Multimodality Management of Esophageal Cancer

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Abstract Esophageal cancer is a morbid disease with a grim prognosis. The outcomes of treatment even in non-metastatic disease undergoing potentially curative surgery are poor with 5-year survival ranging from 20 to 35 %. Several multimodality treatment options have been investigated in well-conducted randomised trials and meta-analyses evaluating both neoadjuvant and adjuvant therapies. However, there is still lack of uniform practice in the management of operable esophageal cancer. We review the current evidence for multimodality treatment of esophageal cancer, critically analysing the evidence supporting the use of each strategy, the pros and cons of each approach and discuss our approach in management. Neoadjuvant chemotherapy or chemoradiotherapy are currently the standard of care in localised esophageal cancer.

Keywords Neoadjuvant · Adjuvant therapy · Esophageal cancer

Esophageal cancer is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012 [1]. In India, it is the sixth most common cancer amongst men and the eighth most common cancer amongst women [1] with an age-adjusted incidence ranging from 3.8 to 32.6 per 100,000 in men and 1.6 to 21.1 per 100,000 in women in various registries [2]. Esophageal cancers include both true esophageal cancers

as well as the junctional (tumors straddling the esophagogastric junction) cancers. The dual histologies of squamous (common in Asia) and adenocarcinoma (common in Europe and North America) make the study of this disease even more complicated. Esophageal cancer is a morbid disease with a grim prognosis and is also a relatively important cause of cancer-related death in India [3]. The outcomes of treatment even in non-metastatic disease undergoing potentially curative surgery are poor with 5-year survival ranging from 20 to 35 % [4–6]. Several approaches have been evaluated to improve these outcomes including screening to detect early stage disease, better surgical techniques to improve radicality of resection and reduce peri-operative morbidity and multimodality treatment protocols.

The poor outcomes of surgical resection alone prompted considerable research on multimodality treatment options in esophageal cancer. The options include neoadjuvant chemotherapy/chemoradiotherapy followed by surgery and adjuvant chemotherapy/radiotherapy/chemoradiotherapy following surgery. Most of these strategies have been evaluated by randomised trials and meta-analyses. However, there is still considerable lack of uniformity in the management of esophageal cancer [7]. This review presents the evidence supporting the use of each of these strategies, discusses the pros and cons of each approach and provides current evidence-based treatment guidelines. Relevant differences in management with esophageal and junctional cancers and squamous and adenocarcinomas have been highlighted in specific areas, while the management of gastric cancers is beyond the scope of this review.

Neoadjuvant Therapy—the Rationale

Neoadjuvant therapy has been a favoured approach in the management of esophageal cancer. The potential advantages of neoadjuvant therapy include increasing the rate of curative

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resections by tumour downstaging, earlier treatment of micro-metastasis and more reliable delivery of non-surgical therapy both due to an intact vascular supply to the tumour and by avoiding the prolonged recovery period following major surgery. The biological basis lies in decreased risk of tumour-seeding at operation and increased radiosensitivity owing to better tumour oxygenation if radiotherapy is given before surgery. Radiation target volumes are also easier to define because of visible disease. Finally, there is the unique opportunity to evaluate the effectiveness of the preoperative treatment by histological examination of the resected esophagus. In addition, patients destined for early relapse owing to occult metastatic disease may avoid surgical resection—a process of natural selection of patients [8, 9]. Earlier studies evaluated the role of neoadjuvant chemotherapy or radiotherapy alone while more recent trials have focused on a strategy of combining chemotherapy with radiotherapy in the neoadjuvant setting. There is no evidence to support the use of pre-operative radiotherapy alone in the radical management of esophageal cancer [10], and this strategy will not be discussed further in this review.

Neoadjuvant Chemotherapy

Several studies [4, 5, 11–20] have evaluated the role of neoadjuvant chemotherapy (NACT) followed by surgery compared with surgery alone in localised esophageal cancer. However, the two largest studies [19, 20] showed contrasting results. The first large trial, the Intergroup trial [19], showed no improvement in long-term survival with neoadjuvant chemotherapy. In this multi-institutional randomised trial comparing NACT with surgery alone, 467 patients with localised, operable esophageal cancer were recruited of which 443 patients were eligible for final analysis; 216 patients received NACT while 227 patients underwent surgery alone. In their initial report, median survival for patients who received NACT was 14.9 months whereas, for those who underwent surgery alone, it was 16.1 months ($p=0.53$ by log-rank test; $p=0.49$ by Cox proportional-hazards analysis) with a relative risk of death of 1.07 in the NACT arm (95 % CI, 0.87 to 1.32). This large trial used one of the most common chemotherapeutic combinations used in the treatment of esophageal cancer (cisplatin+5-fluorouracil) but failed to show benefit. In the long-term follow-up update [4], the median survival of both groups was 1.3 years. While NACT decreased the incidence of R1 resections, it did not improve overall survival. The MRC OE02 trial [20] was a larger trial with 802 patients and randomized patients to two cycles of neoadjuvant cisplatin and 5-fluorouracil or surgery alone. Overall survival was better in the NACT group ($p=0.004$; hazard ratio 0.79; 95 % CI, 0.67–0.93) with an estimated reduction in risk of death of 21 %. Median survival in the NACT and surgery alone groups

were 512 days (16.8 months) and 405 days (13.3 months), respectively. Disease-free survival was also better in the NACT group ($p=0.0014$; hazard ratio 0.75; 95 % CI, 0.63–0.89). In their follow-up update [5], the authors reported a 5-year overall survival of 23 % in the NACT group and 17 % in the surgery alone group.

The reason for the difference in survival outcomes between these studies is unclear. Both trials had similar patient characteristics and chemotherapy regimens. Some of the important differences were that the Intergroup trial also gave post-operative chemotherapy; the total prescribed preoperative doses and duration of chemotherapy in the two trials were different. There was also a difference in the timing and extent of surgical resection. These differences may only be partly responsible for the conflicting results.

In another landmark trial [21] (MAGIC), Cunningham and co-workers randomly assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction or lower esophagus to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Three cycles of chemotherapy (epirubicin, cisplatin and 5 fluorouracil: ECF) were administered preoperatively and three cycles postoperatively. As compared with the surgery group, the perioperative-chemotherapy group had a significantly superior progression-free survival (hazard ratio for progression 0.66; 95 % CI, 0.53 to 0.81; $p<0.001$) and overall survival (hazard ratio for death 0.75; 95 % CI, 0.60 to 0.93; $p=0.009$). Five-year survival rates were 36.3 % (95 % CI, 29.5 to 43.0) among patients in the perioperative chemotherapy group and 23 % (95 % CI, 16.6 to 29.4) among those in the surgery alone group. This trial conclusively demonstrated that, in patients with operable gastric or lower esophageal adenocarcinomas, a perioperative regimen of ECF downstaged the disease and significantly improved progression-free as well as overall survival. Another phase III trial [18] confirmed these results showing a survival advantage in the perioperative chemotherapy group. In this trial, 224 patients from 28 French centres were randomised to perioperative chemotherapy with cisplatin+5-fluorouracil (113 pts) or surgery alone (111 pts). Compared with surgery alone, the perioperative chemotherapy group had a significantly higher overall survival (HR for death 0.69; 95 % CI, 0.50 to 0.95; $p=0.02$) and disease-free survival (HR for recurrence or death 0.65; 95 % CI, 0.48 to 0.89; $p=0.003$). Five-year survival rates were 38 % (95 % CI, 29 % to 47 %) in the perioperative chemotherapy group compared with 24 % (95 % CI, 17 to 33 %) in the surgery alone group. Five-year DFS rates were 34 % (95 % CI, 26 % to 44 %) in the perioperative chemotherapy group compared with 19 % (95 % CI, 13 % to 28 %) in the surgery alone group.

In addition to these major trials, several smaller randomised trials [11–18] evaluating the role of NACT in operable esophageal cancer have also been published. Most of these studies, however, were underpowered to detect clinically important survival differences. Several meta-analyses [22–26]

combining the results of these randomised trials have uniformly demonstrated improved survival with neoadjuvant chemotherapy. The most recent and comprehensive meta-analysis [26] compared survival of 1981 patients randomised to either NACT or surgery alone. Table 1 summarises the details of the trials included in the meta-analysis. Figure 1 shows the Forrest plot showing a significantly superior survival with NACT (hazard ratio for mortality 0.87, 95 %CI 0.79 to 0.96, $p=0.005$) over surgery alone. Most of the individual trials and the meta-analyses showed almost identical perioperative morbidity and mortality with NACT as with surgery alone. Two more recent trials conducted by the MRC, the OE05 and the ST03 trials, have completed accrual, and results are awaited. The OE05 trial compared two different NACT protocols and compared standard chemotherapy of two cycles of cisplatin and 5FU with four cycles of epirubicin, cisplatin and capecitabine (ECX) prior to surgical resection; the ST03 was a phase II/III trial comparing perioperative chemotherapy using ECX with or without bevacizumab.

Neoadjuvant Chemoradiotherapy

Neoadjuvant chemoradiotherapy (NACTRT) has been extensively studied initially in the form of prospective case series and subsequently within randomised trials. One of the early reviews [8] comprehensively evaluated 46 nonrandomised studies between 1981 and 1999 and noted the incidence of complete pathological response, survival and patterns of recurrence. Data from these studies (2,704 patients) suggested that NACTRT was associated with 24–42 % complete pathological also showed that recurrences after NACTRT were distant metastasis rather than locoregional.

Table 1 Summary of randomised trials of neoadjuvant chemotherapy in esophageal cancer

Trial/author	Year	No. of patients	Chemotherapy (cycles)	Histology
Roth	1982	39	Cisplatin/vindesine/bleomycin (2)	Squamous
Nygaard	1983	81	Cisplatin/bleomycin (2)	Squamous
Schlag	1988	46	Cisplatin/5-FU (3)	Squamous
Maipang	1988	46	Cisplatin/bleomycin (2)	Squamous
Law	1989	147	Cisplatin/5-FU (2)	Squamous
Boonstra	1989	169	Cisplatin/etoposide (2)	Squamous
Kelsen	1990	467	Cisplatin/5-FU (3)	Squamous/adeno
Ancona	1992	96	Cisplatin/5-FU (2)	Squamous
Allum	1992	802	Cisplatin/5-FU (2)	Squamous/adeno
Ychou	1995	169	Cisplatin/5-FU (6 periop)	Adeno

Adapted with permission from Sjoquist KM et al.: Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; 12: 681-92

The promising results of these nonrandomised studies however needed validation from randomized trials considering the higher toxicity profile of this therapy. Several randomised trials of NACTRT [12, 27–37] showed ambiguous results in terms of survival benefit but were generally underpowered to show a clinically important benefit. After a successful phase II study showing results favouring NACTRT, the EORTC conducted a large phase III randomised trial [38]. In this multicentric trial, 282 patients were randomised to surgery alone (139) or NACTRT (143). The median survival in both arms was 18.6 months, and the overall survival curves of the two groups did not differ significantly (relative risk of death with NACTRT, 1.0; 95%CI, 0.7 to 1.5; $p=0.78$). Disease-free survival was, however, significantly longer in the NACTRT group (relative risk of recurrence or death from cancer 0.6; 95 %CI, 0.4 to 0.9; $p=0.003$). The authors attributed this benefit mainly to a local effect, based on a longer interval free of local recurrence in the NACTRT group. Other indicators of efficacy of NACTRT were a higher rate of curative resection, clear-cut evidence of a lower disease stage after preoperative therapy and a high rate of major pathological responses.

The most recent randomised trial (CROSS) [6] used neoadjuvant chemoradiotherapy consisting of weekly administration of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy each, five fractions per week, starting on the first day of the first chemotherapy cycle). The CROSS trial enrolled 368 patients of whom 180 were randomly assigned to the NACTRT group, and 188 to the surgery alone group. Patients in the NACTRT group underwent surgery as soon as possible after completion of chemoradiotherapy (preferably within 4 to 6 weeks), and patients in the surgery alone group were treated as soon as possible after randomisation. The overall survival rates at 1, 2, 3 and 5 years were 82 %, 67 %, 58 % and 47 % in the NACTRT arm, compared with 70 %, 50 %, 44 % and 34 % in the surgery alone arm, respectively. The median overall survival was 49.4 months in the NACTRT group versus 24.0 months in the surgery alone group ($p=0.003$ by the log-rank test; hazard ratio 0.657; 95 % CI, 0.49 to 0.87). The morbidity related to NACTRT was acceptable, with grade 3 haematological and non-haematological toxicities noted in 7 and 13 % patients, respectively, in the NACTRT group. The CROSS trial convincingly showed improvement in both overall and disease-free survival with minimal treatment-related morbidity and mortality.

In the recently published follow-up to the CROSS trial [39], the overall recurrence rate in the surgery arm was 58 % versus 35 % in the NACTRT arm. Neoadjuvant chemoradiotherapy reduced locoregional recurrence from 34 to 14 % ($p<0.001$) and peritoneal carcinomatosis from 14 % to 4 % ($p<0.001$). There was also a small but significant effect on haematogenous dissemination in favour of the NACTRT group (35 % vs. 29 %; $p=0.025$).

All-cause mortality for chemotherapy compared with surgery alone

Effects of chemotherapy compared with surgery alone on survival in patients with oesophageal cancer (A) and in subgroups of patients with oesophageal carcinoma (squamous-cell carcinoma or adenocarcinoma histology; B). *Includes ten patients whose histology was unknown or who had mixed tumours. †Includes 12 patients whose histology was unknown or who had mixed tumours.

Fig. 1 Survival after neoadjuvant chemotherapy for resectable esophageal carcinoma Reproduced with permission from Sjoquist KM et al. [19]: Survival after neoadjuvant chemotherapy or chemoradiotherapy for

resectable esophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; 12: 681–692

Similar to NACT, several meta-analyses have also been published on the role of NACTRT in operable esophageal cancer. One of the earliest meta-analysis [40] suggested a survival benefit

at 3 years but also showed a non-significant trend towards increased perioperative mortality with NACTRT. More recent meta-analyses [25, 26] confirmed the overall survival benefit

with NACTRT. The GebSKI meta-analysis [25] identified ten randomised studies with 1,209 patients that compared NACT RT with surgery alone and concluded that NACTRT significantly benefited patients with a hazard ratio for all-cause mortality of 0.81 (95 % CI, 0.70–0.93). The updated meta-analysis [26] included 1,854 patients from 12 randomised trials and demonstrated the superiority of NACTRT over surgery alone (HR 0.78 (95 % CI 0.70–0.88; $p < 0.0001$). Table 2 summarises the randomised trials evaluating the role of NACTRT. Figure 2 demonstrates survival after neoadjuvant chemoradiotherapy for resectable esophageal carcinoma in the Sjoquist meta-analysis.

Neoadjuvant Chemotherapy Versus Neoadjuvant Chemoradiotherapy

Currently, there are unequivocal data to support the role of neoadjuvant therapy in localised and locally advanced (non-metastatic), resectable esophageal cancer. Several randomised trials and meta-analyses have clearly demonstrated that both neoadjuvant chemotherapy and chemoradiotherapy offer superior locoregional control as well as long-term survival compared with surgery alone. However, there is insufficient data to enable the clinician to choose between these two effective neoadjuvant strategies. While the predominant strategy in the United States and some European countries is neoadjuvant chemoradiotherapy, the preferred option in the UK and many Asian countries including Japan is neoadjuvant chemotherapy. Neoadjuvant chemoradiotherapy has the advantages of combining effective local and systemic therapy, the benefits of the radiosensitising effect of chemotherapy, superior R-0 resection rates and a higher rate of complete pathological responses compared with neoadjuvant chemotherapy alone.

However, many studies have also shown a statistically insignificant but definite trend towards increased postoperative morbidity and mortality with NACTRT over surgery while these are not affected by NACT alone [26, 38, 40, 41]. Clearly, the decision to offer NACTRT routinely in all patients needs to be tempered by the fact that treatment-related morbidity and postoperative complications are likely to be higher, especially in patients who have compromised nutrition and performance status at diagnosis.

The 2007 meta-analysis [25] demonstrated survival benefits with both NACT and NACTRT; the pooled hazard ratio showed an absolute benefit of 13 % for NACTRT and 7 % for NACT over surgery alone. The numbers needed to treat (reciprocals of the absolute risk reduction) to prevent one death were 8 and 15, respectively. The authors further concluded that similar benefits were seen for NACTRT and NACT in patients with adenocarcinoma, whereas a benefit was seen with NACTRT but not NACT in patients with squamous-cell carcinoma (SCC). However, these were indirect comparisons and subset analyses, lack sound statistical support and cannot be considered practice-changing.

In 2009, after a successful phase 2 study, Stahl and colleagues [42] launched a randomised phase III trial comparing NACT with NACTRT; however, the study was prematurely closed due to slow accrual. A total of 125 patients were randomised, of whom data of 119 patients were analysed, with 59 patients randomised to NACT and 60 to NACTRT. Pathological complete response was significantly higher with NACTRT (15.6 vs. 2 %, $p = 0.03$) as was the proportion of tumour-free lymph nodes (ypN0, 64.4 % vs. 37.7 %, $p = 0.01$). The R-0 resection rate was considerably higher with NACT RT (88 %) than NACT (79 %). However, when all 119 patients were considered on an intent-to-treat analysis, the rate

Table 2 Summary of randomised trials of neoadjuvant chemoradiotherapy in esophageal cancer

Trial/author	Year	No. of patients	Chemotherapy (cycles)	Radiotherapy	Histology
Nygaard	1983	78	Cisplatin/bleomycin(2), sequential	35Gy/(1.75Gy/#)/4 weeks	Squamous
Apinop	1986	69	Cisplatin/5-FU(2), concurrent	40Gy/(2Gy/#)/4 weeks	Squamous
Le Prise	1988	86	Cisplatin/5-FU(2), sequential	20Gy/10#/12 days	Squamous
Urba	1989	100	Cisplatin/5FU/vinblastine(2), concurrent	45Gy/(1.5Gy/#)/3 weeks	Squamous/adeno
Bosset	1989	293	Cisplatin (2), sequential	37Gy/(3.7Gy/#)/2 weeks	Squamous
Walsh	1990	61	Cisplatin/5FU(2), concurrent	40Gy/15#/3 weeks	Squamous
Walsh	1990	113	Cisplatin/5FU(2), concurrent	40Gy/15#/3 weeks	Adeno
Burmeister	1994	256	Cisplatin/5FU(1), concurrent	35Gy/15#/3 weeks	Squamous/adeno
Tepper	1997	56	Cisplatin/5FU(2), concurrent	50.4Gy/(1.8Gy/#)/5.6 weeks	Squamous/adeno
Lv	1997	160	Cisplatin/paclitaxel(2), concurrent	40Gy/(2Gy/#)/4 weeks	Squamous
Lee	1999	101	Cisplatin/5FU(2), concurrent	45.6Gy/(1.2Gy/#)/28 days	Squamous
Mariette	2000	195	Cisplatin/5FU(2), concurrent	45Gy/25#/5 weeks	Squamous/adeno
Van der Gaast	2004	364	Carboplatin/paclitaxel(5), concurrent	41.4Gy/(1.8Gy/#)/4.6 weeks	Squamous/adeno

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All-cause mortality for chemoradiotherapy compared with surgery alone

Effects of chemoradiotherapy compared with surgery alone on survival in patients with oesophageal cancer (A) and in subgroups of patients with oesophageal carcinoma (squamous-cell carcinoma, adenocarcinoma or pooled histology type subgroups; B). SCC=squamous-cell carcinoma. *Includes all randomised patients.

†Includes four patients whose histology was unknown or who had mixed tumours. ‡Includes three patients whose histology was unknown or who had mixed tumours.

Fig. 2 Survival after neoadjuvant chemoradiotherapy for resectable esophageal carcinoma Reproduced with permission from Sjoquist KM et al. [19]: Survival after neoadjuvant chemotherapy or

chemoradiotherapy for resectable esophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; 12: 681–692

of complete resection was similar in the two groups (72 % with NACTRT vs. 69.5 % with NACT). Although the three3-year overall survival showed a strong trend favouring NACTRT (47.4 vs. 27.7 %), this was not statistically significant ($p=0.07$), probably because of an inadequate sample size. After adjustment for stratification variables, the hazard ratio for mortality with NACTRT was 0.67 (95 % CI, 0.41 to 1.07, $p=0.1$). This prematurely terminated trial failed to demonstrate a survival benefit of NACTRT over NACT. Notably, postoperative in-hospital mortality was higher (10.2 %) in the NACTRT arm compared with the NACT arm (3.8 %). In a phase II study, Burmeister and co-workers found similar results [33]. Both these studies were conducted in adenocarcinomas of the esophagus and gastroesophageal junction.

The 2011 updated meta-analysis [26] combined the results of the two randomised trials listed above and pooled data of the other studies. The HR from the randomised comparisons was 0.77 (95 % CI 0.53–1.12; -0.17), showing no significant difference between NACT and NACTRT. However, in the absence of adequately powered randomised trials or meta-analysis, the question whether NACT or NACTRT should be the treatment of choice for localised and locoregionally advanced esophageal cancer still remains unanswered. We are currently conducting a phase II randomised trial comparing NACT with NACTRT in operable squamous cell carcinoma of the esophagus (CTRI/2013/03/003497).

Adjuvant Therapy

The role of adjuvant therapy in completely resected esophageal and gastroesophageal junction cancers has been studied in several trials. The earlier trials [43–46] evaluated the role of adjuvant radiotherapy after complete resection while some recent trials have investigated the role of adjuvant chemoradiation [47] and chemotherapy [48–50]. However, with the gradual shift towards a neoadjuvant treatment strategy, interest in the role of adjuvant therapy is waning and currently restricted to (unexpectedly) pathologically upstaged patients.

Adjuvant Radiotherapy

Earlier randomised trials [43–45] on postoperative radiotherapy were small trials and showed no benefit in either disease-free or overall survival. The largest trial to date was a randomised study by Xiao and colleagues [46], where 495 patients with esophageal cancer who had undergone radical resection were randomised to observation (220) or adjuvant radiotherapy (275). The overall results of the trial showed no difference in 1-, 3- and 5-year survival between the two groups (5-year survival 37.1 % with surgery alone versus 41.3 % with postoperative RT, $p=0.4474$). Subgroup analyses

showed a trend towards improved survival with postoperative radiation in patients with positive lymph nodes (5-year survival, 29.2 % vs. 14.7 %, $p=0.0698$) and a statistically significant improvement in stage III disease (5-year survival, 35.1 % vs. 13.1 %, $p=0.0027$). However, these were unplanned subgroup analyses without adjustment for multiple comparisons. While these subgroup analyses were not practice changing, they need to be formally evaluated in a randomised trial. A meta-analysis [24] of 995 patients from five randomised trials of adjuvant radiotherapy versus observation after complete surgical resection showed no benefit in overall survival with the addition of adjuvant radiotherapy, with a risk ratio for death at 1 year of 1.23 (95 % CI, 0.95 to 1.59, $p=0.11$). With the growing popularity of NACTRT in operable esophageal cancer, the role of adjuvant radiotherapy is not being evaluated in recent trials. However, units adopting a neoadjuvant chemotherapy protocol should consider a randomised trial of selective postoperative radiotherapy in patients with positive lymph nodes, stage III disease and positive circumferential resection margins.

Adjuvant Chemoradiotherapy

There have been very few studies evaluating the role of adjuvant chemoradiotherapy after esophagectomy, probably because the ability of patients to tolerate concurrent chemoradiotherapy after a major surgery is limited. An Intergroup trial [47] (MacDonald) randomised 556 patients who underwent complete resection for adenocarcinoma of the stomach and gastroesophageal junction to either observation or postoperative chemoradiotherapy with 5-fluorouracil plus leucovorin and loco-regional radiation. Patients who received postoperative chemoradiotherapy had significantly improved relapse-free and overall survival. The hazard ratio for death and relapse in the observation group, as compared with the postoperative chemoradiotherapy, was 1.35 (95 % CI, 1.09 to 1.66; $p=0.005$) and 1.52 (95 % CI, 1.23 to 1.86; $p<0.001$), respectively. This translated into a 9 % improvement in 3-year overall survival with postoperative chemoradiotherapy compared with surgery alone. The MacDonald trial, although considered a landmark trial, has some caveats. First, none of these patients received neoadjuvant treatment (which is now considered standard of care); in units where neoadjuvant chemoradiotherapy is now standard of care, the results of this trial would be redundant. Second, the trial is frequently criticised for suboptimal surgery and lymphadenectomy; only 10 % of patients underwent a D2 lymphadenectomy, and over 50 % had a D0 lymphadenectomy. Whether adjuvant chemoradiotherapy would still offer a survival benefit after radical D2 lymphadenectomy is debatable. Also, these results need to be interpreted cautiously as only 20 % of patients had GEJ cancers (the remaining patients had gastric cancer). Finally, the morbidity of adjuvant chemoradiotherapy was considerable

with over 70 % patients experiencing a grade III/IV toxicity with the concurrent chemoradiotherapy regimen. We currently reserve the MacDonald regimen for unexpectedly node-positive disease after they had been operated without neoadjuvant treatment on a preoperative diagnosis of early stage (T1/2, N0) disease.

Adjuvant Chemotherapy

Adjuvant chemotherapy has been a strategy studied in a series of trials primarily conducted by the Japan Clinical Oncology Group (JCOG). The JCOG conducted a phase III randomised trial [48] assessing the role of adjuvant chemotherapy (5-fluorouracil/cisplatin) in patients with squamous-cell carcinoma of the thoracic esophagus. This multicentric trial was prematurely terminated for “slow accrual” after 242 of a target 290 patients were enrolled, with 122 patients randomised to surgery alone and 120 to surgery with adjuvant chemotherapy. The primary endpoint of 5-year disease-free survival was superior in the adjuvant chemotherapy arm (55 %; 95 % CI, 46 to 64 % vs. 45 %; 95 % CI, 36 to 54 %; $p=0.037$) compared with the surgery alone arm. Five-year overall survival was 61 % (95 % CI, 52 % to 70 %) in the postoperative chemotherapy arm compared with 52 % (95 % CI, 43 to 61 %) in the surgery alone arm ($p=0.13$). Two other randomised trials [49, 50] compared post-operative chemotherapy using cisplatin-based regimens to surgery alone in patients with SCC of the esophagus. However, none of these trials found an improvement in survival associated with the use of post-operative chemotherapy. These negative results were confirmed in a meta-analysis [51] of 1,001 patients with esophageal cancer (SCC and adenocarcinoma). The overall results of this meta-analysis showed that adjuvant chemotherapy did not significantly improve survival. A positive trend toward better survival was found in patients with lymph node metastasis, but this did not reach significance in a subset analysis. In another randomised trial by the JCOG [52], 330 patients with locally advanced esophageal SCC were randomised to adjuvant (166) or neoadjuvant chemotherapy (164) with cisplatin and 5-fluorouracil. In their updated analysis, the 5-year survival was superior in the neoadjuvant arm 55 % versus 43 % (hazard ratio 0.73, 95 % confidence interval 0.54–0.99, $p=0.04$). This study has resulted in neoadjuvant chemotherapy being the current standard of care in Japan.

Practice Patterns in India and the Tata Memorial Centre Experience

Multimodality treatment has been slow on the uptake in India for various reasons. Initially, there was lack of convincing evidence and even demonstrable lack of benefit [53], which

was responsible for surgery being the single modality of treatment till the late 1990s. However, even after growing evidence of the efficacy of multimodality treatment, there has been reluctance from treating physicians and surgeons to adopt it as standard of care. The reasons for this were manifold, including a perceived inability of patients to tolerate the toxicity of multimodality treatment. Other factors were predominantly socio economic, including patients not being able to afford expensive treatment and physicians considering 5–10 % survival benefits as “minor” improvements.

At the Tata Memorial Centre, paralleling the increasing volume of data supporting it, we have gradually moved from primary surgical treatment of resectable esophageal cancer towards multimodality treatment over the last decade. While only 23 % of patients operated in 2003 received neoadjuvant treatment, 93 % of patients operated for esophageal cancer in 2013 received neoadjuvant treatment prior to surgery. Currently, only patients with very early T1/T2, N0 disease stages confirmed on endoscopic ultrasonography are treated with upfront surgery. Our protocol is to administer three cycles of neoadjuvant platinum and taxane chemotherapy for squamous cancers and the MAGIC protocol (three cycles of ECF pre operatively and three cycles postoperatively) for adenocarcinomas of the lower third of the esophagus and the gastroesophageal junction. Our patients have been able to tolerate multimodality treatment without increase in postoperative complications. The reason for adopting NACT over NACTRT has been the clear benefits in survival seen with both these options and the higher postoperative morbidity and mortality with NACTRT in many trials. We are currently conducting a phase II randomised trial comparing NACT with NACTRT for squamous esophageal cancer (CTRI/2013/03/003497).

Summary

Outcomes of treatment of esophageal cancer have improved remarkably over the past two decades. The reasons for this improvement are multifactorial and include standardisation of surgical technique and enhanced recovery programmes, improvement in perioperative and critical care and the increased adoption of multimodality treatment. The role of adjuvant therapy is questionable with current evidence not supporting its routine use. Neoadjuvant chemotherapy or chemoradiotherapy prior to surgery is the standard of care in resectable esophageal cancer.

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