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TOPIC HIGHLIGHT

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Multidisciplinary approach for patients with esophageal cancer

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Abstract

Patients with esophageal cancer have a poor prognosis because they often have no symptoms until their disease is advanced. There are no screening recommendations for patients unless they have Barrett's esophagitis or a significant family history of this disease. Often, esophageal cancer is not diagnosed until patients present with dysphagia, odynophagia, anemia or weight loss. When symptoms occur, the stage is often stage Ⅲ or greater. Treatment of patients with very early stage disease is fairly straight forward using only local treatment with surgical resection or endoscopic mucosal resection. The treatment of patients who have locally advanced esophageal cancer is more complex and controversial. Despite multiple trials, treatment recommendations are still unclear due to conflicting data. Sadly, much of our data is difficult to interpret due to many of the trials done have included very heterogeneous groups of patients both histologically as well as anatomically. Additionally, studies have been underpowered or stopped early due to poor accrual. In the United States, concurrent chemoradiotherapy prior to surgical resection has been accepted by many as standard of care in the locally advanced patient. Patients who have metastatic disease are treated palliatively. The aim of this article is to describe the multidisciplinary approach used by an established team at a single high volume center for esophageal cancer, and to review the literature which guides our treatment recommendations.

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Key words: Esophageal Cancer; Multimodality therapy; Multidisciplinary therapy; Chemoradiotherapy; Esophageal resection; Esophagectomy

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INTRODUCTION

Esophageal cancer is a growing epidemic with approximately 460 000 new diagnosis and 380 000 deaths annually worldwide[1,2]. Adenocarcinoma has increased in incidence while the incidence of squamous cell esophageal carcinoma has decreased in the Western world. This seems to be linked to gastroesophageal (GE) reflux disease and Barrett's esophagus[3-7]. The prognosis for these patients is generally poor because of the advanced stage at the time of presentation. The increase in use of pro-

ton-pump inhibitors over-the-counter has also decreased the impetus to seek physician assistance for reflux symptoms. Hence most of these patients will be diagnosed at a late stage, with approximately 50 percent of patients have advanced unresectable or metastatic cancer[7]. Most patients are not considered curable at diagnosis and are treated with chemotherapy and radiation, mostly with palliative intent. In patients who are fortunate enough to have potentially resectable disease, the data are not clear as to the best approach. Patients with very early disease may only require endoscopic mucosal resection or surgical resection. Others are treated with a combination of chemotherapy plus radiation (chemoradiation) plus surgery if they are deemed resectable. Ideally, we would like to have large randomized trials that were powered properly to support our treatment plans. As these studies do not exist in the esophageal cancer world, we are left to rely mainly on meta-analysis, small randomized trials, and historical reports to make decisions for our patients. These treatments require specialists from surgery, medical oncology, radiation oncology, and gastroenterology. It is imperative that these individuals work in a multidisciplinary fashion in order to deliver comprehensive care. The goal of this paper is to discuss the approach of an established multidisciplinary team in the treatment of patients with locoregionally advanced disease.

EVALUATION OF THE PATIENT

To obtain an adequate volume of tissue for diagnosis, a minimum of 7 core/pinch biopsy specimens in addition to brushings are recommended at the time of endoscopy. This approach improves the accuracy of diagnosis to 98%-100%[7]. In addition, it provides tissue for molecular marker analysis, as cancer therapy is beginning to focus on targeted therapies which may require tumor marker analysis. Staging studies should include a computed tomography of the chest and abdomen, a position emission tomography (PET) scan and endoscopic ultrasound by a specialized gastroenterologist trained and proficient in this technique. Biopsies should be obtained from suspicious lymph nodes if accessible. An esophagram is also helpful in determining the degree of esophageal stricture. With the seventh edition American Joint Committee on Cancer Staging System, it is imperative to determine the histology of the tumor and number of lymph nodes involved. In patients who have respiratory symptoms, a bronchoscopy should be done to evaluate for tracheoesophageal fistula formation. In patients with other pulmonary or abdominal findings on imaging studies, one may wish to pursue thoracoscopy or laparoscopy. In addition, it is important to assess the performance status, the nutritional status and the patient's comorbidities of prior to determining an appropriate treatment plan.

TREATMENT APPROACHES

Treatment of cT1-2N0 disease

Surgery alone remains the standard of care for patients with local disease (cT1N0 and some cT2N0 tumors). At our institution and other high volume institutions, patients with T1aN0 tumors are treated with minimally invasive techniques such as endoscopic mucosal resection. There is limited experience with the use of radiation or chemoradiotherapy in the curative setting for patients with cT1N0 disease[8]. Thirty-four patients with either medically inoperable disease or refused surgery were treated with external beam alone (64 Gy) or external beam (52 Gy) plus 8 to 12 Gy with brachytherapy. The median follow-up was 61 mo, 5-year survival was 59%, 68% local relapse-free survival, and 80% cause-specific survival[8].

For most cT2N0 tumors, surgery alone may not be sufficient since approximately 50% of patients may have lymph node metastasis[9-12]. However, if the nodes are negative (pT2N0m0) there is no role for postoperative adjuvant chemotherapy or chemoradiation.

Treatment of cT3-4 and/or N positive disease

There remains much controversy in what is considered the current standard of care for patients with locally advanced esophageal cancer (cT3-4 and or N positive)[13-15]. Initially, surgical resection was the main modality for esophageal cancer treatment. Since the 1980's, studies have evaluated the utility for perioperative chemotherapy, postoperative and more commonly preoperative chemoradiation to improve outcome. These studies have been criticized for a variety of insufficiencies including inadequate power, the type of chemotherapy regimen, the dosing of chemotherapy, the radiation dose and fraction size, radiation delivery schedules, number of patients enrolled, initial staging, multiple organ sites and histologic subtype. At our institution, we advocate the use of neoadjuvant chemoradiotherapy based on the following data.

DO PATIENTS BENEFIT FROM NEOADJUVANT RADIATION?

There have been five phase Ⅲ trials which evaluated neoadjuvant radiation in esophageal cancer. None of the studies have demonstrated an increase in overall survival or resectability of esophageal cancer patients treated with radiation alone[16-20]. Nygaard *et al*[19] reported a 3-year overall survival benefit only after adding patients who also received chemotherapy to the statistical analysis. A meta-analysis of neoadjuvant radiation revealed a trend toward improved 5-year overall survival but failed to show a statistically significant survival advantage[21]. Data do not support the use of radiation as a single modality in the neoadjuvant treatment of esophageal cancer (Table 1). The role of radiation alone should be limited to palliation.

DO PATIENTS BENEFIT FROM PERIOPERATIVE CHEMOTHERAPY?

Neoadjuvant or perioperative chemotherapy has also

Table 1 Randomized trials of neoadjuvant radiation in esophageal cancer

Ref.	Histology	*n*	Rad dose (Gy)	2-yr survival, %	5-yr survival, %
Launois *et al*[18]	SCC	57	-	11.5	NR
		67	39-45	9/5	NR
Gignoux *et al*[17]	SCC	106	-	10	9
		102	33/12	16	10
Wang *et al*[20]	NR	102	-	33	30
		104	40	37	35
Nygaard *et al*[19]	SCC	50	-	NR	9 (3 yr)
		58	35 (4 wk)	NR	21 (3 yr)
Arnott *et al*[16]	SCC	86	-	NR	17
	AC	90	20 (10 d)	NR	9

SCC: Squamous cell carcinoma; NR: Not reported; AC: Adenocarcinoma.

been evaluated in patients with locally advanced gastric and GE cancer. At least five phase Ⅲ trials have compared cisplatin-based regimens to surgery alone in esophageal cancer and three studies showed a survival advantage (Table 2)[22-26]. The Medical Research Council trial is the largest of these studies as it randomized 802 patients with esophageal adenocarcinoma or squamous cell carcinoma. There was a 5-year overall survival advantage of approximately 6%[24]. The Magic trial randomized 503 patients, predominately gastric cancer patients, and demonstrates a 5-year overall survival advantage of 13%[22]. The French Cooperative Group study randomized 224 predominately gastric cancers with a survival advantage of 14% at 5 years[26]. All of these studies noted no evidence of increased morbidity or mortality in patients who received neoadjuvant chemotherapy. Many studies that evaluated perioperative chemotherapy have shown some overall survival benefit. This is evident in Gebski's meta-analysis that evaluated 1724 patients who received chemotherapy and surgery versus surgery alone in 8 trials. Of note was a 7% absolute benefit in 2 years survival ($P = 0.014$) in adenocarcinoma patients only[27]. These data are complicated because only 2 of the studies evaluate only esophageal cancer[23,24]. While we feel there is some benefit to perioperative chemotherapy, we do not advocate its use as the data suggest neoadjuvant chemoradiotherapy to be superior in esophageal cancer.

DO PATIENTS BENEFIT FROM CONCURRENT CHEMORADIOTHERAPY?

Chemotherapy combined with radiation enhances the effects of radiation by synergistically damaging the DNA following cell cycle synchronization[28,29]. Chemotherapy theoretically also reduces the risk of distant metastatic disease by eradication of micrometastases[30]. Chemoradiation is useful in both the neoadjuvant setting for all esophageal cancer patients or in the adjuvant setting for patients with GE junction tumors. Additionally, in patients who are not surgical candidates chemoradiation may be used as definitive treatment[31]. Ideally, concurrent chemoradiation should be done by a multidisciplinary group proficient in these procedures as many situations may result in a less favorable outcome. Situations which may occur include unnecessarily missed chemotherapy or radiation doses for complications which could be managed by groups more experienced in this technique. Additionally, the use of unconventional chemotherapy or radiation regimens or erroneous staging studies may also be problematic.

Initially, concurrent chemoradiation was evaluated as definitive treatment for patients who were not surgical candidates in the Radiation Therapy Oncology Group (RTOG) 85-01 trial[31]. In this study 134 patients were randomized to cisplatin combined with infusional fluorouracil and concurrent radiation or to radiation alone. The patients predominately had esophageal squamous cell carcinoma. Interim analysis revealed that a statistically significant survival advantage favoring concurrent chemoradiotherapy hence changing the treatment paradigm in inoperable locally advanced esophageal cancer. The 5-year overall survival was 27% *vs* 0% with radiation alone[31]. Despite the reduction in the risk of persistent disease or local recurrence with concurrent chemoradiotherapy compared to radiation alone, the incidence of locoregional failure was a dismal 47%[31]. Hence, in an effort to reduce locoregional failure, radiation dose was then addressed by the INT 0123 trial[32]. A total of 236 patients were randomized to high (68.4 Gy) or low (50.4 Gy) dose radiation all given with concurrent cisplatin and infusional fluorouracil per the RTOG 85-01 regimen. An interim analysis failed to reveal a local control or survival benefit with high dose radiation hence, 50.4 Gy has become standard of care for both neoadjuvant and definitive radiotherapy[32].

Patients with esophageal cancer have unacceptably high locoregional failure rates of approximately 50% with chemoradiation and a dismal prognosis of 20%-25% at 5 years with surgery alone[23,33-35]. Based on the limited success of these two approaches, a number of studies evaluating the combination of chemoradiation and surgery were developed.

DO PATIENTS BENEFIT FROM SURGERY?

Surgery has been considered an essential part of the treatment of patients with esophageal carcinoma[36]. Past experiences showed that a nonsurgical approach was associated with mediocre survival results[37]. However, the better survival achieved with surgical therapy may have a high price. In 1980, Earlam *et al*[38] reviewed the literature and reported 29% mortality for esophagectomy. Today, some still quote these numbers as a justification for nonsurgical approach to esophageal cancer, stating if a patient with esophageal cancer may either die by the tumor or die by the knife. However, it is hard to believe that these numbers remain true after significant improvements in antibiotics, intensive care, surgical equipment, and technique. Additionally, developments in chemotherapy and radiotherapy have occurred as well.

What is the best surgical technique?

There are 3 different basic approaches for esophagectomy: (1) transhiatal; (2) transthoracic; and (3) *en bloc* or radical. The transhiatal approach has a theoretical advantage of a decreased morbidity and mortality due to the avoidance of a thoracotomy (and thus, a decreased operative time and pain). Even though concern has been raised about lesser oncologic radicality, several studies compared the outcomes for transhiatal versus transthoracic esophagectomy. Two meta-analysis in 2 different decades (2001 and 2011) showed no differences in survival comparing these two approaches[39,40]. The transthoracic group; however, had significantly more respiratory complications, wound infections, and early postoperative mortality, whereas anastomotic leak, anastomotic stricture, and recurrent laryngeal nerve palsy rates were significantly higher in the transhiatal group. Population studies reached the same conclusions. Chang *et al*[41] evaluated a pool of 868 patients from the American Surveillance, Epidemiology, and End Results-Medicare linked database (1992 to 2002) with similar results. Additionally, Connors *et al*[42] consulted the registries of 17 395 patients from the American Nationwide Inpatient Sample database and found similar outcomes for both procedures.

The need for lymphadenectomy (radical esophagectomy) is an ongoing debate in esophageal surgery. Also, it is unclear if the patients that may benefit from these procedures are the ones with early cancer or locally advanced tumors. Moreover, the extent of the lymphadenectomy (1 field-thoracic, 2 fields- thoracic and abdominal, 3 fields-thoracic, abdominal and cervical) is a controversial topic. The lack of randomized trials addressing this issue increases the controversy. Although some studies showed better survival after *en bloc* esophagectomy others showed results similar to a transhiatal esophagectomy[43,44]. Morbidity and mortality for this procedure is not always reported; however, it seems to be high, especially in 3-field[45].

Minimally invasive surgery has the advantages of better cosmetic results, reduced operative stress, postoperative immobility, and pain. As far as we are aware, no randomized controlled trials have compared minimally invasive and open esophagectomy to date. Available data, including 3 recent meta-analysis suggests that minimally invasive esophagectomy is similar to conventional esophagectomy in terms of complications, oncologic radicality and survival[46-49].

Modern outcomes for mortality and survival

Different studies from experienced centers show a rate of mortality close to 0 in patients with non-advanced or even advanced tumors[50-53]. The application of standardized protocols with a multidisciplinary team improved significantly the outcomes of esophagectomy. It is not easy to access the survival related to esophagectomy only since most series of surgery alone are related to initial cancer and most surgeons refer patients to neoadjuvant or adjuvant chemotherapy[54]. However, patients with potentially resectable tumor not referred for surgery have a lower survival rate[55].

Relationship between volume and outcomes

Different papers repeatedly reported better outcomes for esophagectomy in high volume centers[42,56,57]. This better results may be attributable to surgeons' experience, since a decrease in more than 50% in the index of complications following esophagectomy is observed when the operation is performed by surgeons experienced in more than 100 esophagectomies[58]. However, hospital volume is also important, since the preparedness of the multidisciplinary team and hospital services to attend esophagectomy patients is crucial to better outcomes. Even low volume hospitals with high nurse ratios, lung transplantation services, complex medical oncology services, bariatric surgery services, and positron emission tomography scanners have lower mortality rates compared with low-volume hospitals with none of these characteristics[59]. Very interestingly, survival was not linked to volume[60].

DO PATIENTS WHO UNDERGO SURGERY BENEFIT FROM NEOADJUVANT CHEMORADIATION?

To date, there have been eleven randomized trials performed evaluating the utility of neoadjuvant chemoradiotherapy added to surgery (Table 3). These trials have incorporated a variety of chemotherapy regimens, doses and fraction sizes of radiation and timing of both chemotherapy and radiation. Of these studies only 3 have shown a benefit with concurrent chemoradiotherapy. The CALGB 9781 study randomly assigned patients to cisplatin, infusional fluorouracil with concurrent radiation and surgery or to surgery alone. The study was unable to adequately accrue due to patient and investigator bias favoring the neoadjuvant arm. Despite the lack of accrual in this study there was an impressive five-year overall survival of 39% with multimodality treatment and 16% with surgery alone (P = 0.002)[61]. The study performed by Walsh *et al*[62] randomized 113 patients with adenocarcinoma to cisplatin, infusional fluorouracil and radiotherapy followed by surgery or to surgery alone. The median overall survival was 16 mo with multimodality treatment and 11 mo with surgery alone (P = 0.01). Three-year survival of 32% with multimodality treatment and 6% with surgery alone (P = 0.01). This study has been criticized for inadequate radiation dose, inadequate fluorouracil dose, survival in the control arm lower than historical controls, and lack of adequate staging prior to chemoradiotherapy[62]. The CROSS trial has been reported in abstract form by van der Gaast *et al*[63]. A total of 363 patients with adenocarcinoma or squamous cell carcinoma were randomized to preoperative paclitaxel/carboplatin plus 41.4 Gy *vs* surgery alone.

Table 2 Randomized trials of peri-operative chemotherapy in gastric and esophageal cancer

Ref.	Histology	Regimen	*n*	Resection	pCR	5-yr survival %	*P* value	Median survival (mo)
Kelson *et al*[23]	SCC (45%)	S	227	59%	NA	23 (3 yr)	NS	16.1
	AC (55%)	CF→S→CF	213	62%	2.50%	26 (3 yr)		14.9
Cunningham *et al*[22]	AC - Gastric	S	253	66%	NA	23	0.009	20
	25% GEJ	ECF→S→ECF	250	69%	0%	36		24
MRC *et al*[24]	SCC (35%)	S	402	54%	NA	17	0.004	13.3
	AC (65%)	CF→S	400	62%	NA	23		16.8
Roth *et al*[25]	AC/SCC	S	20	NR	NR	5	NS	9
		BVC→S	19			25		9
Ychou *et al*[26]	AC							
	75% GEJ	S	111	111	NA	24	0.02	NR
	25% Gastric	CF→S→(CF)	113	113	NR	38		NR

CF: Cisplatin and 5-fluorouracil; SCC: Squamous cell carcinoma; ECF: Epirubicin, cisplatin and 5-fluorouracil; AC: Adenocarcinoma; NA: Not Applicable; GEF: Gastroesphageal junction/distal esophagus; NR: Not recorded; NS: Not significant; S: Surgery; BVC: Bleomycin, vindesine, cisplatin; pCR: Protein catabolic rate; GEJ: Gastroesophageal junction.

Table 3 Randomized trials of neoadjuvant combined modality therapy for esophageal cancer

Ref.	Cell type	*n*	Total dose (Gy)	5-yr survival, %	Median survival (mo)	*P* value	Criticism
Nygaard *et al*[19]	SCC	47	BP + 35 + surg	11.5 (3 yr)	8	NS	Unconventional chemotherapy and low dose RT
		41	Surgery	9.5 (3 yr)	7		
Bosset *et al*[34]	SCC	143	P + 37 + surg		19	NS	Split course RT and unconventional chemo schedule
		139	Surgery	9	19		
Tepper *et al*[61]	SCC (25%)	30	PF + 50.4 + surg	39	54	< 0.001	Only 56 of 475 planned patients entered
	AC (75%)	26	Surgery	16	21		
Walsh *et al*[62]	AC (100%)	58	PF + 40 + surg	32 (3 yr)	16	< 0.05	Only 6% 5 yr survival benefit with surgery alone
		55	Surgery	6 (3 yr)	11		
Gaast *et al*[63]	SCC (25%)	175	Carbo/tax + 41 + surg	59 (3 yr)	49	< 0.001	Only 41 Gy RT
	AC (75%)	188	Surgery	48 (3 yr)	26		
Le Prise *et al*[85]	SCC	41	PF + 20 (split) + surg	19 (3 yr)	10	NS	Only some patients received split course radiotherapy
		45	Surgery	14 (3 yr)	10		chemotherapy
Apinop *et al*[86]	SCC	35	PF + 20 + surg	24	10	NS	Low dose RT
		34	Surgery	10	7		
Lee *et al*[87]	SCC	51	PF + 45.6 (*bid*) +surg	49 (3 yr)	28	NS	1.2 Gy *bid* radiation
		50	Surgery	51 (3 yr)	27		
Urba *et al*[88]	SCC (25%)	47	PF + 45 +surg	30 (3 yr)	17	NS	15% survival benefit but not statistically significant
	AC (75%)	50	Surgery	16 (3 yr)	18		
Burmeister *et al*[89]	SCC (37%)	128	PF + 35 + surg	17	22	NS	Only 35 by radiation delivered
	AC (62%)	128	Surgery	13	19		
Mariette *et al*[90]		97	PF + 45 + surg	NR	32	0.66	TI-2 only, Hi postoperative mortality c CRT
		98	Surgery		44		

P: Cisplatin; BP: Bleomycin and cisplatin; NS: Not significant; PF: Cisplatin and 5-fluorouracil; AC: Adenocarcinoma; SCC: Squamous cell carcinoma; NR: Not reported; NS: Not significant; RT: Radiation; CRT: Chemoradiotherapy.

With a median follow-up of 32 mo patients who received chemoradiation had a significant benefit in 3-year survival (59% *vs* 48%, $P = 0.011$). There was also an increase in (RO) resection rates 67% *vs* 92%, 0.002 favoring chemoradiotherapy[63].

Given the contradictory and inconclusive results in many of the trials evaluating neoadjuvant multimodality treatment based on disparate study populations, differing histology, differing chemotherapy and radiotherapy doses and regimens, and small numbers of patients, data have been pooled in an effort to synthesize the data into larger numbers to discover if a survival benefit exists[64]. The first meta-analysis published by Urschel *et al*[65], included nine randomized controlled trials and 1116 patients. A trend toward 3-year survival improvement favoring neoadjuvant chemoradiotherapy was noted with the most pronounced effect with concurrent chemoradiotherapy as compared to a sequential approach. There was a decreased risk of local-regional recurrence but concerning trend toward increased treatment mortality with multimodality treatment. There was no difference in the risk of distant recurrence. Fiorica *et al*[66] noted an improvement in patients who received neoadjuvant chemoradiotherapy. Gebski *et al*[27] also evaluated neoadjuvant chemotherapy and chemoradiotherapy compared to surgery alone in a meta-analysis. This recent meta-analysis evaluated 1209 patients with both adenocarcinoma and squamous cell carcinoma of the esophagus in

ten trials. A statistically significant benefit was noted with neoadjuvant chemoradiotherapy compared to surgery alone with a 19% decrease in the risk of death corresponding to a 13% absolute difference in 2 year survival. An absolute survival benefit of 7% was noted for neoadjuvant chemotherapy as compared to surgery alone. The Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial (POET) attempted to determine in a prospective, randomized fashion if neoadjuvant concurrent chemoradiotherapy is more beneficial then perioperative chemotherapy[67]. There was a trend toward improved pathologic complete response with neoadjuvant chemoradiotherapy but the study was closed early due to lack of accrual[67]. Given these data, we plan neoadjuvant chemoradiotherapy in our eligible patients.

DO PATIENTS WHO UNDERGO CHEMORADIATION BENEFIT FROM SURGERY?

Two randomized trials examine whether surgery is necessary after chemoradiation. In the FFCD 9102 trial, 445 patients with clinically resectable T3-4N0-1M0 squamous cell carcinoma of the esophagus received initial chemoradiation[68]. Patients initially received 2 cycles of 5-fluorouracil (5-FU), cisplatin, and concurrent radiation (either 46 Gy at 2 Gy/d or split course 15 Gy weeks 1 and 3[68]). The 259 patients who had at least a partial response were then randomized to surgery *vs* additional chemoradiation which included 3 cycles of 5-FU, cisplatin, and concurrent radiation (either 20 Gy at 2 Gy/d or split course 15 Gy). There was no significant difference in 2-year survival (34% *vs* 40%, $P = 0.56$) or median survival (18 mo *vs* 19 mo) in patients who underwent surgery *vs* additional chemoradiation. These data suggest that for patients who initially respond to chemoradiation, they should complete chemoradiation rather than stop and undergo surgery. The German Oesophageal Cancer Study Group compared preoperative chemoradiation followed by surgery *vs* chemoradiation alone[69]. In this trial, 172 patients < 70 years old with uT3-4N0-1M0 squamous cell cancers of the esophagus were randomized to preoperative therapy (3 cycles of 5-FU, leucovorin, etoposide, and cisplatin, followed by concurrent etoposide, cisplatin, plus 40 Gy) followed by surgery *vs* chemoradiation alone (the same chemotherapy but the radiation dose was increased to 60-65 Gy +/- brachytherapy). In patients who underwent surgical resection, 35% had complete pathologic response and 33% had no evidence of lymph node involvement following neoadjuvant therapy[69]. Despite a decrease in 2-year local failure (36% *vs* 58%, $P = 0.003$) there was no statistically significant difference in 3-year survival (31% *vs* 24%) for those who were randomized to preoperative chemoradiation followed by surgery *vs* chemoradiation alone. The practice at our institution is to closely observe patients with esophageal squamous cell cancer who have a complete clinical response. Patients with adenocarcinoma continue to require surgical resection as these studies only evaluate patients with squamous cell cancer and studies to address adenocarcinoma have not been done.

DO PATIENTS WHO HAVE SURGERY BENEFIT FROM ADJUVANT TREATMENT?

In an effort to address locally advanced gastric and GE junction cancers adjuvant chemoradiotherapy was evaluated (MacDonald)[70]. This trial (INT 0116) enrolled 556 patients with gastric and GE junction (approximately 20%) adenocarcinoma. Patients were randomized to surgery alone or surgery followed by adjuvant leucovorin-modulated fluorouracil with concurrent radiation (45 Gy) in cycle 2 of 4 total cycles. There was an improvement in median overall survival with adjuvant therapy 36 mo *vs* 27 mo in the observation group ($P = 0.005$)[70]. Treatment related toxicity prevented completion of the treatment in 17% of patients[70]. There are no data evaluating the utility of adjuvant therapy in patients with more proximal esophageal tumors. At our institution, we plan neoadjuvant chemoradiation in locally advanced esophageal cancer patients. If following surgery, the pathology upstages the cancer, we plan for adjuvant treatment only in cancers of the GE junction.

WHAT IS OUR PRACTICE AND RATIONALE?

In summary, although there is good rationale for its use, it is not clear that the combination of surgery and chemoradiation regardless of the sequence, improves the survival results of either treatment alone. The survival benefit is likely to be 5%-10% with multimodality therapy. Currently, the standard of care in treatment of locally advanced tumors at our institution is to place patients on neoadjuvant chemoradiotherapy provided that it is feasible. We take into account the tumor location, size of the radiation field, comorbidities, and performance status in determining what the best multimodality approach is. There are many institutions, especially in Europe, who use neoadjuvant chemotherapy only. It is our practice to use neoadjuvant chemoradiotherapy because of the findings of the CALGB 9781, Walsh study, multiple meta-analysis and more recently the POET study[27,61,62,67]. The Gebski meta-analysis quoted a 13% absolute benefit in 2 year survival with neoadjuvant chemoradiotherapy and a 7% absolute benefit with neoadjuvant chemotherapy[27]. This is almost a doubling of the benefit conferred with perioperative chemotherapy alone. Additionally, the POET study, the only study which compares neoadjuvant chemotherapy to neoadjuvant chemoradiotherapy demonstrates a trend toward increased pathologic complete response at resection and survival with neoadjuvant chemoradiotherapy[67]. This study was performed in patients with GE junction

tumors and was closed early due to poor recruitment.

Additionally, we feel surgery may not be required in patients with esophageal squamous cell carcinoma provided they have a complete response to neoadjuvant therapy. Given that squamous cell carcinomas often recur locally, observation alone may be acceptable in this small group of patients. For those patients who have adenocarcinoma, we feel resection is still standard of care.

WHAT IS BEING EVALUATED CURRENTLY IN ESOPHAGEAL CANCER?

Despite improvements noted with multimodality treatment in esophageal cancer, cure rates are consistently dismal[27]. With new interest in targeted agents in cancer demonstrating benefit in malignancies of the head and neck, breast, lung, colon and pancreas have generated evaluation in the esophagus[71-73]. Multiple molecular pathways have been evaluated at the molecular level with potential targets in esophageal cancer including cyclin dependent kinases, nuclear factor κ, matrix metalloproteinases, inhibition of cyclooxygenase-2, c-MET (a protooncogene that encodes a protein known as hepatocyte growth factor), epidermal growth factor receptor (EGFR) and vascular endothelial growth factor[72].

Over-expression of EGFR proteins may occur in 30%-70% of both adenocarcinoma and squamous cell carcinoma of the esophagus. Over-expression is associated with increased aggressiveness of the malignancy and poor prognosis[74-76]. Clinical trials have been initiated trying to take advantage of this protein. The Southwest Oncology Group initially targeted this protein by using single agent cetuximab as a second-line therapy with discouraging results[77]. More recent studies have evaluated cetuximab or other monoclonal EGFR antibodies with chemotherapy appear to be more promising[78-80]. Recently, EGFR-2 (Her-2-neu) has also been evaluated in gastric and esophageal cancers over expressing human EGFR-2 HER2 (ToGA trial) with promising results[81]. These targeted agents are currently undergoing evaluation in a multimodality setting with chemoradiotherapy. Safran *et al*[82] have evaluated 57 patients with esophageal cancer with weekly carboplatin, paclitaxel, cetuximab, and concurrent radiation (50.4 Gy). Complete clinical response was achieved in 70% of patients. Forty-nine of patients went on to surgery with a pathologic complete response rate of 27%. The RTOG 0436 is an ongoing phase Ⅲ trial evaluating weekly carboplatin, paclitaxel, and concurrent radiation with or without cetuximab in locally advanced inoperable patients. Additionally, given the results on the ToGA trial trastuzumab is currently under investigation with cisplatin, paclitaxel, and concurrent radiation for locally-advanced, HER2 overexpressing adenocarcinoma of the esophagus[83].

Survival benefits of neoadjuvant therapy appear small, but is should be noted this is similar to other treatments for other lethal malignancies[84]. The need to treat approximately 8 patients with a toxic regimen to cure one additional patient is not ideal, yet these odds must be discussed with a patient who is felt to be medically fit to withstand an esophagectomy[64]. Additionally, patients will often question about adjuvant therapy. While appropriate, in patients who have GE junction tumors only this is poorly tolerated post surgically, involves a larger radiation field, and radiation doses are lower[70]. Hence, our recommendations in the locally advanced resectable patient remain neoadjuvant chemoradiotherapy followed by esophagectomy. How targeted therapies will affect our approach in locally advanced esophageal carcinoma and is currently under investigation[73,76]. Additionally, studies arrived at neoadjuvant concurrent chemoradiation regimens based on PET response to induction chemotherapy are underway.

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