Comparison Between Concurrent Chemoradiation Followed by Surgery vs. Surgery for Locally Advanced Cancer of Esophagus

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Abstract Surgery is an accepted standard in the treatment of localized stage cancer of esophagus. But the ideal approach for locally advanced lesions still remains unknown. Patients with locally advanced lesions (cT3–4N1M0) on the basis of CT chest were subjected either to primary surgery or to preoperative chemoradiation followed by surgery. Major postoperative complications (mortality, anastomotic leak and recurrent laryngeal nerve palsy) did not differ in either arm (P = not significant). Complete pathological response was achieved in 31.2% cases in multimodality arm. Four year overall survival was 10% for whole group. Median survival was 14 months and 20 months in surgery and multimodality arm, respectively (p = .288). In multimodal arm, there was significant survival difference between complete responders and nonresponders (p = .02). For locally advanced lesions, surgery alone gives poor outcome and preoperative chemoradiation followed by surgery should be considered for complete responders.

Keywords Esophageal cancer · Surgery · Neoadjuvant chemoradiation

Introduction

Outcome of esophageal cancer still remains unsatisfactory. Therefore, there has been a continuous search for the better

management. Although surgery is the primary modality that can cure patients, the majority of patients present with recurrences leading to death within 2 years after resection. This is particularly true for high-risk patients with locally advanced tumour stage, where complete resection is impossible in a relevant number of patients and lymph node metastases were observed in almost all the patients [1, 2]. Management varies from simple palliative esophageal stenting to multimodality treatment. There has never been a well documented protocol or results of management of esophageal cancer in our country. We reviewed our results in a tertiary care centre.

Methods

A retrospective review of the patients with the diagnosis of cancer of esophagus, undergoing radical surgery alone or surgery as a part of multimodality treatment was done. The patients were assessed for fitness for surgery on the basis of routine blood tests, biochemistry profile, performance status (only patients with ECOG of 0–1 were included), stair climbing test, spirometry and echocardiography (in selected cases only). If in CT chest, the lesion was suspicious for invasion into the surrounding structures e.g., aorta, lung, trachea-bronchial tree along with enlarged mediastinal nodes, it was classified as locally advanced tumour (T3–4 N1 lesion). Non-bulky excisable celiac nodal disease was not a contraindication for surgery. The lesions which appeared obviously resectable, had trachea-esophageal fistula, positive supraclavicular nodes or with stage IVb disease were excluded. Cases were taken either directly for surgery (s/ s-adj rx) or were subjected to neoadjuvant chemoradiation followed by surgery (crtt-s). Cases taken for multimodality treatment received concurrent chemoradiation with cisplatin -5-fluorouracil (FU). Cisplatin

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(75 mg/ m² – day 1) and FU (1000 mg/ m²–day 1–4) were given in beginning and at the end of radiation. Radiation dose varied from 40 Gy to 66 Gy. 40 Gy, 50 Gy, 60 Gy and 66 Gy were delivered in 4, 8, 2 and 2 cases, respectively. Patients were reinvestigated with basic blood tests and CT chest and abdomen. Surgery was usually performed 4 weeks after completion of preoperative treatment. In both arms, the surgical approach was either transthoracic or transhiatal. Transthoracically, the lesion was approached either through right hemithorax or left hemithorax. In majority of cases, three-incision technique (McKeon's) was used. The details of all the approaches were standard and can be found elsewhere. Lymph nodes were either sampled or a formal two-field (2-FD) or three-field (3-FD) lymph node dissection was performed. After primary surgery or multimodality treatment, if there was R0 resection, simple observation was considered. In cases of positive resection margins, either chemotherapy or chemoradiation was added as adjuvant treatment. But in very few cases of R0 resection in either group, adjuvant chemotherapy was considered as well. The treatment plan depended totally upon the decision of treating oncologist. In ctrt-s arm, complete pathological response was considered as “responders” whereas a partial response, stable disease or progressive disease was considered as “non-responders”.

Patients were seen for the first follow-up 8 to 12 weeks after the end of treatment, and thereafter every 3 months up to 2 years. Afterward, follow-up was planned every 6 months up to 5 years.

Statistical analysis was done using SPSS 16.0 software. Survival curves were calculated employing Kaplan-Meier method and compared using the log rank test. Numerical values were compared using t-test. Categorical variables were compared using Chi-square test. Statistical significance was assumed when a P value fell below .05.

Results

A total of 63 patients were analyzed. In surgery±adjuvant treatment group (s/ s-adj rx), there were 47 patients whereas in concurrent chemoradiation+surgery (ctrl-s) group, there were 16 cases.

Various parameters of both groups with comparison have been presented in Table 1.

Final pathological report and response to neoadjuvant chemoradiation are presented in Tables 2 and 3.

Excluding the 30-day mortality and cases with incomplete follow-up, we could retrieve a complete survival data of 39 patients, which were analysed.

Median survival for whole group was 17 months with 4-year overall survival of 10% (Fig. 1). Median survival time for s/ s-adj rx was 14 months and for ctrl-s group was 20 months (p=.288) (Fig. 2). Figure 3 shows the survival analysis of

Table 1 Various parameters

Variable	s/ s-adj rx	ctrl-s	p
Mean age	58 years	51 years	.01
Mean Hb	13 g/dl	12 g/dl	.038
Mean serum albumin	3.6 mg/ dl	3 g/ dl	.02
Mean duration of dysphagia	3.6 months	5 months	.113
Mean weight loss	9.6 kg	10.6 kg	.4
Mean postop stay	15 days	18 days	.216
Sex			
Male	27	9	
Female	20	7	.933
Smoker	40	10	.054
Tobacco	22	2	.018
Procedure			
Ivor-Lewis	4	0	
McKeon	35	13	
Transhiatal	2	1	
Left thoracic approach	6	1	
Left thoracocolarotomy+neck	0	1	.17
Tumour location			
Cervical	0	2	
Upper	5	3	
Middle	25	7	
Lower	17	4	.06
Level of anastomosis			
Chest	10	1	
Neck	37	15	.263
Mean operative time	300 min	290 min	.6
In-hospital mortality	3	1	1.0
Anastomotic leak	8	6	.16
RLN injury	5	2	1.0
Mean number of dissected nodes	24	13	.013
Mean number of positive nodes	5	2	.076
Resection			
R0	38	14	
R1	2	2	
R2	7	0	.155

responders and non-responders to preoperative chemoradiation. For non-sponders, median survival was 16.5 months; for responders, median survival has yet not been reached as there has been no death till the date of data analysis.

Table 2 Final histopathology

Variable	s/ s-adj rx	ctrl-s	
Squamous cell	38	14	
Adenocarcinoma	7	2	
Adenosquamous	1	0	
Small cell	1	0	p=.881

Table 3 Response to crt

Variable	n	%
Stable	4	25
Partial response	6	37.5
Complete response	5	31.2
Progressive	1	6.2

Discussion

There have been always a lot of controversies in the management of esophageal cancer and its surgical approach as well. Preoperative and postoperative chemotherapy, radiotherapy and preoperative chemoradiation all have been tried with conflicting results. Metanalysis of preoperative chemotherapy did not show any survival advantage to surgery alone. Similarly, the results of preoperative radiation alone, postoperative radiation, postoperative chemotherapy were also disappointing. So far as the results of preoperative chemoradiation are concerned, some of the randomized trials favoured this treatment whereas others did not.

Ten Randomized controlled trials (RCTs) have been performed to address these issues, but the results are not consistent. Many of the RCTs enrolled small numbers of patients; this limits their ability to detect a treatment benefit, even if a benefit exists (inadequate power). Of these ten studies, six were restricted to SCC only, one was restricted to adenocarcinoma and rest three enrolled both SCC and adenocarcinoma. All patients had stages T0-3, N0-1 disease. On the basis of above trials, five meta-analyses have been published which mostly favoured a small though statistically non-significant trend towards increased survival in combined modality arm [3–7]. Though the treatment plan for resectable cancer still remains to be standardized, it is very clear from the meta-analyses that a complete pathological response can

Fig. 1 Kaplan-Meier curve of overall survival **Fig. 2** Kaplan-Meier curve comparing two treatment groups

be reached in 10–43% of cases with majority showing some sort of response in T or N stage.

Results of surgery alone in a locally advanced esophageal cancer are disappointing basically because of inability to get an adequate circumferential margin. Vicinity to major airway and vessels make the later extremely difficult. Therefore, investigators have concentrated on treating esophageal cancer with a bi- or trimodal approach, employing chemotherapy or chemoradiotherapy in addition to surgery before esophagectomy. Logically, concurrent chemoradiation at the same time would control both the local disease and distant micrometastases.

Manzoni et al. showed the results of crt-s for cT4 squamous cell carcinoma of thoracic esophagus with obvious or probable invasion ($n=51$) into adjacent organ. R0 surgery was rarely obtained (39.2%). Pathologic down

Fig. 3 Kaplan-Meier curve comparing responders and non-responders in crt-s group

staging was achieved in 18 cases (35.3%) while a complete response (pT0N0) in 7 (13.7%). The overall median survival time was 11.1 months with a 3-year survival rate of 8.8%. A significantly better survival ($P < 0.001$) was observed after a R0 resection (median survival: 22.3 months; 3-year survival: 25.4%; $P < 0.001$) and for responders to cirt (median: 33.1 months; 3-year survival: 25.7%; $P = 0.019$). Authors concluded, aggressive multimodal therapy with cirt followed by surgery in cT4 SCC of the thoracic esophagus is feasible. Surgery should be limited to patients with significant response to induction treatment and a high probability of R0 resection [8].

In T4 lesions, staged by CT chest showing the invasion of trachea-bronchial tree, aorta, but without tracheoesophageal fistula and without distant metastases, Noguchi [9] compared 24 patients receiving cirt-s with 17 patients receiving definitive cirt. The median overall survival (OS) in cirt-s group was 13.8 months vs. 3.3 months in definitive cirt group ($p < .001$). Complete pathological response (pCR) was observed in 16.7% cases. The complete responders in cirt-s arm had median survival of 38.9 months vs. 8.8 months in non-responders ($p < 0.05$).

Similarly, Ikeda et al. in 13 patients after cirt-s achieved a 5-yr OS of 23% [10].

Stahl et al. [11] randomized 172 patients with cT3-4 N0-1 M0 upper and mid esophageal lesions into induction chemotherapy (ct) followed by cirt-s vs. Induction ct followed by definitive cirt. Staging was done by CT and EUS. pCR could be achieved in 35% cases. Three-year OS in combined modality arm was 31.3% whereas in definitive cirt arm, it was 24.4% ($P = .02$).

Very interesting result was achieved by Bedenne et al. in a randomized trial comparing cirt-s in responders to cirt vs. cirt alone for T3N0-1 M0 for thoracic esophageal tumours of both squamous and adenotype. T3 lesions were defined as tumours of more than 3 cm in diameter but without invasion into adjacent structures on the basis of CT chest. Two-year survival was 34% in cirt-s arm and 40% in cirt arm ($p = .44$). Authors concluded that in patients with locally advanced thoracic esophageal cancers, especially epidermoid, who responded to cirt, there was no benefit for the addition of surgery after cirt compared with the continuation of additional cirt [12].

In our study, most of the basic parameters in both groups were comparable, except the lower level of serum albumin in the cirt-s arm. Though assumed to take more operative time in cirt-s arm, actually it was almost the same ($p = .6$). The major postoperative complications like anastomotic leakage rate, in-hospital mortality rate and rate of recurrent laryngeal nerve did not defer in the two arms ($p = \text{NS}$). The rate of R0 resection as well did not defer. Therefore, it is very clear that cirt-s does not increase the postoperative complication but at the same time it does not produce to

more R0 resection as one would have assumed. The main obvious difference was more numbers of dissected nodes in the s/ s-adj arm ($p = .013$), which would indirectly suggest a major nodal response to chemoradiation in cirt-s arm. Because of poor database system and poor follow-up of the patients, a complete follow-up of data of only 39 patients could be obtained. Though, there was a good pCR (31.2%) in cirt-s arm, this did not lead to an OS advantage (median survival of 14 months in s/ s-adj arm vs. 20 months in cirt-s arm, $p = .288$). But in the cirt-s arm only, there was significant survival difference between responders and non-responders (there has been no deaths in responders till the date of analysis of the data, $p = 0.02$).

The main limitations of our study were its retrospective nature, use of only CT chest and abdomen for staging purpose and less number of patients. Nevertheless, our results showed that for locally advanced lesions, surgery alone or in combination with chemoradiation gives similar though dismal result. Therefore, surgery should be recommended only to those patients who respond to chemoradiation.

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