13 Multimodality Therapy for Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

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Abstract There is considerable controversy over the level of recommendations from randomized trials underpinning management decisions for patients presenting with localized adenocarcinoma of the esophagus and esophagogastric junction. Despite a paucity of Level 1 recommendations compared with other gastrointestinal sites, in particular rectal cancer, there is an emerging consensus in practice to consider multimodal approaches in all cases that present with T3 or node-positive disease. There is also an optimism that new approaches, including response prediction based on sequential ^{18}FDG-PET scanning following induction chemotherapy, and novel drugs targeted at EGF, EGFR, VEGF, and tyrosine kinase inhibition may improve treatment pathways and outcomes. In this review, we assess the level of recommendations from the major published trials and discuss new trials and approaches.

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13.1 Introduction

Adenocarcinoma of the lower esophagus and esophagastric junction (EGJ) has markedly increased in the West over 20–30 years, with a corresponding reduction in squamous cell carcinoma (Daly 2000; Blot et al. 1991). Esophageal and junctional tumors are often advanced at presentation. The 5-year survival overall is between 10–20 and 35–50% for resectable localized disease (Portale et al. 2006). The classification of tumors at this site has been greatly enhanced by the topographical classification advanced by Siewert and colleagues (Siewert and Stein 1998; Siewert et al. 2000), with adenocarcinoma of the esophagogastric junction (AEG) divided into true esophageal, arising from Barrett esophagus (AEG 1), true cardia (AEG II), and subcardia (AEG III), with cardia and subcardiac tumors being predominantly of gastric histiogenesis. Several advances in standards of care have emerged in recent years that have improved management. First, comprehensive staging with CT, endoscopic ultrasound (EUS), and ^{18}FDG-PET imaging and the judicious use of laparoscopy permit improved selection of patients for curative approaches and avoid surgery for purely palliative intent. Second, unassailable evidence supports the case

P.M. Schneider (ed.), *Adenocarcinoma of the Esophagogastric Junction*,
Recent Results in Cancer Research 182, DOI: 10.1007/978-3-540-70579-6_13,

for esophagectomy to be performed in high-volume hospitals by high-volume surgeons, and policies underpinning reform have taken place in many countries through action from third-party payers, government, and the profession itself (Enzinger and Mayer 2003; Birkmeyer et al. 2002). Third, palliation of esophageal cancer has been simplified and made safer with the advent of self-expandable metal endoprostheses. Finally, neoadjuvant and adjuvant therapies are considered in most centers for patients with localized esophageal adenocarcinoma and, although controversial, subgroups of patients may benefit from this approach (Enzinger and Mayer 2003; Fiorica et al. 2004). The broad principles underpinning achieving optimum outcomes in adenocarcinoma at these sites are developed in other chapters in this book, and this article focuses exclusively on the evidence and controversies relating to neoadjuvant and adjuvant multimodality protocols, and the promise of novel approaches.

13.2 Multimodal Therapy

In a review of esophageal cancer published in the New England Journal of Medicine in 2003, the authors conclude that "despite the widespread use of preoperative chemotherapy and radiotherapy, there remains no proof of principle that this strategy is effective in patients with esophageal cancer" (Enzinger and Mayer 2003). From a rigorous academic assessment of existing trials, this interpretation cannot be criticized, and no trial has been published since 2003 that would alter this conclusion. In fact, no randomized trial has been conducted in patients with adenocarcinoma of the esophagus and junction that is adequately powered exclusive to this pathology or tumor site. Notwithstanding this analysis, the reality is that mutimodality approaches have steadily supplanted surgery-alone as the standard approach to adenocarcinoma at these sites. This relates to several factors, including a strong theoretical rationale due to high relapse rates following surgical resection alone Wayman et al. 2002), the evidence from the similar management paradigm of rectal cancer where multimodal approaches are the established standard of care for locally advanced disease, the evidence-base support from a few key randomized trials and meta-analysis, and the outcomes achieved with patients who have an excellent clinical, metabolic, or histomorphologic response to neoadjuvant therapy.

13.3 The Evidence-Base for Neoadjuvant and Adjuvant Approaches

13.3.1 Neoadjuvant Chemotherapy

There are three key studies (Table 13.1). An appropriately powered Phase III randomized study of 467 North American patients (US Intergroup 0113) with esophageal adenocarcinoma ($n=236$ esophageal or junctional) or squamous cell cancer showed no benefit from pre and postoperative combination 5-FU and cisplatin, with a 2-year survival of 35% in the combination group compared with 37% in the surgery-alone group, and a median survival of 15 and 16 months, respectively (Kelsen et al. 1998). A complete pathological response was observed in 2.5% of cases. A similar study of 802 patients conducted by the Medical Research Council (OEO2), which randomized patients to 2 cycles of preoperative ciplatin and 5-FU vs. surgery-alone, was powered to detect a 10% increase in 2-year survival from 20 to 30%. This trial reported a significantly improved survival at 2 years (43 vs. 34%) in the combined modality group, and a median survival of 16.8 vs. 13.3 months (MRC Group 2002). The principal

Table 13.1 Randomized trials of neoadjuvant chemotherapy vs. surgery

References	Chemotherapy regimen	Tumor type	Sample size	Primary outcome
Cunningham et al. (2006)	3 Cycles: cisplatin, 5-fluorouracil (5-FU), epirubicin	Adenocarcinoma	503[a]	Prolonged survival in chemotherapy arm at 5 years
Kelsen et al. (1998)	3 Cycles: cisplatin, 5-fluorouracil	SCC and adenocarcinoma	467	No difference in overall survival
MRC (2002)	2 Cycles: cisplatin, 5-fluorouracil	SCC and adenocarcinoma	802	Prolonged survival in chemotherapy arm at 2 years

[a]Fourteen percent of 503 had tumors of the lower oesophagus

differences between the Intergroup and MRC study was that the total preoperative chemotherapy administered was greater in the Intergroup trial, there was a longer delay to surgery (median 93 vs. 63 days), and the median survival in the surgery-alone arm was improved (16 vs. 13 months). Notwithstanding the different outcomes in both studies, in the U.K. neoadjuvant chemotherapy is accepted as standard of care. In the U.K., the OEO5 study following on from the OEO2 study has been activated; it has a target accrual of 1,300 patients in a patient cohort of resectable adenocarcinoma of the esophagus and junction (AEG I and AEG II), and compares preoperative cisplatin and fluorouracil (2 cycles) with epirubicin, cisplatin, and capecitabine (ECX; 4 cycles).

The recent findings of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial provide further support for proponents of neoadjuvant chemotherapy (Cunningham et al. 2006). This phase III trial 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). Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin and cisplatin and a continuous intravenous infusion of 5-FU (ECF). Postoperative morbidity and 30-day mortality did not differ between the two arms (46 vs. 45% and 5.6 vs. 5.9%, respectively). Compared with patients receiving surgery-alone, the patients on the trial regimen had significantly improved overall ($p=0.009$) and progression-free survivals ($p<0.001$). The 5-year survival rate was 36% for combined modality therapy compared with 23% for patients with surgery-alone ($p=0.008$ log-rank test), a hazards ratio of 0.75 corresponding to a 25% relative reduction in the risk of death. The toxicity profile was acceptable, and less than 12% of patients had Grade 3 or 4 toxicity. In the MAGIC trial approximately 75% of patients had gastric tumors, 14% had tumors of the lower esophagus, and 11% had junctional tumors. The effect was consistent for each site, with a hazards ratio of 0.81, 0.44, and 0.75 for gastric, junction, and esophageal, respectively. The principle of neoadjuvant therapy is supported by MAGIC, but the trial was not powered to address junctional and esophageal adenocarcinoma, and therefore, no Level 1 evidence is provided for tumors at these sites. Nonetheless, the MAGIC trial is a high quality study and does provide a compelling rationale for considering neoadjuvant chemotherapy for gastric adenocarcinoma including junctional tumors of gastric origin (AEG II and AEG III). In the U.K, the MAGIC B trial is currently recruiting and compares 6 cycles (3 pre and 3-postoperative), cycles of

ECX with ECX combined with bevacizumab in patients with operable gastric and junctional (AEG III) tumors. Of note, the oral fluoropyrimidine capecitabine (X) and oxaloplatin are increasingly replacing fluorouracil and cisplatin, respectively, in new clinical trials, and recently Cunningham and colleagues in the National Cancer Research Institute of the United Kingdom proved in a random assignment study of over a thousand patients with advanced esophagogastic cancer that this new combination was not inferior to the previous standard, and that the toxicity of oxaloplatin was less than cisplatin (Cunningham et al. 2008).

The use of ^{18}FDG-PET as a marker of tumor responsiveness to induction chemotherapy is a novel approach developed principally by Siewert and colleagues in Munich. In preliminary studies a decrease in the standardized uptake value of ^{18}FDG after 2 weeks of chemotherapy was evident in patients who went on to achieve a significant histomorphologic response (Weber et al. 2001; Ott et al. 2006). These studies paved the way for the MUNICON (metabolic response evaluation for individualization of neoadjuvant chemotherapy in esophageal and esophagogastric adenocarcinoma) phase II study (Lordick et al. 2007). In this prospective single-centre trial, 119 patients with locally advanced adenocarcinoma of the distal esophagus and junction were assigned to 2 weeks of cisplatin and 5-FU and a second PET scan was performed. Those with decreases in ^{18}FDG avidity, predefined as decreases of 35% or more at the end of the evaluation period, were defined as metabolic responders. Responders continued to receive neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery. Metabolic nonresponders discontinued chemotherapy after the 2-week evaluation period and proceeded to surgery. One hundred and ten patients were evaluable, of whom 49% were classified as metabolic responders. One hundred and four patients had tumor resection (50 in the responder group and 54 in the nonresponder group). After a median follow-up of 2.3 years, the median overall survival was not reached in metabolic responders, whereas median overall survival was 25.8 months in nonresponders ($p=0.015$). The median event-free survival was 29.7 months in metabolic responders and 14.1 months in nonresponders ($p=0.002$). A major histopathological response defined as less than 10% residual tumor cells in the resected specimen was noted in 58% of the metabolic responders, but no histopathological response was seen in metabolic nonresponders. This is an important study as it is the first clinical trial to incorporate early response evaluation to neoadjuvant chemotherapy as measured by ^{18}FDG-PET into a treatment algorithm.

13.3.2 Neoadjuvant Chemoradiotherapy (Table 13.2)

The interpretation of trials of combination chemotherapy and radiation therapy prior to surgery and meta-analysis is more difficult compared with trials using chemotherapy alone for several reasons. Only one trial, a negative study, appears adequately powered with over 200 patients (Burmeister et al. 2005); there is a mix of pathologic types, adenocarcinoma, and squamous cell cancer in most studies, and the total dose of radiation therapy administered, and treatment fractions, is different across trials.

There are two positive studies. The Dublin trial, performed at this center between 1990 and 1995 in patients with adenocarcinoma of the esophagus ($n=75$) and cardia ($n=39$), randomized to preoperative cisplatin and fluorouracil in combination with 40 Gy (15 fractions) prior to surgery or surgery-alone (Walsh et al. 1996). Median survival was 16 vs. 11 months ($p=0.01$), the 3-year survival was 32 vs. 6% ($p=-0.01$), and 42% compared with 82% had pathological nodal involvement ($p<0.0001$) in multimodality compared with surgery-only cohorts, respectively ($p=0.01$). The interpretation of the trial may be

Table 13.2 Randomized trials of neoadjuvant chemoradiotherapy vs. surgery

References	Chemotherapy regimen	Radiotherapy regimen	Concurrent or sequential	Tumor type	Sample size	Outcome
Burmeister et al. (2005)	1 Cycle: cisplatin, 5-FU	35, 2.3 Gy/fraction	Concurrent	SCC and adenocarcinoma	256	ns
Tepper et al. (2008)	2 Cycles: cisplatin, 5-FU	50.4, 1.8 Gy/fraction	Concurrent	SCC and adenocarcinoma	56	$p<0.05$
Urba et al. (2001)	2 Cycles: cisplatin, 5-FU, vinblastine	45, 1.5 Gy/fraction	Concurrent	SCC and adenocarcinoma	100	ns
Walsh et al. (1996)*	2 Cycles: cisplatin, 5-FU	40, 2.7 Gy/fraction	Concurrent	Adenocarcinoma	113	$p<0.05$

compromised by relatively small numbers, limited cross-sectional imaging in pretreatment staging, and an outcome in the surgery-alone arm (6% 3-year survival) below standard benchmarks (Walsh et al. 1996). The lack of T or N staging prerandomization in combination with an absence of strict pathologic quality assurance with respect to R classification suggests that the poor outcomes in the surgery-only arm relate to the inclusion of many patients in the trial who had palliative resection, cohorts that would now be excluded from the design of randomized trials for localized disease. The second positive Phase III study (CALBG 9781) recruited 56 patients of a planned 475 before closing due to poor accrual. Patients were randomized to surgery-only or cisplatin, fluorouracil, and radiation therapy (50.4 Gy; 1.8 Gy/fraction). The intent to treat analysis showed a median survival of 4.48 vs. 1.79 years favoring the treated group, with a 5-year survival of 39 vs. 16% (Tepper et al. 2008).

Notwithstanding the relatively tenuous data from which it is drawn, these trials as well as meta-analysis (Fiorica et al. 2004) have resulted in widespread adoption of combination chemotherapy and radiation therapy, particularly in the United States. The Patterns of Care studies from the United States showed that multimodal therapy increased from 10.4% during 1992–1994, to 26.6% in 1996–1999 (Suntharalingam et al. 1999). Apart from the above phase III trials, some outcome indicators from negative trials provide proxy support for this approach. In an adequately powered Australasian, both the R0 resection rate (80 vs. 59%) and node negativity (67 vs. 43%) were significantly better in the multimodal vs. surgery-alone group (Burmeister et al. 2005). In the University of Michigan trial of 100 patients (Urba et al. 2001), which was powered to detect a large increase in median survival, the overall survival was 30% at 3 years in the treated (CF and vinblastine; 45 Gy/1.5 Gy fractions) arm compared with the surgery-alone (16%) cohort ($p = 0.15$).

The surrogate target of a complete or major pathological response is achieved by neoadjuvant chemoradiation in approximately 20–30% of traditional regimens. Where major tumor regression is achieved, this translated into an approximate 50% chance of cure (Geh et al. 2001; Reynolds et al. 2007; Gebski et al. 2007), and the attainment of such a response, as well as high R0 resection rates, is undoubtedly a factor in the increasing use of multimodal regimens. In this latter regard,

new approaches to increase the complete pathological response rate would appear to have a sound rationale. The addition of paclitaxel to cisplatin and fluorouracil-based regimens have increased pCR rates, but may result in significant toxicity. A recent study using a paclitaxel, carboplatin, and fluorouracil chemoradiotherapy regimen in patients with stage II and III disease but with a reduced paclitaxel dose demonstrated acceptable toxicity along with a complete pathological response rate of 38% and R0 resection rate of 96% (van de Schoot et al. 2008).

Finally, the increasing use of chemoradiotherapy prior to surgery is also supported by the increasing acceptance of a multimodal approach for other cancers, in particular rectal cancer (Sauer et al. 2004; Habr-Gama et al. 2004). Surgical and pathological quality assurance, as well as uniform definition, have been applied in the major rectal cancer trials and convincing conclusions reached from large studies, and it can be argued that the improvement in local control in the best rectal trials from preoperative therapy provides a logic to applying the same principle in the similar paradigm of locally advanced esophageal cancer.

A caveat with respect to the multimodal approach relates to the potential for increased operative risks. A large randomized trial in patient with esophageal squamous cell cancer was stopped because of increased postoperative mortality in the multimodal arm (Bosset et al. 1997). Meta-analysis of phase III trials has also confirmed increased postoperative mortality (Fiorica et al. 2004), and this unit and others have reported increased major postoperative respiratory morbidity in patients on multimodal protocols compared with case-matched controls undergoing surgery-only (Reynolds et al. 2006; Lee et al. 2003).

13.3.3 Postoperative Combination Therapy

The Intergroup Study 0116 (INT 0116; Macdonald et al. 2001) enrolled 556 patients with pathological stage IB through IV M0 and R0 resection gastric and junctional adenocarcinoma, and randomly assigned to surgery-alone or postoperative chemoradiation (fluorouracil and leucovorin plus external beam radiation (45 Gy/1.8 Gy/days × 5 weeks) delivered to the site of the gastric resection and the areas of draining lymph nodes). These patients were at significant risk of relapse as 85% had lymph node metastases and 65% had stage T3 or T4 tumors. Approximately 20% of patients had proximal gastric tumors. Median survival in the surgery-only and chemoradiation groups was 27 and 36 months, respectively ($p = 0.005$ by the log-rank tests; the corresponding figures for disease-free survival were 19 and 30 months ($p < 0.001$). Although a positive trial, with a hazards ratio of 0.75 for improvement with the combination regimens, equivalent to what was observed in the MAGIC trial, a number of cautionary messages emerge from this trial that merit emphasis. First, 64% of randomized patients completed the post-operative regimen, 17% stopped due to toxicity, and Grade 3 or greater hematological toxicity occurred in 54% of patients. Overall Grade 3 toxicity occurred in 41% of patients and Grade 4 in 32%, with 3 deaths from toxicity (1%). Second, although an extensive lymphadenectomy (D2) was recommended, this was performed in only 10% of patients, with a D1 dissection in 36% and an D0 lymphadenectomy in 54% of patients. Finally, akin to the MAGIC trial, the study was not powered to address the question with respect to junctional tumors. Nonetheless, it does provide support for this approach in patients who have had initial surgery and are shown to have node-positive disease or adverse pathologic features such as poor differentiation and vascular or lymphatic invasion in the primary tumor.

13.4 New Combinations and Novel Agents

Recent advances in molecular biology have led to a better understanding of the molecular pathways involved in the development and progression

of esophageal and junctional adenocarcinoma. Elucidation of these pathways has led to the development of targeted therapies that can potentially inhibit or reverse the progression of disease, and this has resulted in the design of novel clinical trials (Peters and Fitzgerald 2007). The epidermal growth factor receptor (ErbB1 or EGFR) and the ErbB2 (HER2/neu) receptor represent the two main members of the tyrosine kinase type ErbB-receptor family. EGFR overexpression occurs in esophageal adenocarcinoma and is associated with a poor prognosis. Cetuximab is an anti-EGFR monoclonal antibody, which has been approved for the treatment of metastatic colorectal cancer and advanced squamous cell cancer of the head and neck (Cunningham et al. 2004). A phase II study to determine the feasibility and toxicity of the addition of cetuximab with paclitaxel, carboplatin, and radiation for locally advanced esophageal cancer demonstrated that cetuximab can be safely administered with concurrent chemoradiation with a complete clinical response rate of 70% (Safran et al. 2008). While dermatologic toxicity and hypersensitivity reactions were associated with the addition of cetuximab, there was no increase in radiation-enhanced toxicity.

Erlotinib (Tarceva) and Gefitinib (Iressa) are orally active selective reversible inhibitors of EGFR tyrosine kinase. A recent phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma demonstrated an overall clinical response rate of 11% and associated toxicities were mild (Ferry et al. 2007).

Vascular endothelial growth factor (VEGF) is the most potent of the endothelial growth factors and is central to angiogenesis. Direct VEGF stimulation of cancer cells results in tumor cell proliferation, increased survival, and migration. VEGF is overexpressed in 30–60% of esophageal cancer specimens, and overexpression of VEGF is associated with poor outcomes in patients undergoing curative resections (Kleespies et al. 2004). Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that binds to all isoforms of human VEGF, thereby neutralizing VEGF and inhibiting its angiogenic activity (Presta et al. 1997). The multicentre phase II trial of bevacizumab, irinotecan, and cisplatin in metastatic gastric and GEJ adenocarcinoma patients demonstrated an overall response rate of 65% and that the median time to disease progression was improved over historical controls by 75% (Shah et al. 2006). As mentioned previously, Bevacizumab in combination with ECX is being compared with ECX alone in the MAGIC B trial of patients with gastric and AEG III adenocarcinoma.

Most targeted studies to date have been in patients with advanced or metastatic disease. For adjuvant studies, the incorporation of anti-EGFR and anti-VEGF monoclonal antibody therapies (Table 13.3) and EGFR tyrosine kinase inhibitors (Table 13.4) into multimodal therapies for resectable esophageal and junctional cancer is ongoing and results from these phase II trials are eagerly awaited and will form the basis for phase III studies.

13.5 Conclusions

The specific title of this article relates to multimodal management of adenocarcinoma of the esophagus, junction, and proximal stomach, and it is unassailable from the literature that the evidence-base is not underpinned by Grade A recommendations for this pathologic type and these locations. Moreover, the lack of standardization in surgery and radiation therapy and the relative rarity of the tumor make it difficult to conduct definitive trials that may require over a thousand patients, akin to rectal cancer trials. Outside clinical trials, a pragmatic approach is therefore adopted in most specialist units that is based on risk assessment, accurate staging, an adherence to the fundamental principles of cancer surgery, and a reasonable interpretation of the evidence-base from neoadjuvant and adjuvant studies.

In this unit, a multimodal approach is offered to patients who have locally advanced

Table 13.3 Ongoing and planned trials of cetuximab and bevacizumab in resectable esophageal cancer

Trial identifier	Phase	Intervention	Planned sample size	Trial eligibility	Trial start date	Scheduled follow-up (years)	Trial close	Primary outcome
NCT00165490	II	Cetuximab plus chemoradiotherapy and surgery	39	Resectable esophageal cancer	June 2004	3	2009	Response to the combination of cetuximab, cisplatin, irinotecan, and radiation therapy
NCT00551759	II	Cetuximab plus chemoradiotherapy and surgery	42	resectable adenocarcinoma of esophagus or junction	October 2007	3–5	2009	Complete pathological response rate
NCT00445861	I/II	Cetuximab plus chemoradiotherapy and surgery	27	Resectable locally advanced esophageal cancer	January 2007	3	2009	Limiting toxicity of radiotherapy in combination with chemoimmunotherapy
NCT00544362	II	Cetuximab plus chemoradiotherapy and surgery	45	Resectable carcinoma of thoracic oesophagus	July 2007	2		Complete pathological response rate
NCT00354679	II	Bevacizumab plus chemoradiotherapy and surgery	33	Locally advanced esophageal adenocarcinoma	April 2006	3	April 2009	Safety and toxicity
NCT00450203	II/III	Bevacizumab plus chemotherapy vs. chemotherapy alone	1100	Operable adenocarcinoma of stomach and GEJ	Not yet recruiting			Safety, efficacy, and overall survival

Table 13.4 Ongoing trials of EGFR tyrosine kinase inhibitors in resectable esophageal and junction cancer

Trial identifier	Phase	Intervention	Planned sample size	Trial eligibility	Trial start date	Scheduled follow-up (years)	Trial close	Primary outcome
NCT00499564	II	Erlotinib plus chemoradiotherapy and surgery	64	T2-4, N1, Squamous or adenocarcinoma of esophagus	April 2007	2	April 2009	Pathological complete response
NCT00493025	II	Gefitinib plus chemoradiotherapy and surgery	36	Operable adenocarcinoma of the esophagus	April 2005	5	June 2008	Pathological complete response
NCT00258323	II	Gefitinib plus chemoradiotherapy before and after surgery	80	Advanced esophageal or GEJ cancer	October 2005	5		Survival at 1 year; distant metastatic control at 1 year
NCT00290719	I/II	Gefitinib plus chemoradiotherapy before surgery	20	Resectable esophageal cancer	November 2005		July 2008	Complete and partial pathological response
NCT00100945	II	Gefitinib posttherapy with curative intent	72	Locally advanced esophageal cancer	July 2005	5		1-Year overall survival rate

adenocarcinoma of the esophagus or AEG 1 junctional tumors. Patients must have excellent physiological reserve and are advised of the increased operative risks that we and others have observed (Reynolds et al. 2006; Bosset et al. 1997). In our experience, and in contrast to the experience with induction chemotherapy and the MUNICON trial, sequential ^{18}FDG-PET scanning is not helpful to identify early responders after induction chemoradiation, possibly because of the early inflammatory response to radiation therapy (Gillham et al. 2006).

For adenocarcinoma of the cardia (AEG II) or subcardia (AEG III), our view, consistent with that of the Munich group, is that the majority of these are of gastric origin. Since the publication of the MAGIC trial, this regimen is now considered in all patients except predicted T1-2 N0 cases. We had previously used the Macdonald regimen of combination chemoradiation postoperatively in this scenario, but now this is preserved for patients who have had surgery initially, and pathology reveals node positively or adverse features. The surgical preference is increasingly a radical total gastrectomy, D2 lymphadenectomy, and distal esophagectomy, rather than a proximal gastrectomy. Preoperative radiation has not been considered previously because of the risk of radiation damage to the gastric conduit, but the shift in surgical preference makes this potentially feasible to study within future trials.

In the next decade, the results of several clinical trials may clarify some matters and hopefully improved outcomes. A collaborative group in the Netherlands is comparing neoadjuvant chemoradiation and surgery-alone in esophageal adenocarcinoma in an adequately powered study. In the U.K., the OEO5 study and the MAGIC B trial will be of interest, and the evaluation of targeted therapy in phase II and III trials may uncover effective strategies that may increase complete or major pathological response rates. Finally, we should be cautiously optimistic that the explosion of knowledge in genomics, proteomics, and transciptiomics, along with the use of functional imaging, may allow pretreatment or early posttreatment response prediction of response to induction therapy, so that new trials and treatments may be developed based on a better understanding of the biological behavior of the tumor.

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