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CONTINUING EDUCATION– GASTROINTESTINAL ONCOLOGY

Should Multidisciplinary Treatment Differ for Esophageal Adenocarcinoma Versus Esophageal Squamous Cell Cancer?

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ABSTRACT Current treatment of locally advanced esophageal cancers (ECs) centres on a multimodal approach regardless of histology. While surgery remains the mainstay of curative intent therapy, its implementation alone results in suboptimal outcomes, which have improved significantly with the increased utilization of induction regimens comprising of concurrent chemoradiation (CRT) or chemotherapy alone followed by surgery. Due in large part to the positive results of the CROSS trial, neoadjuvant CRT has become the predominant standard applied in the West. However, the bulk of the data published to date suggests that a more nuanced approach to the management of locally advanced EC is required with respect to the application of radiation, which related to the differential sensitivity of esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (SCC) to radiation. While the latter demonstrates excellent radiosensitivity, which has translated into improved survival outcomes, the same cannot be said for patients with EAC who may be subject to greater toxicity without any benefit. Herein, the differential effectiveness of CRT in patients with EAC versus SCC is highlighted, with a focus on the randomized evidence to date.

Esophageal cancer (EC) remains an important cause of cancer-related mortality worldwide. It is currently the eighth most common cause of cancer-related death and its incidence, particularly that of esophageal adenocarcinoma (EAC) is increasing.[1–3] A diagnosis of EC, be it squamous cell carcinoma (SCC) or EAC implies a poor prognosis, which is in part related to the fact that the majority of patients present with advanced disease, perhaps as a result of a rich submucosal lymphatic network resulting in early radial and axial tumour spread along lymphovascular channels.[1] This observation portends an increased risk of systemic spread that ultimately limits survival in this patient population.[1] While surgery has remained the mainstay of disease management, its sole use in curative intent treatment has been disappointing in patients with locally advanced disease due to both locoregional and distant treatment failure.[4,5]

Given these clinical features, curative intent therapy in EC necessitates a multimodal approach.[4–6] Adequate local control is currently achieved though complete surgical resection with or without the addition of radiation. Systemic chemotherapy (CT), while facilitating complete resection, is administered to minimize the risk of systemic spread, which is the major determinant of long-term survival.[4,6–9] Thus, currently acceptable standards for the management of EC include preoperative concurrent chemoradiotherapy (CRT) followed by surgery, or neoadjuvant CT alone followed by surgery.[4–10] This being said, contemporary multimodal approaches to the management of EC tend to be applied based on stage alone, with minimal importance given to histology or tumour-specific features that may predict outcome. With respect to histology, inherent differences do exist. First, SCC tends to be more radiosensitive than EAC.[5,11] Second, patients who present with SCC tend to demonstrate worse perioperative outcomes. This has been attributed to older age, malnutrition and worse comorbid status due to the association with alcohol intake and smoking.[12] Conversely, EACs tend to be more radioresistant, with recent genetic evidence suggesting that these tumours are strikingly similar to chromosomal unstable variants of gastric cancers, and could be considered the same entity.[5,13,14] This distinction highlights differences in tumour biology and, by extension, natural history and response to therapy among the

histologic subtypes of EC. Given these differences, the questions as to whether a more nuanced treatment approach is reasonable in patients with EC arises. Specifically, should the multimodality approach to the management of locally advanced EC differ in patients with EAC and SCC? To answer this question, the effectiveness of current treatment regimens with respect to locoregional and systemic control in locally advanced EC patients will be reviewed. When reviewing the evidence to date, it is important to highlight that locoregional control is predominantly determined by the R0 resection rate after surgery and the magnitude of pathologic response following the administration of neoadjuvant therapy, be it CRT or CT alone. Systemic control, which is reflected predominantly in overall survival (OS), is thought to be determined for the most part by the effectiveness of systemic therapy.[6] Therefore, the discussion regarding whether or not one therapeutic regimen should be adopted over another depends on the efficacy of preoperative therapies in facilitating the achievement of an R0 resection and the ability of the therapeutic regimen to stave off the development of metastatic disease.

LOCOREGIONAL THERAPY

As previously stated, the efficacy of a given locoregional treatment is reflected by the ability to provide a subsequent R0 resection.[15] Whether the optimal strategy necessitates the addition of radiation therapy or CT alone remains a hotly debated topic. However, the esophagus is an organ that spans the upper abdomen, chest and neck, therefore, the optimal local therapeutic strategy in EC is influenced to some extent by the location of the primary tumour. Anatomic location dictates not only the portion of the esophagus necessitating resection but also the lymph node basins that need to be removed and/or radiated. This particular feature adds significantly to the complexity of local management in EC and complicates the interpretation of studies comparing the efficacy of CRT with CT alone. While both strategies, namely CT alone and CRT, increase R0 resection rates, the impact on survival is less obvious.[10,16–18] For example, strategies that confer excellent local effects will improve R0 resection rates without a dramatic improvement in OS, while highly effective systemic regimens may have a more modest impact on R0 rates, with a greater effect on OS.[10,16–18] This being said, some specifics regarding locoregional therapy warrant discussion in order to help conceptually frame the results of randomized controlled trials (RCTs) examining the efficacy of a given multimodal regimen.

LOCAL THERAPY

Proximal lesions, which are nearly exclusively esophageal SCCs (ESCCs) may necessitate concomitant laryngectomy if surgery is to be applied as the sole therapeutic modality for local control. This has led to the majority of centres adopting definitive CRT regimens in this context, with surgery resolved as a salvage option for patients with persistent or recurrent disease. Similarly, mid-esophageal lesions, in which ESCC again predominates, frequently abut the major airways, rendering surgical resection more complex. This has similarly led many centres to opt for a CRT regimen in order to facilitate R0 resection. However, in the same clinical context, local strategies employing surgery alone as local therapy have been reported, with excellent results. For example, in the recent small phase II trial by Ohnuma et al., 28 patients with locally advanced, predominantly middle-third ESCCs were treated preoperatively with triplet CT comprising a taxane, platinum and 5-fluorouracil. R0 resection was achieved in 100% of patients, highlighting the feasibility of this approach.[19] More distal lesions do not necessarily present the same anatomic challenges, with respect to surgical resection, as more proximal ones. Distal cancers tend to represent the predominant lesions treated in Western centres and are therefore overrepresented in contemporary trials.[4,11,17,18,20–25] Furthermore, the surgical approach selected, for example whether a transthoracic *en bloc* versus a transhiatal approach is employed, particularly in distal tumours, is highly variable and depends more on institutional experience than randomized data. Given this variability and the relative paucity of randomized trials comparing surgical approaches, it is imperative to assess the quality of the locoregional approach selected.

EXTENT OF LYMPHADENECTOMY

Optimal local control implies elimination of both the primary tumour and all draining lymphatic basins. Any effective regimen must take this into account, both from the standpoint of surgical resection and the delivery of radiation. The pattern of lymph node metastasis in EC is complex and differs according to histology and the location of the primary tumour.[26] In the East, where upper- and mid-esophageal squamous tumours predominate, optimal surgical management entails a three-field transthoracic approach,[26,27] which is based on the pattern of lymphatic spread observed in patients who harbour predominantly mid and proximal ESCCs. For example, in the study by Udagawa et al., the incidence of lymph node metastasis was determined following three-field esophagectomy in 906 patients with EC.[28] Of these, 861 had ESCCs, while

only 20 had EACs. In keeping with this observation, 648 patients harboured mid or proximal esophageal lesions, while the remaining 258 patients harboured distal lesions. In patients with upper-third lesions, cervical esophageal lymph nodes were involved in approximately 20% of patients, while lymph nodes along the recurrent laryngeal nerves were involved in approximately 30% of patients. Lesions located in the middle or distal third of the esophagus were associated with lymph node metastases in these locations approximately 10–15% of the time. Hence, involvement of cervical esophageal lymph nodes in patients with distal cancers compared with middle and proximal cancers was associated with significantly worse 5-year survival. Determining the incidence of lymph node metastasis according to lymph node station, and multiplying it by the 5-year survival observed in the cohort of patients, allowed for the calculation of the efficacy index (EI), a presumptive marker of the efficacy of lymph node dissection for a particular lymph node station. In keeping with the hypothesis of sequential nodal spread in EC, the EI for dissection of paratracheal and cervical nodes was greatest for patients with upper-third lesions, and declined steadily as tumour location migrated distally to the point that it is not considered routinely beneficial for patients with distal lesions. The overall results of the study were taken to indicate the relative efficacy of three-field dissection over a two-field dissection in patients with proximal and middle-third esophageal lesions, and helped establish this approach as a standard of care in Japan. The results of this study have since been corroborated in meta-analyses.[27]

Routine three-field esophagectomy has not been adopted in North America, and may be inappropriate given the predominance of distal EAC over ESCC.[29] The pattern of lymph node metastasis in patients with esophagogastric junction (EGJ) and distal EAC is associated with the Siewert classification.[30–35] Siewert I and distal third tumours demonstrate high rates of lymph node metastases involving the lower and middle mediastinal nodes in the range of 40–50%.[30–35] Upper mediastinal nodes are less frequently involved, particularly in patients with EAC, in the order of 5%.[30–35] Abdominal lymph nodes are the most frequently involved, accounting for approximately 40–50% of lymphatic metastases in these patients.[30–35] The most frequently involved abdominal nodes are those located along the lesser curvature of the stomach and along the left gastric artery, demonstrating involvement in approximately 20–30% of resected specimens.[30–35] The pattern of lymph node involvment in Siewert II tumours is similar, however nodal involvement within the abdomen is more common, while a concomitant decrease in the incidence of mediastinal disease is observed.[30–35] For example, in the study by Kurokawa et al., the pattern of lymph node metastasis

and lymph node recurrence in 315 patients with pT2-4 Siewert II EGJ adenocarcinoma was determined in a retrospective cohort study. Upper, middle and lower mediastinal nodal disease was observed in 4, 7 and 11% of resected tumours, respectively.[33] In addition, the incidence of nodal disease was directly related to the distance of the proximal edge of the tumour to the gastroesophageal junction (GEJ), reflecting, to some extent, local disease burden.[33] For example, tumours whose proximal edge was located > 3 cm from the GEJ exhibited relatively higher rates of upper and middle mediastinal node involvement compared with smaller lesions. Similarly, lower mediastinal node involvement was significantly increased in patients with tumours whose proximal edge was located > 2 cm from the GEJ. With respect to abdominal nodal involvement, Siewert II tumours have a predilection for lymph nodes located along the GEJ/hiatus, lesser curvature and celiac trunk.[33] Siewert III lesions demonstrate a pattern of node involvement more in keeping with true gastric tumours, with lower mediastinal node involvement observed in approximately 12% of patients, and higher rates of lymph node metastases involving the greater curvature and splenic artery, in the order of 10 and 15%, respectively.[30–35]

PATTERNS OF RECURRENCE

Recurrence following curative intent treatment remains the greatest obstacle to long-term survival in patients with EC.[36] In keeping with the variability in primary tumour location, lymphatic spread, and response to therapy observed among ESCC and EAC patients, recurrence patterns following curative intent therapy also differ according to histology.[37] Nevertheless, timing and patterns of recurrence are poorly described and poorly understood overall. This is in part due to differences in R0 resection rates seen in trials comparing neoadjuvant therapy with surgery alone in patients with locally advanced disease. This discrepancy makes the attribution of recurrence, particularly locoregional recurrence, to inadequate locoregional therapy tempting; however, the locoregional contribution of systemic therapy is difficult to ascertain in this context.[37] A follow-up study to the FFCD9901 trial addressed some of these issues by comparing recurrence patterns in patients with early-stage disease (T1 and T2 EC) who had similar R0 resection rates (> 90%).[37] While a locoregional benefit with respect to recurrence was observed in patients treated in the neoadjuvant setting, no distant benefit was observed.[37] Furthermore, patients with EAC tended to manifest more distant recurrences than patients with ESCC. Similarly, time to systemic recurrence was shorter in patients with EAC regardless of preoperative therapy.[37]

These histology-specific differences have been corroborated by additional studies.[38] For example, the large multi-institution retrospective review by Xi et al.[38] characterized patterns of treatment failure following multimodal treatment of EC using an induction CRT regimen. No significant differences in OS or recurrence-free survival (RFS) were noted; recurrence patterns differed markedly between the two groups. Overall, pathologic complete response rates, as expected, were higher in patients with ESCC compared with those with EAC (45% vs. 26%; $p < 0.001$). Furthermore, in patients who did not achieve pCR, locoregional failures were more frequent in patients with ESCC compared with those with EAC (16.7% vs. 6.3%).[38] Conversely, distant failures were more common in EAC patients (17.5% vs. 32.5%, respectively).[38] To some extent, this may account for the observation that cancer-specific mortality was higher in EAC patients (74.7%) compared with ESCC patients (70.5%). Along these lines, ESCC patients exhibited a greater predilection towards regional and supraclavicular lymph node recurrence compared with a higher rate of hematogenous spread identified in EAC patients. Nonetheless, significantly more EAC patients received salvage treatment compared with the ESCC group (74.4% vs. 57.7%, respectively).[38]

Collectively, the data presented thus far highlights the inherent differences in ESCC and EAC, with significant implications with respect to patient outcomes. Thus, the blanket application of any curative intent treatment regardless of histology is likely to provide a disservice to patients with EC as a whole. With this in mind, the results of contemporary RCT comparing curative intent regimens in patients with EC are reviewed in a histology-specific manner.

CHEMOTHERAPY IN ESOPHAGEAL CANCER

Contemporary CT regimens in the management of EC are structured around 5-fluorouracil and a platinum, administered as a doublet. Triplet therapies of various types have been applied over the years with contemporary regimens, including a taxane or anthracycline.[4,16,39] Objective response rates with these regimens tend to be in the range of 20–50% based on historical data, however significantly higher response rates for triplets have demonstrated response rates approaching 60% when looking at phase II studies.[16,40,41] In the perioperative setting, two strategies have been put forward in general with respect to the administration of CT. In the preoperative setting, patients are generally more able to tolerate CT, permitting completion of planned cycles.[42–44] Furthermore, therapy is administered with the tumour in situ and an intact blood supply, possibly improving its effectiveness.[45] Finally,

preoperative administration allows for an assessment of response to therapy, which in itself is a powerful prognostic factor. Conversely, administration in the postoperative setting is advantageous in that surgery is not delayed, mitigating the possibility of progression while patients undergo therapy and wait to recover for surgery.[45] Second, it allows for the omission of toxic therapies in patients who are potentially overstaged in the preoperative setting.[45,46] With this in mind, it is critically important to assess the effectiveness of preoperative CT followed by esophagectomy in patients with SCC and EAC alone.

CHEMOTHERAPY-ALONE SQUAMOUS CELL CARCINOMA (SCC)

To date, eight RCTs have been published relating to the application of perioperative CT versus surgery for patients with SCC alone (Table 1). These include the studies by Kelsen et al., Schlag, Law et al., Boonstra et al., Ancona et al., and all three trials by Ando et al.[8,42–44,47–50] Although the early trials were negative overall, important information regarding the efficacy of CT can be gleaned. Overall, the data strongly supports the notion that neoadjuvant CT, in particular with a regimen comprising 5-fluorouracil and cisplatin, improves the R0 resection rate and confers improved OS in patients with SCC compared with surgery alone. In the study by Kelsen et al., survival in patients who demonstrated a major (47%) or complete (5%) response to vinblastine-, cisplatin-, and bleomycin-based CT exhibited improved survival (median survival 20 months vs. 6 months; $p = 0.008$) compared with patients who did not. Patients who responded to preoperative therapy also fared better than patients who received surgery alone.[8] Similarly, Schlag demonstrated significant increases in survival for patients with SCC who demonstrated a response (minor 12%, major 32%, complete 6%) to three cycles of neoadjuvant cisplatin and 5-fluorouracil compared with surgery alone. Reduced recurrence rates, predominantly as a result of improved locoregional control in patients who received CT, were observed. This finding likely relates to higher R0 resection rates in CT-treated patients (67% vs. 35%; $p = 0.003$), although the surgical quality in this older trial might be called into question given the very low R0 resection rate in the resection-alone arm. In patients who demonstrated a response, median and 2-year survival times were improved (CT vs. surgery, 42.2 months vs. 13.8 months, $p = 0.008$; and 59% vs. 33%, respectively).[47] Ancona et al. randomized patients to two cycles of preoperative cisplatin and 5-fluorouracil or curative intent surgery alone. The combined complete pathologic and major response rate of resected tumours in the neoadjuvant arm was 40%, with a pCR rate of 12.8%.

TABLE 1 Randomized trials comparing preoperative chemotherapy versus surgery alone in patients with locally advanced esophageal squamous cell carcinoma

Study	Year	N	Histology	Regimen	R0	Response rate	Survival	P
Schlag et al.	1992	69	SCC	Cisplatin, 5FU 3 cycles preop. Re-staged after first cycle. If response 2 additional if no response surgery	44% versus 42%	50% pCR 6%	Median 8 mo versus 9 mo	NS
Law et al.	1997	147	SCC	Cisplatin, 5FU 2 preop cycles	67% versus 24%*	58% pCR 7%	Median 16.8 mo versus 13 mo	NS
							2 year 44% versus 21%	
Ando et al.	1997	205	SCC	Cisplatin, Vindesine 2 cycles postop	NA	NA	5 year 45% versus 48%	NS
Roth et al.	1998	36	SCC	Cisplatin, Vinblastine, Bleomycin	NA	47% pCR 5%	3 year 25% versus 5%	NS
				3 Cycles pre 3 Cycles Post			Median 10 mo versus 10 mo	
Ancona et al.	2001	96	SCC	Cisplatin, 5 FU 2 cycles preop + 1 additional if response	79% versus 74%	40% pCR 12.8%	Median 25 mo versus 24 mo	NS
							5 year 44% versus 22%	
Ando et al.	2003	242	SCC	Cisplatin, 5FU 2 cycles post op	100% (enrolment criteria)	38% pCR 7%	5 year 45% versus 55%	0.037
Boonstra et al.	2011	169	SCC	Etoposide, Cisplatin up to 4 preop cycles	71% versus 57%	23% pCR 7%	1 year 64% versus 52%	0.003
							5 year 26% versus 17%	
Ando et al.	2012	330	SCC	Cisplatin, 5FU 2 cycles pre OR post op	96% versus 91%*	NA	5 year 55% versus 43%	0.04

pCR pathologic complete response, *SCC* squamous cell carcinoma, *NS* non-significant, *NA* not available, *5FU* 5-fluorouracil, *preop* preoperatively, *postop* postoperatively

No difference in median survival was noted on an intention-to-treat basis (24 and 25 months for surgery alone vs. neoadjuvant CT, respectively). In the 40% of patients who demonstrated a major response to CT, a significant improvement with respect to median (53 months) and 3- (74%) and 5-year (60%) survival was observed compared with patients undergoing surgery alone (28 months, 46%, 26%, respectively; $p = 0.01$) and non-responders to CT (19 months, 38%, 19%, respectively; $p < 0.05$). In keeping with this theme, the survival benefit was most pronounced in the 12.8% of patients who demonstrated a complete response.[49] Boonstra et al. demonstrated a partial response rate of 40% and complete response rate of 7% following neoadjuvant CT. A significant survival advantage in patients receiving CT was noted (median, 2- and 5-year survival CT vs. surgery alone: 16 months vs. 12 months, 42% vs. 30%, and 26% vs. 17%, respectively; $p = 0.03$), relating to the fact that a greater proportion of CT-treated patients were ultimately found to harbour resectable tumours.[50]

In 2003, Ando and colleagues published a Japanese Clinical Oncology Group multi-institutional phase III trial investigating postoperative cisplatin and 5-fluorouracil in patients with completely resected SCC versus surgery alone. This positive study, with improved disease-free survival in the CT arm, lead to a follow-up study comparing the same regimen administered either pre- or postoperatively. In this study, preoperative versus postoperative CT was directly compared with surgery alone, highlighting the superiority of the former over the latter. Overall response rates to CT were 38%, which translated into fewer preoperative-treated patients being found to harbour T4 or N + tumours. Furthermore, significantly more patients who received neoadjuvant CT underwent curative (R0) resection (96% vs. 91%; $p = 0.04$). Patients in the adjuvant arm experienced increased toxicity and reduced completion (75% vs. 85%; $p = 0.04$) of therapy compared with patients in the adjuvant arm. OS was significantly improved in patients who received preoperative compared with postoperative therapy, with a 5-year survival rate of 55% versus 43% ($p = 0.04$).[43]

When these results are taken together, what becomes clear is that patients who receive preoperative therapy will benefit in terms of improved locoregional control, as evidenced by R0 resection, and systemic control, as evidenced by OS. Nonetheless, the magnitude of this benefit is directly proportional to the magnitude of their response. Overall response rates ranged from 23 to 58%, with Law et al. demonstrating the highest overall rate of the randomized studies.[48] Overall, the bulk of studies demonstrate

response rates in the 40–50% range.[8,42–44,47–50] Pathologic complete response rates were significantly lower, ranging from 6 to 12%, with the bulk of studies demonstrating rates below 10%.[8,42–44,47–50] Thus, the data demonstrate that in patients with SCC, meaningful responses to CT are observed in a significant proportion of patients and are associated with improved locoregional and systemic control.

CHEMOTHERAPY ALONE IN ESOPHAGEAL ADENOCARCINOMA (EAC)

With respect to EAC, only two randomized studies to date have been published examining the efficacy of preoperative CT followed by esophagectomy over esophagectomy alone in patients with advanced EAC (Table 2).[4,51] In the trials by Cunningham et al. (MAGIC) and Ychou et al., accrual was restricted to adenocarcinoma, but on both sides of the diaphragm, with more gastric than esophageal/EGJ in the MAGIC trial, and the reverse in the study by Ychou et al.[4,51]. The recently completed FLOT 4 trial has yet to be published, but, as in the MAGIC trial, recruitment was restricted to adenocarcinoma, and preliminary results are in keeping with the results of the randomized studies listed above. The trial by Kelsen et al., as well as the MRC/OE2 trials, recruited patients with mixed histology and are included here due to their relatively high proportion of patients with EAC

and information regarding response rates to CT.[9,52] The former was a negative trial; however, the remaining three were positive on an intent-to-treat basis, supporting the use of neoadjuvant CT over surgery alone in patients with locally advanced EAC. Therapeutic regimens included cisplatin and 5-fluorouracil-based doublets, with the exception of the Cunningham (MAGIC) trial, which administered triplet therapy encompassing an anthracycline in addition to cisplatin and 5-fluorouracil.[4] Most studies administered CT in the pre- and postoperative periods, with the exceptions being the MRC and Kelsen et al. trials, where CT was administered in the preoperative setting only.[9,52]

The trials by Ychou et al. and Cunningham et al. included patients with EAC of the oesophagus and stomach. Ychou et al. randomized patients, of whom 75% harboured lower oesophageal or GEJ tumours, to receive perioperative cisplatin and 5-fluorouracil versus surgery alone. Patients randomized to preoperative therapy demonstrated improved outcome with respect to the R0 resection rate (87% vs. 74%; $p = 0.04$) and OS (5-year survival CS vs. surgery alone: 38% vs. 24%; $p < 0.05$). Overall response rates to CT in this study were not assessed.[51]

In the study by Cunningham et al., patients with gastric and lower esophageal/GEJ tumours (25%) were randomized to receive perioperative CT with 5-fluorouracil, cisplatin and epirubicin. In patients receiving perioperative

TABLE 2 Randomized trials comparing preoperative chemotherapy versus surgery alone in patients with locally advanced esophageal adenocarcinoma

Study	Year	N	Histology	Regimen	R0	Response rate	Survival	P
MRC/OE2	2002/2009	802	SCC/EAC	Cisplatin, 5FU 2 cycles pre op	60% versus 54%*	NA	Median 16.8 mo versus 13.3 mo 2 year 43% versus 34%	0.004
Cunningham et al. (MAGIC)	2006	503	EAC	Epirubicin, Cisplatin, 5FU 3 cycles pre and post op	79.3% versus 70.3%*	NA	5 year 36% versus 29%	0.009
Kelsen et al.	2007	440	SCC/EAC	Cisplatin, 5FU 3 cycles preop	63% versus 59%	19% pCR 2.5%	5 year 19.4% versus 21%	NS
Ychou et al.	2011	224	GEJ AC	Cisplatin, 5FU 3 cycles prep, 3 cycles post	87% versus 73%*	NA	5 year 38% versus 24%	0.02
Al-Batran (FLOT4)	2016	716	EAC	ECF/ECX versus FLOT	NA	*43% pCR 6% versus 55% pCR 20%	Median OS 35 mo versus 50 mo 3 year OS 48% versus 57% Median PFS 18 mo versus 30 mo	0.004

*Unpublished data, response rates drawn from the previously published phase II/III trial by the same author[41]

pCR pathologic complete response, *EAC* esophageal adenocarcinoma, *SCC* squamous cell carcinoma, *OS* overall survival, *PFS* progression-free survival, *NS* non-significant, *NA* not available, *5FU* 5-fluorouracil, *preop* preoperatively, *postop* postoperatively, *ECF* epirubicin, cisplatin, and fluorouracil, *ECX* epirubicin, cisplatin and capecitabine, *GEJ* gastroesophageal junction, *AC* adenocarcinoma

therapy, an improvement in the R0 resection rate (CS vs. surgery alone: 79.3% vs. 70.3%; $p = 0.03$) and a tendency for smaller tumours and less advanced nodal disease was noted. In keeping with these findings, improved OS was noted in the CT arm compared with surgery alone (hazard ratio [HR] 0.75, 95 confidence interval [CI] 0.6–0.93, $p = 0.009$; 5-year survival 36.3% vs. 23%). Again, no pathologic response rates were reported.[4]

In the MRC/OE2 study, preoperative cisplatin and 5-fluorouracil was associated with a significant reduction in primary tumour size and regional lymph node positivity compared with specimens from untreated patients. This was associated with improved R0 resection rates (60% vs. 54%, $p < 0.001$) and OS (median and 2-year survival CS vs. surgery: 16.8 months vs. 13.3 months, and 43% vs. 34% respectively; HR 0.79, 95% CI 0.67–0.93, $p = 0.004$).[9]

Kelsen et al. randomized patients with both SCC and EAC, in approximately equal proportions, to three cycles of preoperative cisplatin and 5-fluorouracil or curative intent surgery alone. The complete response rate in patients receiving CT was 2.5%, with a major objective response observed in 19% of patients. In keeping with previous studies, survival was only improved in patients who demonstrated a major response (response vs. no response; HR 2.83, 95% CI 1.84–4.35, $p < 0.001$).[52]

The variability in outcomes noted in patients receiving CT alone is likely dependent, at least in part, on the variability observed in CT regimens. The Cunningham trial formed the basis for the recommendation of epirubicin, cisplatin, and fluorouracil (ECF) in patients with operable esophagogastric cancer. While randomized studies have cast doubt on the utility of 5-fluorouracil-based triplet with an anthracycline, phase II data have suggested that triplets including 5-fluorouracil and a platinum agent in conjunction with a taxane may provide improved treatment response over standard doublet therapies.[16,41,53] The results of the phase III RCT by Al-Batran et al. appear to confirm these findings. The FLOT-4 trial, which has been published as an abstract to date, randomized patients with locally advanced esophagogastric adenocarcinoma to three preoperative cycles of ECF versus four preoperative cycles of FLOT (docetaxel, oxaliplatin, 5-fluorouracil, leucovorin).[54] Patients randomized to the former demonstrated improved OS and progression-free survival (PFS) compared with ECF/ECX (epirubicin, cisplatin and capecitabine) (median OS: 50 months vs. 34 months, $p < 0.012$; 3-year OS: 57% vs. 48%; median PFS: 30 months vs. 18 months; $p = 0.004$). Although the response rates have not been reported to date in the FLOT 4 trial, the FLOT 3 trial, a phase II study in patients with advanced esophagogastric adenocarcinoma disease demonstrated impressive major response rates in the order of 60%, with pCR rates of 10%.[41]

The results of the randomized studies to date demonstrate that neoadjuvant CT in patients with locally advanced EAC improves both locoregional and systemic disease control, as evidenced by improved R0 resection rates, PFS and OS. Furthermore, OS is improved in patients who demonstrate a response to neoadjuvant therapy. Finally, as chemotherapeutic regimens become more effective, a concomitant improvement in outcomes could be expected.

CHEMORADIATION IN SCC

Radiation therapy has predominantly been utilized as an adjunct in the management of EC. Its contemporary implementation is based on its purported benefits with respect to improved R0 resection rates, improved rates of pCR compared with CT, and improved survival. Randomized studies have confirmed some of these effects in patients with SCC. The studies by Nygaard et al., La Prise et al., Bosset et al., Cao et al. and Lv et al. were all conducted exclusively in patients with SCC and are outlined in Table 3.[13,55–58] Pathologic complete response rates ranged between 10 and 26%. Nygaard et al., Bosset et al., Cao et al. and Lv et al. were all able to demonstrate improved R0 resection rates, ranging between 55 and 97.4% following neoadjuvant CRT.[13,55,57,58] All of these studies demonstrated an improvement in the R0 resection rate compared with surgery alone, which ranged between 37 and 80% across studies, with the low R0 rate in some studies again calling into question surgical quality.[13,55–58] Evidence of improved locoregional control in SCC patients can be further inferred from the results of these studies. Both Bosset et al. and La Prise et al. demonstrated a reduction in T3 and T4 tumours in patients treated with neoadjuvant CRT compared with those subject to surgery alone[13,56]. In addition, Bosset et al. demonstrated a reduction in N + disease in SCC patients following neoadjuvant RT in the order of 50%.[13] With the exception of the trial by Le Prise et al., all of these studies demonstrated a survival benefit in the order of 15% at 3–5 years.

CHEMORADIATION ADENOCARCINOMA

Neoadjuvant CRT has also demonstrated a benefit in patients with EAC, although the benefit is less pronounced than in patients with SCC. Only the study conducted by Walsh et al. recruited patients harbouring exclusively EAC. This was a positive study, demonstrating a pathologic complete response rate of 25% and a significant downstaging effect, with an approximate 50% reduction in node-positive disease following neoadjuvant CRT.[7]

TABLE 3 Randomized trials comparing preoperative chemoradiotherapy versus surgery alone in patients with locally advanced esophageal squamous cell carcinoma

Study	Year	Patients	Histology	Regimen	Response rate	R0	Survival	p
Nygaard et al.	1992	186 (88 XRT)	SCC	(1) Sx Alone (2) 2 cycles Cisplatin, Bleomycin Preop (3) 35 Gy Preop (4) Chemo + XRT	NA	(1) 37% (2) 44% (3) 40% (4) 55%	3 years (1) 19%, (2) 3%, (3) 21%, (4) 17% (1 + 2) 6% (3 + 4) 19%	Any XRT versus no XRT $p = 0.009$
Le Prise et al.	1994	104	SCC	Sequential 5FU, Csiplatin + 20 Gy	pCR 10.3%	NA	Median 10 mo in both groups	NS
Bosset et al.	1997	282	SCC	Sequential Cisplatin + 18.5 Gy	pCR 26% 25% N + versus 57% Sx alone	81% versus 69%*	Median survival 18.6 mo overall	NS
Cao et al.	2009	473	SCC	(1) Cisplatin, 5FU, Mitomycin + Sx (2) 40 Gy + Sx (3) 1 + 40 Gy (4) Sx Alone	(1) 1.7% (2) 15.2% (3) 22.3%*	(1) 86.6% (2) 95.7% (3) 98.3% (4) 73.3%*	3 year (1) 57.1% (2) 69.5% (3) 73.3% (4) 53.4%	Any XRT versus no XRT $p < 0.05$
Lv et al.	2010	238	SCC	Preop Cisplatin, Paclitaxel + 40 Gy versus Postop Cisplatin, Paclitaxel + 40 Gy versus Sx alone	NA	(1) 97.4% (2) 78% (3) 80%*	Median Preop 53 mo versus Postop 48 mo versus 36 mo Sx 5 year Preop 43.5% versus Postop 42.3% versus Sx 34%	$p = 0.004$ versus Sx alone

*Denotes statistical significance

XRT radiation therapy, *SCC* squamous cell carcinoma, *SX* surgery, *preop* preoperatively, *postop* postoperatively, *Chemo* chemotherapy, *5FU* 5-fluorouracil, *NA* not available, *pCR* pathologic complete response, *NS* non-significant

IS TREATMENT RESPONSE DIFFERENT IN PATIENTS WITH EAC VERSUS SCC

Five trials listed in Table 4 comparing outcomes following neoadjuvant CRT versus surgery alone were conducted in patients with mixed histology. The results of these studies predominantly indicate an improvement in SCC response to neoadjuvant CRT compared with EAC. Pathologic complete response rates in EAC in the studies by Urba et al., Shapiro et al., Burmeister et al., Van Hagen et al. and Bass et al. hovered around 25% (range 9–27%).[5,59–62] Conversely, the pCR rate in patients with squamous histology ranged between 24 and 49%. Even in studies enrolling patients with mixed histology, neoadjuvant CRT was associated with an improved R0 resection rate, ranging between 80 and 96%, compared with surgery alone.[5,59–62]

With respect to locoregional control, a differential response between SCC and EAC patients can similarly be appreciated.[5,59–62] Although the results of the CROSS trial (Van Hagen et al./Shapiro et al.) demonstrate a reduction in node-positive disease following neoadjuvant CRT (31% vs. 75% following surgery alone), this effect is clearly more pronounced in SCC.[5,61] pCR rates were in the order of 23%

in adenocarcinoma patients and 49% in patients with squamous histology. Bass et al. demonstrated node negativity in 85% of SCC patients following neoadjuvant CRT, versus 58% in EAC patients.[62]

The results with respect to OS in these studies are more varied. The first large phase III trial to definitively demonstrate a benefit of any form of neoadjuvant therapy was published by Walsh and colleagues.[7] The 3-year survival was improved by the addition of CRT, from 7 to 37%; however, this study has been heavily criticized for its surgical quality as the very low survival in the resection-alone arm does not meet international benchmark standards set by prior and subsequent trials.

Although a negative study, the trial by Bossett et al. assessed both local and systemic control and determined that the benefit using their CRT regimen was only effective with respect to local control, with no difference in systemic recurrence rates between both treatment arms. The authors demonstrated a significant reduction in node-positive disease following CRT, i.e. 25% versus 57% in patients treated with surgery alone. This was also associated with improved R0 resection rates of 81% compared with 67% following surgery alone; however, median survival was 18.6 months regardless of the addition of CRT.[63] Indeed,

TABLE 4 Randomized trials comparing preoperative chemoradiotherapy versus surgery alone in patients with locally advanced esophageal carcinoma—esophageal squamous cell and adenocarcinoma

Study	Year	Patients	Histology	Regimen	Response rate	R0	Survival	p
Urba et al.	2001	100	SCC/EAC	Concurrent Cisplatin, 5FU, Vinblastine + 45 Gy	pCR 28% pCR SCC 38% pCR EAC 24%	96% versus 90%*	Median 19.9 mo versus 17.6 mo 3 year 30% versus 16%	NS
Burmeister et al.	2005	257	SCC/EAC	Concurrent Cisplatin, 5FU + 35 Gy	pCR 16% pCR SCC 27% pCR EAC 9%	80% versus 59%*	Median 22.2 mo versus 19.3 mo	NS
Tepper et al.	2008	56	SCC/EAC	Cisplatin, 5FU + 50.4 Gy	pCR 40%	NA	Median 4.48 yrs versus 1.79 yrs 5 year 39% versus 16%	$p = 0.002$
Van Hagen/ Shapiro et al. (CROSS)	2012/ 15	368	SCC/EAC	Concurrent Paclitaxel, Carboplatin + 41.4 Gy	pCR 29% pCR SCC 49% pCR EAC 23%	92% versus 69%*	Median 49.4 mo versus 24 mo 5 year 47% versus 34%	$p = 0.003$
Bass et al.	2014	211	SCC/EAC	5FU, Cisplatin + 40 Gy	pCR SCC 31% pCR AC 25% 29% N + versus 64% sx alone	NA	Median 63.8 mo versus 23.41 mo	$p < 0.001$

*Denotes statistical significance

pCR pathologic complete response, *SCC* squamous cell carcinoma, *EAC* esophageal adenocarcinoma, *5FU* 5-fluorouracil, *AC* adenocarcinoma, *Sx* surgery, *NA* not available, *NS* non-significant

Urba et al. arrived at the same conclusion, with an approximate 60% overall systemic recurrence rate in both treatment arms as site of first recurrence.[59] Both of these negative studies highlight a recurring issue with this disease, i.e. the high rate of distant recurrence, suggesting that improvements in outcome might be achievable by enhancing systemic (hence CT) rather than local (radiotherapy) control.

The CROSS trial was one of the few studies to clearly demonstrate improved systemic control in patients treated with neoadjuvant CRT; however, the benefit depended on histology and was only significant in patients with SCC (HR for death of 0.75, 95% CI 0.56–1.01, on multivariate analysis at 5 years). There was a trend towards improved survival in EAC patients but this was not as pronounced and did not achieve statistical significance on multivariate analysis (HR 0.75, 95% CI 0.57–1.01). However, for the entire cohort of patients, the HR for distant recurrence was 0.63 (95% CI 0.46–0.87). Similarly, Bass et al. demonstrated a durable improvement in survival for both EAC and SCC patients following neoadjuvant CRT, with follow-up times of over 200 months. This suggests at least some element of systemic control, which is thought to be due to the systemic effects of the CT administered with radiation.[5]

In keeping with the observation that neoadjuvant CRT is more effective in patients with ESCC, the results of the study by Lv et al. demonstrate improved survival in patients receiving neoadjuvant CRT compared with patients undergoing radical resection alone.[58] The survival benefit was noted up to 10 years, indicating a higher rate of cure (24.5% neoadjuvant CRT vs. 12.5% surgery alone; $p = 0.04$). Furthermore, significantly more patients in the surgery-alone arm died as a result of systemic recurrence than patients receiving neoadjuvant CRT (38% vs. 25%; $p = 0.011$). A similar finding was noted by Burmeister et al. in which 5-year PFS rates were significantly improved following CRT compared with surgery alone at 5 years in patients with squamous histology, but not in patients with adenocarcinoma.[60] This is consistent with a common message emerging from these studies suggesting that CRT prior to surgery is more effective for squamous cell histology than for adenocarcinoma.

CHEMOTHERAPY VERSUS CHEMORADIOTHERAPY

Randomized trials directly comparing neoadjuvant CRT with perioperative CT alone are outlined in Table 5. All of the studies published to date are negative with respect to demonstrating a clear survival benefit of one regimen over another. Furthermore, these studies suffer from several drawbacks, such as low accrual, low power and no inclusion of *en bloc* esophagectomy. Three additional studies

TABLE 5 Randomized trials comparing preoperative chemoradiotherapy versus chemotherapy alone in patients with locally advanced esophageal carcinoma—esophageal squamous cell and adenocarcinoma

Study	Year	N	Histology	Regimen	Response rate	R0	Survival	p
Stahl et al.	2009	119	GEJ/ EAC	Chemo 2 cycles Cisplatin, 5FU CRT: 2 cycles Cisplatin, 5FU + Cisplatin, 5FU, Etoposide + 30 Gy (concurrent)	Chemo: pCR 2% CRT: pCR 15.6%*	69.5% versus 72%	Median 21.1 mo versus 33.2 3 year 27.7% versus 47.4%	NS closed early due to poor accrual
Burmeister et al.	2011	75	EAC	Chemo: 2 cycles Cisplatin, 5FU CRT: 2 cycles Cisplatin, 5FU + 35 Gy	Chemo: pCR 0% CRT: pCR 13%*	80.5% versus 84.6%*	Median 26 mo versus 32 mo 5 year 36% versus 45%	NS
Klevebro et al.	2016	181	SCC/ EAC	Chemo: 3 cycles Cisplatin, 5FU CRT: 3 cycles Cisplatin, 5FU + 40 Gy	Chemo: pCR 9% CRT: pCR 28%*	74% versus 87%*	3 year 47% versus 49%	NS
Nakamura et al. (JCOG1109)	2013	501 (target)	NA	Arm A: 2 cycles preop Cisplatin 5FU Arm B: 3 cycles preop Docetaxel, Cisplatin, 5FU Arm C: 2 cycles preop Cisplatin, 5FU + 30 Gy	NA	NA	NA	NA
Reynolds et al. (NeoAEGIS)	2017	594 (target)	NA	MAGIC versus CROSS	NA	NA	NA	NA
Leong et al. (TOPGEAR)	2015	752 (target)	NA	Chemo: 3 cycles Epirubicin Cisplatin 5 FU 3 cycles pre 3 cycles post CRT: 2cycles ECF pre + 45 Gy + 3 cycles ECF post	NA	NA	NA	NA

*Denotes statistical significance

pCR pathologic complete response, *SCC* squamous cell carcinoma, *GEJ* gastroesophageal junction, *EAC* esophageal adenocarcinoma, *NA* not available, *5FU* 5-fluorouracil, *Chemo* chemotherapy, *CRT* chemoradiation, *preop* preoperatively, *postop* postoperatively, *ECF* epirubicin, cisplatin, and fluorouracil, *NS* non-significant

are underway and are included in Table 5, including the JCOG1109, NeoAEGIS and TOPGEAR studies, which may shed additional light on the utility of CRT versus CT in this patient population.[24,64,65]

Stahl et al. randomized patients with distal one-third and EGJ adenocarcinoma to receive preoperative CT with cisplatin and 5-fluorouracil or preoperative concurrent CRT with the same regimen in addition to 30 Gy of radiation. In total, 126 patients were enrolled, with 64 patients randomized to CT and surgery and 62 randomized to CRT, however the trial was terminated early due to poor accrual. Patients receiving CRT demonstrated improved pCR (15.6% vs. 3%; $p = 0.03$) and a node-negative surgical specimen (36.7% vs. 64.4%; $p = 0.01$). However, the important metrics of efficacy mentioned above, as well as R0 resection rate and OS, did not differ significantly.[66]

In the study by Burmeister et al., patients with oesophageal or EGJ adenocarcinoma were randomized to a 5-fluorouracil/cisplatin-based regimen, either alone or in conjunction with 35 Gy of radiation. Overall, 75 patients were randomized, with 36 receiving CT and 39 receiving CRT prior to surgery. As in the study by Stahl et al., the study was terminated early due to poor accrual. The R0 resection rate was comparable at 80.5 and 84.6% in patients receiving CT or CRT, respectively. The pCR rate was 13% in patients who received CRT versus 0% in those who received CT alone; however, this difference was not associated with reduced locoregional, distant recurrence or survival benefit.[67]

In a phase II trial from Sweden, Klevebro et al. randomized 181 patients to three cycles of cisplatin and 5-fluorouracil with or without concomitant 40 Gy of radiation. The study predominantly included patients with EAC, however nearly one-third had squamous histology. As in the prior two studies, pCR was increased in patients receiving neoadjuvant CT compared with CT (22% vs. 9%; $p = 0.002$). Similarly, pCR was associated with negative regional nodes on final pathology in 90% of patients. Accordingly, 35% of CT-treated patients were found to be node-negative, compared with 65% of CRT patients, despite a 63% rate of node positivity on initial staging in both groups; however, this did not translate into a survival benefit on an intention to treat or per protocol analysis. Subgroup analysis for survival based on histology, showed that patients with SCC did slightly better with chemoradiation, and patients with adenocarcinoma did slightly better with CT. Although none of these subset analyses were significantly positive, they do confirm the trends that were seen in the prior studies looking at CT or chemoradiotherapy versus surgery alone. Furthermore, a trend towards increased severe postoperative complications was appreciated.[10]

A recently published systematic review and meta-analysis further supports the hypothesis that treatment efficacy is affected by the underlying tumour histology. Deng et al. identified five studies from the literature to date specifically outlining tumour response rates and survival data based specifically according to underlying histology.[68] This feature allowed for the direct comparison of outcomes according to treatment within a given histology. The studies included those by Nygaard et al., Stahl et al., Burmeister et al., Cao et al., and Klevboro et al. As stated previously, the studies by Nygaard et al. and Cao et al. were conducted exclusively in patients with ESCC. Both studies demonstrated improved locoregional control, as evidenced by R0 resection rates, and pCR, as demonstrated by the Cao et al. study.[55,57] Furthermore, both studies demonstrated improved 3-year survival following the addition of CRT to any induction regimen compared with surgery alone. In conjunction with the three randomized studies above, overall analysis of the published series to date reveals no improvement in OS rates in patients with EAC following the addition of radiation therapy to CT alone and surgery.[68] Pooled estimates of survival following CRT compared with CT alone did not reach statistical significance in patients with EAC (relative risk [RR] 1.13, 95% CI 0.88–1.45). In keeping with randomized studies to date, this was not observed in patients with SCC, where a survival benefit was appreciated (RR overall 3-year survival 1.31, 95% CI 1.06–1.43). The addition of radiation was associated with improved locoregional control in both EAC and SCC, as evidenced by increased R0 resection rates (EAC: 1.18, 95% CI 1.07–1.30; SCC: 1.14, 95% CI 1.04–1.24) and pCR (EAC: 4.69, 95% CI 1.92–11.45; SCC: 6.73, 95% CI 2.81–16.12). The results of this most recent analysis are important as they are the first to suggest the implementation of alternate treatment strategies depending on tumour histology in patients with EC. While clearly demonstrating the superiority of neoadjuvant therapy, be it CRT or CT alone, over surgery alone in patients with locally advanced tumours, previous meta-analyses have yet to delineate the superiority of one regimen over another.[69]

CONCLUSIONS

ESCC and EAC represent distinct clinical entities that exhibit a differential response to currently recommended multimodal treatment regimens. In particular, the radiosensitivity of SCC highlights the efficacy of regimens that implement it in the preoperative setting, with some strategies challenging the use of surgery altogether in selected patients.[11] The converse appears to be true in

patients with EAC. In this context, no improvement following the addition of CRT over surgery and CT alone has been clearly demonstrated in studies to date.[68] Furthermore, some studies suggest that in patients with EAC, CRT regimens may be associated with more severe postoperative complications without conferring a clear survival benefit.[10,68,70] In any event, ongoing improvements in locoregional control seem to confer minimal improvements in OS, which is ultimately determined by effective systemic control. This is reflected through the efficacy chemotherapeutic regimens in both histologies. These differences in treatment response highlight inherent differences in tumour biology. Current treatment regimens in both predominant histologies fail to target these differences specifically, and this is reflected in the ongoing poor survival outcomes in locally advanced EC overall. A more nuanced approach to EC, with a focus on effective systemic control, is therefore critical. The emergence of novel therapeutic strategies such as targeted therapies and immune modulation are based on underlying biology as opposed to histology alone and hold promise for the improvement in patient survival in the future.

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