more than 50% residual carcinoma) has been reported to have an excellent interobserver agreement among pathologist on grading the extent of residual carcinoma.

In some retrospective studies ,FDG uptake on a single post treatment PET scan was the only predictive factor that correlated with pathologic response and survival. Bruzzi et al reported that PET scan has only a limited utility for assessing therapeutic response, although it was useful in the detection of distant metastasis in patients with locally advanced ,potentially resectable esophageal cancer. In patients who are treated with preoperative chemoradiation , RT induced ulceration has been associated with false-positive results on PET-CT ,precluding accurate detection of residual esophageal tumor[9]. Sensitivity and specificity of PET-CT for detection of locoregional metastasis in esophageal cancer were 51% and 84% respectively[10].

The other parameter which influences survival outcome was age of the patient .Patients with age less than 50 years were better tolerating neoadjuvant chemoradiation and esophagectomy compared with patients with age group more than 50 years hence influencing survival outcome in our study.(HR-3.35; 95%CI 1.59-7.00: p value 0.001) (figure-2). Low grade tumors behaves better compared with high grade tumors .(HR-1.87;95%CI 0.96-3.65; p=0.065).(fig-3)

Surgery provides a significant survival benefit in patients with locally advanced oesophageal cancer achieving clinical response to preoperative chemoradiation.[11] Retrospective study that compared the outcomes of surveillance vs surgical resection in patients with oesophageal cancer achieving complete clinical response after preoperative chemoradiation, surgical resection was independently associated with less recurrence and better median survival.[11] Swisher et al reported that preoperative chemoradiation was associated with pCR of 28% which is equal to our study(28%)[12].

Of the 21 patients who had complete clinical response in our study , 18 patients had pCR. At present, no methods short of surgical resection can accurately determine which patients will be found to have no residual tumor in the resected esophageal specimen after chemo radiation. Bates et al [13] noted a 41% false negative rate with preoperative endoscopy and biopsy.Sarkaria et al [14]reported 31% pCR vs 76% cCR. Flamen et al [15]evaluated sensitivity and positive predictive value of PET scans for identifying pCR ,which were 67% and 50% respectively.



Lymph nodes harvested does not influences survival outcome. In Upfront surgery, higher the nodal harvesting, better is the survival outcome[16]. But in post-neoadjuvant settings , lesser the nodal burden (≤8LN)was better correlated with survival (34.5% vs 25.9%,p value 0.817).But in our study, nodal harvesting and positive nodes does not influences survival. It could be due to small sample size.

Gender had no better survival outcome which was similarly reported in CROSS study[17].The effect of histologic type (adenocarcinoma vs Squamous cell carcinoma) is unclear. Most series suggest that Squamous cell cancers have a higher response rate compared with adenocarcinoma. However, no clear difference in outcome was found. Until randomized trial reports available, it reasonable to treat both types of lesions in a similar fashion.

Conclusion

Most of the patients had residual cancer post neoadjuvant chemoradiotherapy hence esophagectomy is warranted to improve overall survival. Survival outcome is influenced mainly by patholo gical residual status.

Conflicts of interest

There is no conflict of interest.

References

1. Bosetti C et al. Trends in oesophageal cancer incidence and mortality in Europe .Int J Cancer. 2008 Mar 1;122(5):1118-29.
2. kleinberg et al . Chemoradiation in the management of esophageal cancer .J clin oncol 2007;25:4110-4117
3. Urschel et al .Meta analysis of RCT that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer.Am J surg 2003; 185:538-543.
4. Schneider PM et al. Histomorphologic tumor regression and lymph node metastasis determine prognosis following neoadjuvant chemoradiotherapy for esophageal cancer:implication for response classification.Ann Surg 2005;242:684-692.
5. Ancona E: only pCR to neoadjuvant chemotherapy improves long term survival of patients with SCC- RCT of preop chemotherapyVs surgery alone.cancer2001;91:2165-2174
6. Rohatgi et al-failure pattern correlate with proportion of residual carcinoma after preop CRT for ca esophagus cancer2005; 104:1349-1355
7. chirieac LR et al- post therapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. cancer2005; 103:1347-1355.
8. Wu et al.Grading the extent of residual carcinoma after preoperative chemoradiation in esophageal and OG junction cancers.A reliable predictor for patient outcome.Am J surg Pathol 2007;31:58-64
9. Erasmus JJ Preoperative chemo-radiation-induced ulceration in patients with esophageal cancer: a confounding factor in tumor response assessment in integrated computed tomographic-positron emission tomographic imaging. Thorac Oncol. 2006 Jun;1(5):478-86.
10. Van Westreenen et al.systematic review of staging performance of PET scan in esophageal cancer: J clin onco. 2004 sep 15;22(18) ;3805-12
11. Piessen G.Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. Ann Surg. 2013 Nov;258(5):793-9;799-800.
12. Swisher et al. improved long term outcome with chemoradiotherapy strategies in esophageal cancer.Ann Thoracic surg 2010;90:892-898
13. Bates et al.Concurrent ChemoRT followed by esophagectomy for localized esophageal carcinoma.J clin oncol 1996;14:156-163[PMID:8558191].
14. Sarkaria et al.post treatment endoscopic biopsy-poor predictor of pathologic response in patients undergoing chemoRT for esophageal cancer.Ann surg 2009;249:764-767.[PMID:19387328].
15. Flamen et al. PET for assessment of response to induction chemoRT in locally advanced esophageal cancer.Ann oncol 2002;13:361-368.[PMID:23994746]
16. Peyre CG et al.Number of lymphnodes removed predicts survival in esophageal cancer.ann surg.2008;248(4)549-556
17. Van Hagen et al, preoperative chemoradiotherapy for esophageal cancer Nengl J Med 2012;366:2074-2084