Esophageal Cancer

Robert L. Eil, F. E. M. Voncken, J. Torres-Roca, and Charles R. Thomas Jr.

Contents

R. L. Eil
Department of Surgery,
Oregon Health & Science University,
3181 SW Sam Jackson Park Road,
Portland, OR 97239, USA

F. E. M. Voncken
Department of Radiotherapy,
The Netherlands Cancer Institute-Antoni
van Leeuwenhoek Hospital, Plesmanlaan 121,
1066 CX, Amsterdam, Netherlands

J. Torres-Roca
Department of Radiation Oncology,
H Lee Moffitt Cancer Center,
12902 USF Magnolia Dr,
Tampa, FL 33612, USA

C. R. Thomas Jr. (✉)
Department Radiation Medicine,
Oregon Health & Science University,
3181 SW Sam Jackson Park Road,
Portland, OR 97239, USA
e-mail: thomasch@ohsu.edu

Abstract

Despite ongoing advances, the vast majority of those afflicted with esophageal cancer go on to die of their disease. While some respond notably to chemoradiotherapy, others-with seemingly similar disease characteristics based on existing clinical assays-have a limited or absent response. The current climate is suitable for the development of predictive tools and novel methods of evaluation to aid in individualised patient treatment planning. In the preoperative setting our clinical staging and varied imaging modalities, although imperfect are used to determine which patients will likely receive from chemoradiotherapy. No permutation of the data currently available can predict, with a satisfactory accuracy, whether an individual patient will have a substantial response to neoadjuvant treatment with minimal morbidity. Potentially, the addition of molecular assays in tandem with standardization of radiologic data will allow the development of increasingly powerful tools to predict the likelihood of response to treatment without complication for an individual patient.

1 Introduction

Esophageal cancer is a significant worldwide health problem, of which the incidence in the USA and Western Europe is rapidly increasing (Holmes and Vaughan 2007;

Siegel et al. 2012). Patients frequently present with advanced stage disease, poor performance status, and have a poor prognosis. Over recent years, the addition of neoadjuvant chemoradiotherapy (CRT) to surgery has improved 5-year survival probability from 34 % for patients treated with surgery alone to 47 % for patients treated with chemoradiotherapy and surgery (van Hagen et al. 2012).

However, responses to neoadjuvant treatment vary, with heterogeneous responses for patients with similar clinical stage. If neoadjuvant treatment produces a pathologically complete response (pCR), outcomes are better: patients with a pCR can expect a 5-year survival rate of 48 vs. 18 % for non-responding patients (Berger et al. 2005).

Without the benefit of knowing the pathologic stage, it is difficult to select patients who will benefit from this aggressive treatment. So far, three characteristics on which prediction can be based have been identified: clinical factors, biomarkers, and imaging modalities. While these last two are promising, at this current time no combination of available clinical data is reliable enough to indicate which patients are going to have a robust response to CRT and benefit from esophagectomy, and which should be treated with only selected modalities. Thus, traditional clinical factors such as tumor stage, age and performance status are still used to select the best therapy for a particular patient.

With regard to biomarkers, new strategies for subdividing esophageal cancer patients into prognostic groups may result in patients being selected for CRT or not on the basis of molecular assays, in addition to the 'traditional' methods of stage and imaging modalities. While these markers are promising, the exact clinical setting in which biomarkers will routinely be of utility in guiding treatment has yet to be defined.

The third characteristic, imaging, involves the use of modalities such as endoscopic ultrasound (EUS), computed tomography (CT), positron emission tomography (PET)-CT and magnetic resonance imaging (MRI). As a group, the information these assays provide continues to play an important role in staging and re-staging and thus in patient selection for CRT.

Combining these clinical data allows for our growing field of interest, where prognostic models and nomograms attempt to predict individual prognosis and response to CRT, with the potential to individualize treatment and isolate high-risk groups for novel treatments.

The above patient and tumor characteristics are the main basis upon which multidisciplinary treatment plans are made. In this chapter we review these decision tools and their implications for prognosis, treatment response and toxicity in the progressively individualized treatment of esophageal cancer.

2   Prognosis and Treatment Response

2.1   Disease Characteristics

Currently, no single clinical parameter can be used to predict which patients will achieve a pathological complete response (pCR) following CRT or survive their disease. However, there are several clinical and oncologic factors that have consistently proven to be significantly associated with outcome.

2.1.1   Patient Characteristics

Several patient-related factors are associated with survival and response to CRT. Factors as AJCC stage, male gender, performance status, location of the tumor, high lifetime alcohol consumption, forced expiratory volume in 1 s (FEV1), number of involved lymph nodes and cigarette smoking are independent predictors of survival (Thrift et al. 2012; Situ et al. 2012). Parameters as gender, tumor grade, baseline EUS T-stage and histology are related to a pCR (Ajani et al. 2012). Achievement of pCR or any tumor response corresponds with better overall survival (Berger et al. 2005).

2.1.2   Histologic Characteristics

Histology of the tumor is an important differentiating factor, as the response at treatment differs substantially between adenocarcinomas and squamous cell carcinomas (SCC) (Rizk et al. 2007; Heath et al. 2000; Urba et al. 2001; Burmeister et al. 2005). Squamous cell carcinomas have a much higher likelihood to achieve a pCR than adenocarcinomas: a pCR in adenocarcinomas occurs in 20–30 % whereas for SCC, pCR occurs in up to 50 % of the patients (van Hagen et al. 2012). Although in general, achievement of a pCR is commonly associated with improved survival (Berger et al. 2005), this does not apply to SCC patients, since a higher rate of pCR for SCC patients does not seem to translate into better overall outcomes. Additionally, it is worth noting that while patients that have a pCR do have better prognosis when compared to all other patients with remaining invasive disease, a significant number of patients will succumb to their disease, with almost indistinguishable OS when compared to patients with stage I (Rizk et al. 2007). If one desires to predict which patients can safely go on to esophageal salvage following CRT, novel prognostic assays and use of the currently available data is required.

Histologic grade is a predictor for a pCR, long-term outcome (Ajani et al. 2012), and is implemented in initial staging for differentiating prognostic groups. However, with increasing use of neoadjuvant therapy, this grading is solely

based on endoscopic biopsy. With the accuracy of grade assessment on biopsy being only 73 %, it should be interpreted with caution (Dikken et al. 2012).

2.2 Staging Systems

Esophageal cancer staging has an important role in selecting patients for the appropriate treatment strategy and is related with long-term outcomes (Talsma et al. 2012). The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for esophageal cancer is used universally and was recently revised. A major change between the 2002 (Union Internationale Contre le Cancer 2002) and the 2010 (Rice et al. 2010) editions were the development of separate stage groupings according to histology and a better description of the tumors located at the esophagogastric junction (EGJ) (Tables 1, 2, 3 and 4).

These tumors, at the esophagogastric junction (EGJ) and proximal 5 cm of the stomach that extend into the EGJ or esophagus, are staged as esophageal cancers (Table 5). While all other tumors with an epicenter in the stomach >5 cm from the EGJ, or those within 5 cm of the EGJ without extension into the esophagus are staged as gastric cancers. A sub classification of these junctional tumors can be made by the classification described by Siewert and Stein (1998) (Table 6).

A validation study of this 7th edition of the UICC-AJCC staging system was performed by Talsma et al., which showed for surgical esophageal cancer patients that the 7th edition of staging provided more accurate prognostic stratification for OS in comparison to the 6th edition (Talsma et al. 2012).

2.3 Imaging

Imaging modalities as EUS, CT, PET-CT and MRI currently play an important role in staging and in patient selection before CRT. They may also be utilized for post CRT clinical re-staging (ycTNM) after induction treatment or response monitoring during treatment, however the results should be interpreted with caution in this setting (Ribeiro et al. 2006). During these different phases of the patient care some have attempted to identify a distinctive role for each modality.

2.3.1 EUS

2.3.1.1 Staging
Endoscopic ultrasound (EUS) uses a high frequency ultrasound transducer to obtain detailed images of the tumor mass and the relationship with the five-layered structure of

Table 1 TNM staging of esophageal squamous cell cancer (SCC) UICC-AJCC 7th edition (Rice et al. 2010)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia (HGD)
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G)	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage grouping as G3 squamous

the esophageal wall. EUS attempts to provide measurements of tumor thickness and is regularly used to estimate tumor extension in initial staging for esophageal cancer (Ribeiro et al. 2006). The discriminatory power for distinguishing between early stage tumors and those with deeper invasion may approach 80–90 %. Some have found this gross distinction prognostic in identifying those patients at risk for a positive circumferential resection margin (CRM), if treated with isolated surgery (Reid et al. 2012). However, its exact TNM accuracy is the least prognostic of available clinical information in predicting pre operative stage (Reid et al. 2012; van Vliet et al. 2008; Thosani et al. 2012).

While, EUS remains a frequently used clinical estimate of primary tumor staging, there are technical limitations to its ubiquitous use. Not all patients are capable of receiving a complete EUS due to esophageal stenosis. Additionally, the accuracy of EUS is operator dependent and is subject to a

Table 2 Prognostic groups by TNM stage/anatomic stage for squamous cell carcinoma UICC-AJCC 7th edition (Rice et al. 2010)

Stage	T	N	M	Grade	Tumor location
Anatomic stage/prognostic groups					
Squamous cell carcinoma					
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Table 3 TNM staging of esophageal and esophagogastric junction (EGJ) adenocarcinoma UICC-AJCC 7th edition (Rice et al. 2010)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia (HGD)
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (*G*)	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage grouping as G3 squamous

learning curve (Fockens et al. 1996). Ultimately, preoperative staging of lymph node status is challenging. A recently proposed tool from Gaur et al. (2010) for predicting pathologic lymph node involvement based on clinical information is discussed in further detail below in Nomograms and Predictive models section.

2.3.1.2 Re-staging

For response evaluation, EUS continues to be used as the primary diagnostic modality. However, the accuracy of EUS restaging varies significantly across several recent retrospective analyses (Ribeiro et al. 2006; Giovannini et al. 1997; Chak et al. 2000).

Different methods have been proposed for response assessment with EUS. The first method is to restage according to the TNM staging system (Fockens et al. 1996), second method is to measure the relative reduction in thickness of the tumor (Gaur et al. 2010; Giovannini et al. 1997) and a third method is to measure the relative tumor shrinkage at the maximum cross-sectional area (MCSA) (Gaur et al. 2010; Chak et al. 2000). However, with these different methods the accuracy is still poor and ranges from 17 to 59 % (Sloof 2006; Hirata et al. 1997; Zuccaro et al. 1999; Bowrey et al. 1999). Even when a EUS is combined with biopsy, the accuracy does not exceed 31 % to correctly predict a pCR (Sarkaria et al. 2009). Of patients that have a negative biopsy on restaging endoscopy (cCR) less than 30 % will have a pCR (Sarkaria et al. 2009).

A possible explanation for this discrepancy between endoscopic staging and subsequent pathologic staging is that EUS may not be able to differentiate between post-treatment inflammation or fibrosis and residual tumor (Jamil et al. 2008).

2.3.2 CT

2.3.2.1 Staging

Computed tomography (CT) is usually one of the first steps in staging esophageal cancer patients and is used to evaluate the region of the primary tumor and evaluate for distant metastases. However, the accuracy for locoregional staging is limited. Accuracy for tumor staging has been reported with a range of 42–68 % (Lowe et al. 2005; Wu et al. 2003) and for regional lymph node metastases the pooled sensitivity and specificity is only 0.50 (95 % C.I. 0.41–0.6)

Table 4 Prognostic groups by TNM stage/anatomic stage for adenocarcinoma UICC-AJCC 7th edition (Rice et al. 2010)

Anatomic stage/prognostic groups				
Adenocarcinoma carcinoma				
Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1–2, X
IB	T1	N0	M0	3
	T2	N0	M0	1–2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

Table 5 Primary site of esophageal cancer based on proximal edge of tumor according to the UICC-AJCC 7th edition (Rice et al. 2010)

Anatomic name	Esophageal location	Anatomic boundaries	Endoscopic distance from incisors
Cervical	Upper	Hypopharynx to sternal notch	15 to <20 cm
Thoracic	Upper	Sternal notch to azygos vein	20 to <25 cm
	Middle	Lower border of azygos vein to inferior pulmonary vein	25 to <30 cm
	Lower	Lower border of inferior pulmonary vein to esophagogastric junction	30 to <40 cm
Abdominal	Lower	Esophagogastric junction to 5 cm below esophagogastric junction	40–45 cm
	Esophagogastric junction/cardia	Esophagogastric junction to 5 cm below esophagogastric junction	40–45 cm

Table 6 Siewert classification (Siewert and Stein 1998)

Type	Description
Type I	Located between 5 and 1 cm proximal to the anatomical cardia. Adenocarcinoma of the distal esophagus that usually arises from an area with specialized intestinal metaplasia
Type II	Located between 1 cm proximal and 2 cm distal to the anatomical cardia. True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia
Type III	Located between 2 and 5 cm distal to the anatomical cardia. Subcardial gastric carcinoma that infiltrates the EGJ and distal esophagus from below

(van Vliet et al. 2008). Also, when used for screening for distant metastases CT-scans have difficulty recognizing small distant metastases, while a PET-CT is more sensitive (van Vliet et al. 2008).

2.3.2.2 Re-staging
CT scan is the most commonly used diagnostic modality in monitoring response of nonsurgical therapy for solid tumors. For esophageal cancer restaging, however, its role remains ambiguous. CT gives good visualization of the tumor bulk in majority of the patients. However, when tumor shrinkage is correlated to pathological response following neoadjuvant treatment some have found a clear correlation (Swisher et al. 2004; Voncken et al. 2012), while others failed (Griffith et al. 1999; Jones et al. 1999).

This difference could be due to an overestimation of edema, inflammation and fibrosis for residual tumor (Westerterp et al. 2005). While, CT remains one of many modalities in re-staging after induction treatment, primary tumor response should be interpreted with caution.

2.3.3 PET
FDG-PET is a nuclear imaging modality that evaluates tumor physiology and allows for a quantitative functional assessment of the primary via the standardized uptake value (SUV). Nearly all primary esophageal cancers have high levels of cellular metabolism, increased glycolysis, and an increased number of glucose transporters. In almost all cases, SCC primary tumors have a high uptake of FDG. In adenocarcinomas this FDG accumulation is more variable, with a minority (6 %) of the tumors being non-avid, usually the mucous containing and poorly differentiated tumor types or tumors too small to detect (<5 mm) by FDG-PET (Wagner et al. 2009; Stahl et al. 2003; Wong and Chambers 2008).

2.3.3.1 Staging
FDG-PET can provide information in initial staging, especially for finding regional nodal metastases and silent distant metastases, where it has a role in selecting patients that

will benefit from neoadjuvant CRT. In addition, FDG-PET can contribute to localization, size measurement and GTV definition of the primary tumor and lymph nodes (Katsoulis et al. 2007).

2.3.3.2 Restaging

PET-CT provides several pieces of clinically relevant information in restaging after induction treatment. A PET-CT can detect occult metastases after induction treatment and thus saving patients from undergoing a non-curative esophagectomy. A PET-CT after induction treatment detects metastases in 8 % of patients with a consequent adjustment in therapeutic plan (Bruzzi et al. 2007).

An additional advantage of response monitoring with PET-CT is the prognostic value in the decrease, or lack there of, in SUV of the primary tumor. While a PET-directed therapy does have the potential to change clinical practice and improve outcomes, it cannot currently be considered a standard approach in isolation. Standardization of quantitative results across facilities continues to be a technical roadblock. Several methods have been proposed as standard procedure for metabolic response analysis using the standard uptake value (SUV) as a semi quantitative measure of FDG uptake. Proposed methods are: SUV pre-treatment, SUV after chemoradiation, percentage of decline of SUV, attainment of a metabolic complete response after chemoradiation and to show an early metabolic response 14 days after start of chemoradiation.

These different methods were analyzed in a systematic review of Omloo et al. evaluating 31 studies (Omloo et al. 2011). Fifteen of these studies tested the pretreatment FDG uptake as a predictive factor. On univariate analysis, SUV was a predictor of survival in 12 out of 15 studies and multivariate analysis showed only in two out of eight studies that SUV was an independent predictor of survival. SUV decrease after completion of neoadjuvant treatment was predictive in only two out of six studies. Finally, there were six studies looking at the SUV decrease and prognosis early during neoadjuvant therapy. SUV decrease was a predictor of response in all of these six studies and a predictor of survival in five of these six studies.

Comparative analysis across FDG-PET articles is challenging due the non-standardization of the image acquisition process and subsequent analytic thresholds. Since the methodology for image acquisition varies, the SUV threshold to predict prognosis varies significantly between analyses (from 3 to 10.5) and cutoff values for amount of SUV change differentiating responders from non-responders also varies depending on the publication (from −30 to −70 %) (Omloo et al. 2011). This illustrates the difficulty to translate these results to clinical practice, although the field of treatment stands to benefit from an adequately powered prospective trial evaluating the true relevance of early SUV

decline during CRT. In conclusion, early SUV response assessment holds promise to potentially guide ongoing treatment, but the implementation and technical applicability have not yet developed to the extent required to find a clinical role for routine use.

2.3.4 MRI

The recent development of functional MRI imaging has opened a new window of opportunities for staging esophageal tumors, monitoring response to treatment and potentially even predicting biological behavior (Chang 2009; Riddell et al. 2007). Esophageal imaging with MRI has some technological challenges due to local cardiorespiratory motion artifact. However, with an accurately tuned sequence accurate images can be acquired.

For staging the esophageal tumor, EUS is the modality of first choice, however for 6 % of newly diagnosed patients, EUS is not possible due to a narrowing of the esophageal lumen and subsequent inability to pass the endoscope. CT is less accurate in differentiating depth of tumor invasion, thus for staging those patients, MRI could be an alternative (Riddell et al. 2007).

Staging the depth of tumor growth with MRI has an accuracy of about 60 % (Jamil et al. 2008), but with the MRI technique still under development, imaging reaches a higher level of precision, however this has not yet been correlated with accuracy of overall stage (Riddell et al. 2007). MRI cannot differentiate each layer of the esophageal wall, therefore an alternative T differentiation standard is described by Botet et al. (1991) and by Riddell et al. (2007) (Table 7).

Recently developed MRI techniques such as diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI may provide a relative increased accuracy in clinical staging and response assessment of esophageal tumors.

In diffusion-weighted magnetic resonance imaging (DWI) each voxel reflects the amount of water diffusion at that location. This diffusion process can be quantified by measuring the apparent diffusion coefficients (ADCs) of a voxel. ADC measurements have been suggested for staging or as predictive markers. However, its role for staging looks not as promising as its role as a predictor (Sakurada et al. 2009; Aoyagi et al. 2011). Further investigation is warranted to determine the exact role of DWI.

Dynamic contrast enhanced (DCE-) MRI has the ability to show alterations of vascular integrity that result from pathologic angiogenesis. Esophageal cancer is associated with a higher vascularization and an increase in vascular density, compared with normal esophageal tissue. In DCE-MRI, after a bolus of gadolinium chelate is administered intravenously, flow signal and leak can be observed. Two parameters are of importance, the contrast reagent transfer

Table 7 Radiographic staging criteria as described by Botet et al. (1991) and Riddell et al. (2007)

	Staging according to Botet	MRI features defined by Riddell
T stage		
T1	Thickening less than 5 mm	No discernable tumor
T2	Thickening of the wall greater than 5 mm and less than 15 mm	Intermediate signal intensity within the high signal submucosa and muscularis propria (low signal). Low signal outer margin of muscularis propria clearly defined and remains intact
T3	Thickening of the wall greater than 15 mm with irregularity of the outer margin	Nodular irregularity of the outer margin of the muscularis propria. Intermediate signal intensity nodules extending from the esophageal wall into the peri-esophageal tissues
T4	Tumor invasion of adjacent structures such as the trachea, aortic pericardium, or vertebral body	Intermediate signal intensity tumor extending into adjacent structures. Loss of a high signal fat plane between intermediate signal intensity tumor and an adjacent structure
N stage		
N0	Lymph nodes less than 10 mm in diameter were considered benign nodes	Uniform high signal intensity returned from peri-esophageal tissues
N1	Lymph nodes greater than 10 mm in short axis diameter were considered abnormal	Nodular intermediate signal intensity nodules >2 mm in size within the peri-esophageal tissues

between plasma and interstitial space (Ktrans) and the volume fraction of the interstitial space (Ve). These parameters can help distinguishing normal tissue from tumor tissue. DCE-MRI could have a role in the staging phase as it distinguishes histologic subtypes (Oberholzer et al. 2008). But it also perceives tumor microvascular density changes during chemoradiotherapy and can be imaged by DCE-MRI signal (Chang et al. 2008). Therefore, for monitoring response following CRT it holds the most promise.

2.3.5 Molecular Markers/Signatures

2.3.5.1 Background
Concurrent chemoradiation with or without surgery is commonly utilized as primary management of patients with non-metastatic disease. However, there is significant heterogeneity of response, suggesting that there are sub-populations that derive differential treatment benefit from RT. For example, approximately 30 % of patients experience a complete pathological response (Berger et al. 2005; Donahue et al. 2009). A molecular diagnostic that can identify these patients could be utilized clinically to avoid surgery for these patients. In contrast for patients that are predicted to be less responsive to RT, their management could be impacted by either offering RT dose intensification and/or prioritization of surgery (without RT).

At its most basic, a molecular signature is a collection of features that attempt to explain a complex phenotype. While a single predictive molecular marker would be ideal, such an isolated predictor of response to therapy in esophageal cancer has not been documented. In lieu of such a discovery, the technique of combining multiple analytes provides an opportunity to develop a predictive molecular assay;

there continue to be a relatively small number of molecular signatures that are routinely part of clinical practice.

2.3.5.2 Molecular Signature Development
Developing a molecular signature typically involves two steps. In the first step, features (genes, proteins, microRNAs etc.) are selected that define the phenotype of interest (i.e. responders to radiation therapy). Once the features are selected then an algorithm is generated to predict the phenotype in an unknown sample. A classic approach is to use samples in a dataset as a "training set" to identify the features and develop the signature. Once the signature is developed, its predictive accuracy is tested on a validation set, ideally independent of the training set. A significant problem in the field of molecular signatures has been their inherent dependence on the "training set" and thus a lack of robust validation analysis (Watanabe et al. 2006; Dalton and Friend 2006).

2.3.5.3 Radiation Therapy Molecular Signatures
The majority of molecular signatures in the literature have been developed to describe disease prognosis (independent of treatment), molecular subtypes and/or response prediction to chemotherapy. However, two independent groups have developed RT-specific signatures that have considerable clinical validation. Weichselbaum and colleagues developed an interferon-related gene signature for DNA damage, which was independently validated as a predictor of adjuvant chemotherapy efficacy and for local–regional control after RT in breast cancer (Weichselbaum et al. 2008). Separately, Eschrich and colleagues utilized a systems biology approach to identify a molecular signature of intrinsic tumor radiosensitivity (Eschrich et al. 2009a, b). Using ten specific genes they modeled a radiosensitivity

index (RSI) that has been independently validated in multiple disease sites (rectal, esophagus, head and neck, breast) in over 1,000 patients. Of the two signatures, RSI has been validated in a small dataset of esophageal cancer patients (n = 12). The predicted RSI was significantly different in responders (R) vs. nonresponders (NR) in esophageal (RSI R vs. NR 0.37 vs. 0.50, p = 0.05). A low RSI value is consistent with a more radiosensitive tumor. The range of RSI values for 7 responders was 0.11–0.53 and for 5 non-responders was 0.46–0.54. Therefore it is possible that this signature can be adjusted to support specific clinical decisions to improve clinical care for esophageal cancer patients.

2.3.5.4 Clinical Applications for an RT Molecular Signature in Esophageal Cancer

A challenge to the development of a clinically relevant radiosensitivity molecular signature stems from RT's broad applicability as a therapeutic agent in cancer. Since RT is used in different settings depending on disease site, the clinical utility of the signature would vary depending on the clinical application. A requirement for any signature that is to be applied routinely in the clinic is the development of a standardized and reliable process for tissue acquisition, processing, RNA isolation and gene expression measurement. Recently, the National Cancer Institute selected RSI for commercial development through the recently created Clinical Assay Development Program (CADP). The purpose of the project is the development of an analytically validated, commercial-grade diagnostic platform for RSI that will be ready for testing in clinical trials.

There remains significant opportunity to improve the clinical outcomes for esophageal cancer patients by identifying biological sub-populations that will derive differential treatment benefit from RT. Tailoring RT to fit a particular molecular RT profile will lead to the development of biology-based radiation oncology and result in better RT utilization.

3 Toxicity

The evolution of treatment for locally advanced esophageal cancer from single-modality surgery or radiotherapy to multimodality therapy has resulted in improved outcomes. Unfortunately, CRT comes with a potential increase in toxicity and resultant detriment to a patient's short-term quality of life (van Meerten et al. 2008).

The risks vs. benefits of the treatment are decisive in patient's decision to receive CRT. To make a well-considered decision, patients should be counseled before start of treatment about the potential toxicities. We give an overview of potential risks and toxicities for patients receiving multimodality treatment or single modality radiotherapy. We provide parameters, where available, that predict toxicity.

Among the many challenges with estimating toxicity risk based on the available publications, is that toxicity scoring systems are not uniform—making direct comparison impossible. The most frequently used scoring systems for toxicity are the Common Terminology Criteria for Adverse Events (CTCAE) (Trotti et al. 2003) of the National Cancer Institute (NCI) and the toxicity criteria from the Radiation Therapy Oncology Group (RTOG) system.

3.1 Esophagitis

The most common acute and late toxicity, excluding fatigue, for esophageal cancer patients treated with (chemo-) radiotherapy is, as expected, esophagitis.

3.1.1 Acute Esophagitis

Radiation induced acute esophagitis presents as dysphagia with resultant malnutrition and dehydration, requiring nutritional support (enteral or parenteral) in 17–35 % of the patients (Ahn et al. 2005).

The incidence of acute esophagitis (any grade) ranges from 19 to 79 % and grade ≥ 3 esophagitis is reported in 1–43 % of patients. This broad scale of the reported esophagitis depends, primarily, on the differences in toxicity reporting and definition. Other potential risk factors for esophagitis include dose schedules and treated volume of the esophagus. Finally, the incidence of esophagitis increases with the addition of chemotherapy to radiotherapy and may vary depending on the chemotherapy schedule given (Meluch et al. 2003; Urba et al. 2003; van Meerten et al. 2006; Cooper et al. 1999; Ajani et al. 2008).

3.1.2 Late Esophageal Toxicity

Late esophagitis can present as dysphagia, stricture, necrosis or fistula of the esophagus. The incidence rates of this late toxicity are mainly based on definitive chemoradiation studies. Late esophageal toxicity of any grade occurs in about 35 % of the patients and a grade ≥ 3 late esophageal toxicity has been seen in 8–21 % of the patients (Cooper et al. 1999).

The strongest predictor for late esophageal toxicity is the severity of acute esophagitis, as a result of consequential late effects. Other predicting parameters for esophageal toxicity are dosimetric.

3.1.3 Parameters Predicting Esophagitis

From lung cancer series we have learned several predicting parameters for acute and late esophageal toxicity. As described earlier, the strongest parameter is the severity of

the acute toxicity, but other parameters are a combination of radiation dose and treated volume of the esophagus.

A number of dosimetric parameters have been developed in an effort to reduce the continuously distributed dose-volume histogram (DVH) to a few clinically relevant indices. These relevant indices include: the percent organ volume receiving at least a certain dose (V_{20Gy}, V_{30Gy}, V_{40Gy}); the surface area receiving at least a certain dose (SA_{20Gy}, SA_{30Gy}, SA_{40Gy}); the length of the esophagus included in the radiation field to a threshold dose ($LETT_{20Gy}$, $LETT_{30Gy}$, $LETT_{40Gy}$); the mean esophageal dose (MED), defined as the average dose to the esophagus; and the maximal dose, defined as the highest point-dose within the irradiated esophageal volume (Milano et al. 2007; Rose et al. 2009).

Rose et al. (2009) provided a clear review of 18 lung cancer studies reporting dosimetric parameters predicting esophagitis. They identified 83 unique dosimetric parameters, of which only 6 were evaluated in 5 or more studies that were significantly associated with radiation esophagitis: MED, V_{20Gy}, V_{30Gy}, V_{40Gy}, V_{45Gy} and V_{50Gy}. Correlation was found for acute radiation esophagitis with MED, V_{20Gy}, V_{30Gy}, V_{40Gy} and V_{45Gy}. Correlation with the combined endpoint of acute and chronic radiation esophagitis was found with MED and V_{50Gy}. Logistic models relating DVH parameters to clinically significant acute esophagitis were identified.

For esophageal cancer, dosimetric predictors for esophagitis have not been reviewed with this precision and one could argue that these dosimetric predictors for esophagitis could be similar for esophageal cancer patients as for lung cancer patients. However, the etiology of esophageal cancer is different from lung cancer and the esophagus of esophageal cancer patients has been subjected to other treatment modalities and received greater inflammatory insult than the esophagus of lung cancer patients. Therefore it is not certain if the relatively normal esophagus of lung cancer patients is proportionally as sensitive to radiation damage and may not respond similarly. It may not be appropriate to extrapolate these dosimetric parameters to esophageal cancer patients.

3.2 Pneumonitis

Radiation pneumonitis (RP) is a major adverse event after thoracic irradiation. While the majority of patients with RP present with mild symptoms such as a dry cough, RP can result in severe morbidity and potential mortality.

Incidences of radiation pneumonitis grade ≥ 2 have been reported as high as 20–22 % (Hsu et al. 2009; Nomura et al. 2012) for esophageal cancer patients treated with definitive chemoradiation.

3.2.1 Parameters Predicting Pneumonitis

Predictive factors for RP have extensively been reported for irradiated lung cancer patients (Vogelius and Bentzen 2012), but there are only a few reports of esophageal cancer available (Hsu et al. 2009; Nomura et al. 2012; Wang et al. 2008; Asakura et al. 2010; Tucker et al. 2006). Predictive parameters for RP in lung cancer patients include clinical factors such as older age, disease located in mid-lower lung (Vogelius and Bentzen 2012), and dosimetric parameters such as mean lung dose (MLD) (Kwa et al. 1998), the percent of lung volume receiving at least 20 Gy (V_{20Gy}), 13 Gy (V_{13Gy}), 10 Gy (V_{10Gy}) or 5 Gy (V_{5Gy}) (Palma et al. 2012).

For esophageal cancer patients, predictors for pulmonary complications were studied on much smaller study cohorts and mainly on studies involving neoadjuvant chemoradiation and surgery. Pulmonary complications in these studies include both radiation pneumonitis as pneumonia, atelectasis, pleural effusion and pulmonary embolism. Significant predictors for pulmonary complications were the clinical parameters: stage IV, induction chemotherapy before CRT (Wang et al. 2006) and impaired pulmonary function (FEV1) before surgery, as well as the dosimetric parameters of mean lung dose, effective dose, V_{10Gy} and absolute volume of lung receiving <5 Gy were significant predictors for pulmonary complications.

Radiation oncologists have to balance all dosimetric and patient specific predictors for pulmonary complications of radiotherapy before approval of the treatment plan.

3.3 Hematologic Toxicity

Hematologic toxicity is the most common side effect in patients treated with chemotherapy. The severity of these adverse events depends on the chemotherapy regimen and number of cycles given.

Generally, these hematologic toxicities consist of neutropenia, anemia, and thrombocytopenia. As expected, regimens that use lower doses and fewer cycles report lower toxicity rates (Urba et al. 2001; Minsky et al. 2002; David 2008).

The most common regimens used are 5-fluorouracil (5-FU) and cisplatin based, but other regimens including carboplatin combined with paclitaxel are increasingly employed, likely due to better patient tolerance (van Hagen et al. 2012). Still, their remains a great variety of chemotherapeutic regimens, prescribed doses and number of cycles used.

In the studies that subdivide hematologic toxicity, the most common toxicity reported is neutropenia and with incidences of 9–78 % (van Hagen et al. 2012; Urba et al. 2001) with the highest incidence of myelotoxicity reported for triple agent chemotherapy regimens.

3.4 Cardiac Toxicity

The most common manifestation of late radiation injury to the heart is pericardial effusion, which may present as acute pericarditis, chronic pericardial effusion, or remain asymptomatic. Although myocardial damage is less frequent, it can result in severe toxicities, such as myocardial infarction.

From long term survivors of Hodgkin lymphoma and left sided breast cancer we have learned that radiation induced cardiac pathology leads to significant morbidity and mortality. With the overall survival of esophageal cancer patients improving, along with increasing numbers of long-term survivors, late cardiac toxicity becomes a growing concern.

In a study of 101 patients treated with definitive chemoradiation for esophageal cancer 28 % developed pericardial effusion and V_{30Gy} was found to be the only significant predictor (Wei et al. 2008). Incidence of cardiopulmonary toxicity has been reported as high as 29 % in elderly compared to 3 % for younger patients (Morota et al. 2009).

Myocardial perfusion defects were detected in 54 % of the esophageal cancer patients treated with radiotherapy compared to 16 % of patients treated with surgery alone, 42 % had mild inferior wall ischemia compared to 4 % of the surgery only group. The perfusion defects were related to the area of the heart receiving ≥ 45 Gy (Gayed et al. 2006).

Other dosimetric predictors for late symptomatic cardiac toxicity besides V_{30Gy}, V_{45Gy} are mean heart dose (MHD) ≥ 40 Gy (Hashimoto et al. 2008) and thresholds for toxicity defined as $V_{20Gy} \geq 70\,\%$, $V_{30Gy} \geq 65\,\%$ and $V_{40Gy} \geq 60\,\%$ of the cardiac volume (Konski et al. 2012). Important risk factors for development of symptomatic cardiac toxicity is advanced age and female gender.

Validation of these predictors is necessary before these parameters can be implemented as constraints in treatment planning.

3.5 Quality of Life

It is increasingly recognized that health-related quality of life (HRQoL) is a central and increasingly quantified clinical outcome measure in oncology. Quality of life outcomes are important in new treatment regimens under evaluation or intensified regimens with small benefits in long-term outcomes. In a group of 202 patients comparing multimodality treatment with surgery alone there was a negative impact in HRQoL before surgery but postoperatively the HRQoL was similar to those who had surgery alone (Reynolds et al. 2006). This temporary negative effect of the HRQoL confirmed by the results of van Meerten et all, where the HRQoL scores were restored or even improved 1 year postoperatively (van Meerten et al. 2006). Chemo-radiotherapy has a temporary negative effect on the quality of life.

In conclusion, the use of multimodality therapy of esophageal cancer results in a significant negative impact in the short-term quality of life. However, this is a temporarily effect and 1 year after surgery the HRQoL was restored and similar for patients treated with multimodality and surgery-alone.

4 Treatment Technique

Over the past several decades there has been a tremendous evolution of technological advances in radiotherapy treatment planning. Although two dimensional treatment planning was once the standard of care, the implementation of the computed tomography (CT) to treatment planning has made 3D conformal radiation therapy (3D-CRT) possible. With better anatomical visualization and target delineation, this technique created the first step to sparing normal tissue.

Recently, this 'classic' 3D-CRT evolved to intensity-modulated radiotherapy (IMRT) using multiple beams, allowing more concave dose distributions around the target volume and therewith avoiding normal structures. IMRT plans improve target conformity and spares organs at risks when compared with 3D-CRT.

Volumetric-arc-therapy (VMAT) is the novel form of IMRT where intensity modulated radiation is delivered during one or more gantry arcs, with continuous variable beam aperture, variable dose rates and gantry speed modulation. This has advantages in terms of simplicity of optimization and fast delivery. This fast delivery results in a shorter beam-on time. Subsequently, with a VMAT plan, as compared to IMRT plan, there is a reduction of the amount of monitor units given of 20–67 % (Vivekanandan et al. 2012; Yin et al. 2012; Van Benthuysen et al. 2011). VMAT further reduces the dose to the heart and lungs and slightly improves the dose coverage to the PTV.

4.1 Parameters to Evaluate Treatment Plans of Different Techniques

Irradiation of esophageal cancer comes with the risk of significant toxicity, with the organs at risk being the heart, lung, esophagus and spinal cord. The aim of the implementation of these novel techniques is to reduce the toxicities to these organs while retaining or improving target coverage.

4.2 Heart

VMAT and IMRT treatment plans reduce the heart dose compared to 3D-CRT. When the parameter V_{30Gy} of the heart is measured, a significant reduction from 55 to 31 % with VMAT vs. 3DCRT (Hashimoto et al. 2008) is seen, for IMRT vs. 3DCRT this is from 61 to 24.8 % (Konski et al. 2012) and a reduction of 33.5 % in favor of VMAT over IMRT (Wei et al. 2008). This dosimetric parameter V_{30Gy} is correlated to symptomatic cardiac disease (Vogelius and Bentzen 2012) and a reduction of the dose to the heart should lead to a reduction in late cardiac toxicity. Long-term studies are necessary to determine the contribution of this dose reduction to the incidence and severity of cardiac toxicity.

4.3 Lung

A similar reduction is also seen for lung doses, where there is a general reduction of the dosimetric parameters (V_{10Gy}, V_{20Gy}, V_{30Gy}) (David 2008; Wei et al. 2008) when comparing VMAT to IMRT. However, there is a slight increase of the mean lung dose (MLD) of 2 % and an increase up to 13 % of the V_{5Gy} in thoracic esophageal tumors (Wei et al. 2008). How this reduction of the V_{20Gy} and increase of V_{5Gy} and MLD will affect pulmonary toxicity remains unclear.

A retrospective review compared 676 patients treated with 3DCRT and IMRT. Treatment modality IMRT (vs. 3DCRT), in addition to known prognostic factors as stage and performance status, was associated with overall survival, locoregional control and noncancer-related death (Lin et al. 2012).

IMRT and VMAT plans result in better target dose coverage, reduces doses to the heart and high dose volumes to the lung and potentially leads to better outcomes. VMAT reduces the amount of monitor units given, reduces the high dose to heart or lung even further, but slightly increases the low radiation dose to body or lungs.

5 Nomograms and Prognostic/Predictive Models

5.1 Goals of Predictive Models in Esophageal Cancer

Clinical prediction tools used in the management of esophageal cancer aim to estimate the likelihood of specified outcomes, both dichotomous and time to event data, based on relevant clinical variables. Particularly for esophageal cancer—due to its baseline poor survival and the high morbidity of the required medical intervention, accurate and applicable estimates of treatment outcomes are essential for medical decision-making, patient counseling, and clinical trial design. Recent randomized and appropriate powered clinical data demonstrates the survival benefit of neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy rather than isolated esophagectomy for specified patient populations (Berger et al. 2005). However, in this investigation, similarly, groups were stratified based on TNM staging and a heterogeneous pathologic response to CRT was observed. The survival benefit observed within the advanced stage patients is not uniformly shared, concentrated within those patients that have a pathologic response and may be entirely absent for those with no observable downstaging.

Estimates of the survival benefit derived from CRT for a particular patient given their demographic information and oncologic staging can be an aid for patient education while aiding in medical decision making and potentially improving outcomes by employing therapies predicted to be the most beneficial for each patient. It is likely that the variables included in relevant decision tools will include data beyond classical TNM staging and may ultimately involve molecular markers and novel post treatment restaging data (molecular and genetic markers were covered already in this chapter and will not be discussed in this subsection).

Standard pathologic TNM staging from the surgical specimen following neoadjuvant CRT (ypTNM) continues to be more prognostic of survival than any restaging or pre operative data—despite a, currently unpredictable, variable downstaging effect. A neoadjuvant treatment strategy makes estimating the survival benefit of chemoradiotherapy based on surgical stage difficult given that the final pathologic stage may not be the same as the stage at diagnosis. Concurrently, current techniques for clinical TNM staging and restaging techniques are unreliable.

Tools beyond predicting response and survival benefit to neoadjuvant CRT are required to model the risk for an individual patient undergoing or abstaining from some portion of trimodal therapy. Accurately predicting an individual patient's risk of morbidity and mortality from each treatment, particularly esophagectomy, will be an important tool in recommending an individualized treatment plan.
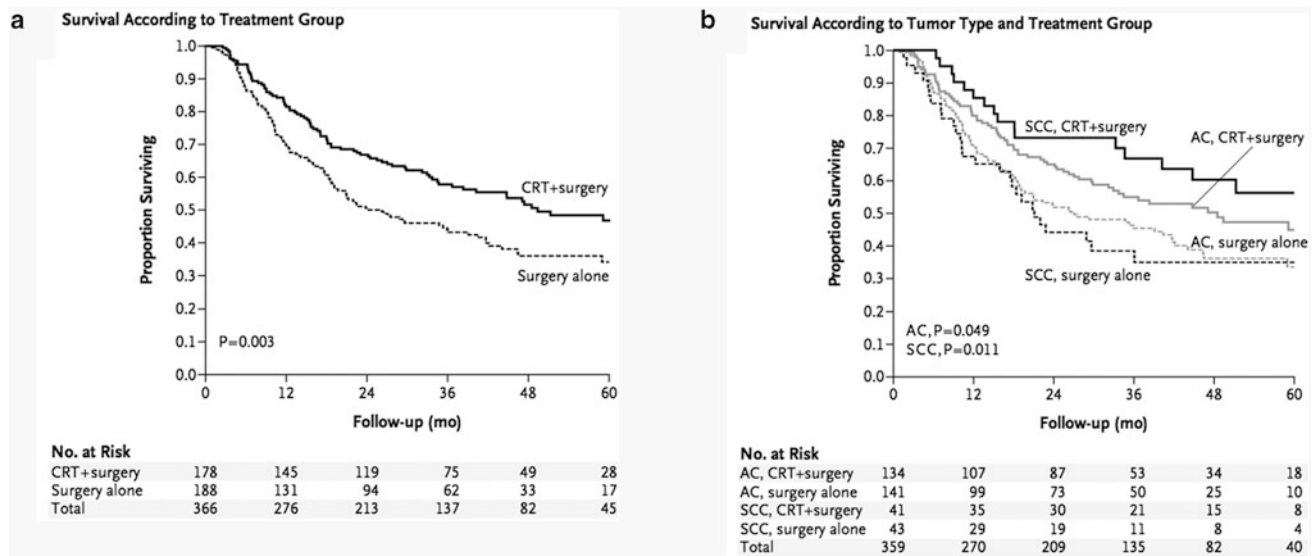
While nomograms are available for many of the aspects of esophageal cancer treatment mentioned above, careful examination of the data used, the covariates analyzed, and the patients included is required to avoid inappropriate application of a prediction tool to a specific patient. The general technical considerations of nomogram creation, propensity weighting, regression analysis, and data interpretation are covered separately in "Statistics of Survival Prediction and Nomogram Development'' of this text and will not specifically be addressed here.

Fig. 1 Kaplan–Meier plots of estimated overall 5-year survival. **a** Scohows a Kaplan–Meier plot of the estimated overall 5-year survival among patients with esophageal or esophagogastric-junction cancer who underwent neo-adjuvant chemoradiotherapy (CRT) followed by surgery (178 patients) or surgery alone (188), acrding to an intention-to-treat analysis. **b** Shows a Kaplan–Meier plot of the estimated overall 5-year survival among the 134 patients with adenocarcinoma (AC) treated with neoadjuvant chemoradiotherapy followed by surgery and the 141 treated with surgery alone, and the 41 patients with squamous-cell carcinoma (SCC) treated with chemoradiotherapy followed by surgery and the 43 treated with surgery alone, according to an intention-to-treat analysis. Other tumor types were excluded from this analysis. Adapted from van Hagen et al. (2012)

5.2 Predicting Benefit from Neoadjuvant Chemoradiotherapy

Accurately predicting the benefit for a specific patient and evaluating the response to neoadjuvant treatment continues to a challenge and potential point of controversy. Although already discussed in this chapter, it is appropriate to again address the recent evidence supporting neoadjuvant CRT in subpopulations of those affected with esophageal cancer. A recently published, appropriately powered, randomized controlled trial from van Hagen et al. (van Hagen et al. 2012) evaluating patients with disease beyond T1N0 and up to T3N1 based on clinical staging, demonstrated an overall statistically significant survival benefit, seen below in Fig. 1a (all patients) and 1b (stratified by histology). Overall, patients receiving trimodality therapy had a median survival of 49.4 vs. 24.0 months in the surgery only group (p = 0.003).

Traditional Kaplan–Meier survival analysis demonstrates that their selected population will have an overall survival benefit from neoadjuvant CRT. When performing subgroup survival analysis, this benefit remained statistically significant both for adenocarcinoma (AC) and for squamous cell (SCC) histology.

However, the survival benefit of chemoradiotherapy is likely not distributed evenly across all patients. Those patients who have a pathologic complete response (pCR), with no residual tumor identifiable in the surgical specimen, or even those with partial response following neoadjuvant CRT have a better prognosis than those that have no appreciable or minimal response to CRT. Identification of a molecular or histologic marker predictive of response to CRT, similar to the RSI discussed above, would provide useful adjunctive clinical information. Several institutions have attempted to predict clinical surrogates for benefit from CRT (Ajani et al. 2012). However, ypTNM remains a useful prognosticator of outcome and was recently employed in the construction of a predictive web based tool (Eil et al. 2013).

While the prognostic power of the ypTNM has been validated previously (Holmes and Vaughan 2007) the exact benefit of neoadjuvant CRT on patients by their documented ypTNM has not been examined. Eil et al. (2013) proposed a survival prediction tool applicable to resected patients with or without neoadjuvant CRT based on a SEER-Medicare database of 824 patients. The multivariate regression coefficients and OR are shown below in Table 8. A web browser based nomogram was built from this model to create individual estimates of survival and is available at http://skynet.ohsu.edu/nomograms/.

The beta coefficients and odd ratios predicted from the regression model are represented in Table 8. The predicted survival benefit from neoadjuvant CRT persisted for advanced stage disease present after treatment (Eil et al. 2013). For example, based upon the model, a 70 year old male with adenocarcinoma and 12 lymph nodes harvested

Table 8 SEER—medicare predictive log logistic multivariate regression model parameters

Covariate	Beta coefficient	P	OR	95 % CI
(Intercept)	6.4560	0.0096		
Age	−0.0310	0.4026	1.1	0.9–1.18
Age′	−0.3009	0.0680	1.7	0.9–2.8
Age″	0.8060	0.0218	0.3	0.01–0.8
Sex = female	0.3055	0.0002	0.6	0.5–0.8
Tstage = 2	−0.3188	0.0097	1.7	1.13–2.6
Tstage = 3	−0.8054	<0.0001	3.9	2.6–5.7
Tstage = 4	−1.1091	<0.0001	6.4	3.5–11.8
Tx = CRT	−0.8059	<0.0001	3.8	2.5–5.9
Histology = squamous	−0.2701	0.0003	1.6	1.23–2.0
Nodes = 1	−0.7019	<0.0001	3.2	2.2–4.7
Nodes = 2	−0.9804	<0.0001	5.2	3.3–8.1
Nodes = 3	−1.2394	<0.0001	8.0	3.6–17.4
TotalLN	0.0286	<0.0001		
Tstage = 2 × tx = CRT	0.5523	0.0011		
Tstage = 3 × tx = CRT	0.6674	<0.0001		
Tstage = 4 × tx = CRT	1.2559	<0.0001		
Tx = CRT × nodes = 1	0.9149	<0.0001		
Tx = CRT × nodes = 2	0.3996	0.0262		
Tx = CRT × nodes = 3	0.4749	0.1284		
Tx = CRT × totalLN	−0.0167	0.0243		
Log (scale)	−0.5176	<0.0001		
Log (scale)	−0.5176	<0.0001		

Log logistic multivariate regression model beta coefficients. The associated odds ratio (OR) and 95 % CI are also provided. Note: age modeled using restricted cubic spline function with four knots, requiring three independent coefficients: Age, Age′, and Age″. Interaction terms indicate how the influence of adjuvant chemo-therapy or CRT varies by T and N stages and total LN (Eil et al. 2013)
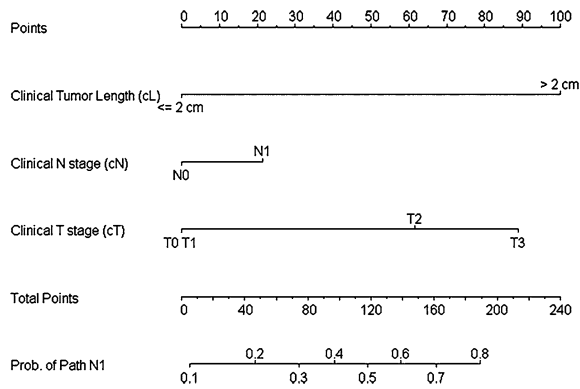
with ypT4N2 stage having received neoadjuvant CRT would have a predicted 3 year OS of 29 vs. 12 % without CRT. A similar patient with ypT2N1 disease is predicted to have a 3 year OS of 64 % with neoadjuvant CRT vs. 45 % with isolated esophagectomy (Eil et al. 2013).

This analytic tool, being based on pathologic stage, is most applicable in the post-operative setting—when the ypTNM stage is available for postoperative counseling, comparison, and treatment planning. Additionally, such risk modeling is helpful in the design of research protocols for identifying homogenous high risk groups. One would expect the model to underestimate of the benefit of neoadjuvant therapy due to its expected downstaging effect on ypTNM as compared to cTNM. The ultimate goal of a predictive decision aid for designing an individualized treatment course would include early identification, or even prediction, of responders and non-responders—leading to avoidance of ineffective and dangerous application of both chemoradiotherapy and surgery.

With the above predictive tool, one can estimate the benefit of neoadjuvant CRT based on the final pathologic stage. However, this definitive information is not available when considering whether to administer neoadjuvant treatment. Pre-treatment knowledge, or at least likelihood of nodal status would aid in guiding treatment—as patients N1 or greater benefit significantly from neoadjuvant treatment (Eil et al. 2013). In 2010, with a training sample of 164 patients resected with curative intent at M.D. Anderson Cancer Center and excluding those that received neoadjuvant therapy Gaur and colleagues developed a tool for predicting nodal involvement based on preoperative clinical characteristics (Gaur et al. 2010). The nomogram was validated externally, showing a concordance index (CI) of 0.77. Their predictive tool, represented in Fig. 2 below, was adapted into a traditional point system with the strongest clinical indicator being valued at 100 points and other variables being weighed against this as described by Jasonos et al. (2008).

In reviewing their point scale weighting, the most heavily weighted variable was tumor length, which the authors chose to dichotomize at 2 cm. Clinical evaluation of nodal status (cN), or EUS, was not significantly associated

Points   0 10 20 30 40 50 60 70 80 90 100

Clinical Tumor Length (cL)   <= 2 cm   > 2 cm

Clinical N stage (cN)   N1 / N0

Clinical T stage (cT)   T2 / T0 T1 / T3

Total Points   0 40 80 120 160 200 240

Prob. of Path N1   0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8

Fig. 2 Nomogram to predict pathologic lymph node involvement (path N1) using clinical measurements for M. D. Anderson training set. The nomogram consists of six rows. Row 1 (points row) is the point assignment for each variable. Rows 2–4 correspond to the variables included in the model. For an individual patient, each variable in rows 2–4 is assigned a point value, which is determined by drawing a vertical line from the appropriate position on the variable row to the points row. The assigned points for all three variables are added, and the total is marked in row 5 (total points). Then, the risk of path N1 is calculated by drawing a vertical line from the appropriate position on the total-points row to the final row (predicted path N1 probability). Point scale nomogram adapted from Gaur et al. (2010)

with pathologic nodal status on multivariate analysis, with an OR of 1.5 (0.5–5.5; p = 0.5). This predictive tool estimates that a cT2N0 patient with a tumor that measures <2 cm has only a 27 % chance of having N1 disease, while a cT2N0 patient with a tumor >2 cm has a 72 % of having N1 disease. This is troubling data given the inherent clinical confidence most place in EUS data, as well as the need for certainty in predicting nodal status—which many weight heavily when determining whether to offer neoadjuvant therapy. Additionally, the lowest risk oncologic features as measured by Gaur's nomogram, a T2 patient maintains a 27 % risk of having nodal disease. Many would consider this a high enough likelihood to consider CRT, given the documented benefit. More precise predictive tools are required to narrow the spectrum of patients considered for trimodal treatment.

5.3 Predicting Pathologic Complete Response After Neoadjuvant Chemoradiotherapy

The ability to confidently predict which patients with an apparent clinical CR (cCR) will have a pCR would provide an opportunity to further stratify which patients may not obtain a survival benefit from esophagectomy following chemoradiotherapy. However, a pCR does not guarantee disease free survival. Many patients with a documented pCR have documented disease recurrence and ultimately succumb to their disease. However, the prognosis is significantly improved and the likelihood of a local failure is

greatly reduced for patients with no residual disease when compared to all other patients with residual disease (Chirieac et al. 2005; Donahue et al. 2009; Brucher et al. 2006). Those patients that respond with a pCR, approximately 30 % of those undergoing neoadjuvant CRT, demonstrate a 55 % 5 year survival vs. 34 % for all patients treated with neoadjuvant CRT followed by surgery. The prognostic power of the pathologic response has been reproducible, with some advocating for its addition to the traditional TNM stage (Swisher et al. 2005). Of those who achieve a preoperative cCR, a small minority have a true pCR. Some are found to have a partial response, and others have no demonstrable response to neoadjuvant CRT in comparison to estimated pretreatment TNM (cTNM). However, based on the SEER-Medicare based nomogram discussed above, even patients with advanced ypTNM stage benefitted from neoadjuvant CRT (Eil et al. 2013). Given the reliable prognostic power of response to CRT, the accuracy of the clinical stage found prior to neoadjuvant treatment is critical to ultimately determining which strategy will result in the greatest survival benefit.

Several series have demonstrated post neoadjuvant CRT restaging techniques to be concerningly inaccurate. Post treatment biopsies have an accuracy approaching 30 % and are not prognostic of outcome. Post treatment endoscopic biopsy reveals no residual malignancy in approximately 80 % of patients, while the incidence of pCR is 25–30 %.

Regarding the accuracy of EUS ycTNM, Kalha and colleagues performed a retrospective review of 83 patients from MD Anderson revealed that EUS restaging correctly identified the T stage in only 29 % of patients (Kalha et al. 2004). The sensitivity for detecting nodal disease was only 51 %. Of the 22 patients who responded to the neoadjuvant chemoradiotherapy with a complete pathologic response, 19 were restaged by EUS as having residual disease. Given the above findings, some have endeavored to find modes of post treatment evaluation other than clinical restaging to estimate the patient's state of disease and response to treatment.

Of the diagnostic modalities currently available, the change in PET standard uptake value (SUV) before and after treatment has proven to be the most reliable indicator of response (Ajani et al. 2012). In the setting of these diagnostic limitations, at the end of 2012 a predictive nomogram with an end point of pCR based on clinical parameters following CRT was released based on the institutional database of MD Anderson. The strongest predictor of pCR was the SUV after treatment. Unfortunately, PET scanning calibration is not standardized across institutions. In the face of these limitations, they produced a model with a bias-corrected area under the curve (AUC) of 0.7 (95 % CI = 0.64–0.73). Figure 3 represents their point scale nomogram.
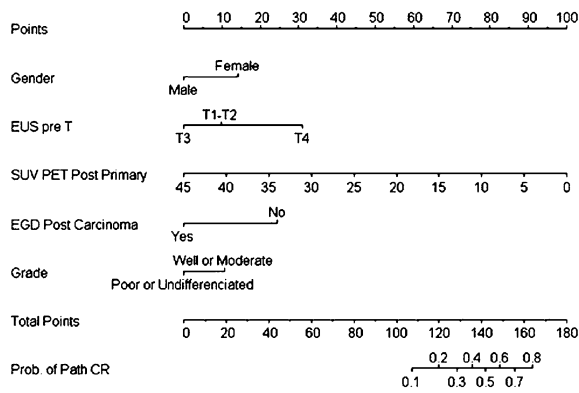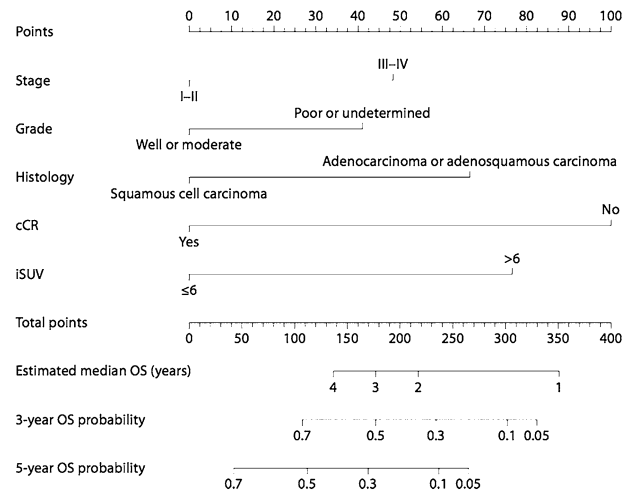
Fig. 3 The nomogram consists of eight rows. Row 1 (points row) is the point assignment for each variable. Rows 2–6 correspond to the variables included in the model. For an individual patient, each variable is assigned a point value, which is determined by drawing a vertical line from the appropriate position on the variable row to the points row. The demonstrates that combining variables can increase the probability of predicting pathCR to as high as 80 % if a patient scores >160 points. Among the most influential factors for attaining the highest scores for predicting pathCR were lower postchemoradiation SUVmax and the absence of cancer cells on postchemoradiation biopsy specimens. Point scale nomogram adapted from Ajani et al. (2012)

While these predictive tools hold promise for improving individualized treatment regimens, their discriminatory power is not yet such that one could depend upon it for embarking upon an esophageal preservation strategy for a specific patient. Molecular markers and oncogenetics hold promise to increase our predictive power in the future. This topic is discussed elsewhere in this chapter and will not be addressed in this section.

5.4 Predicting Survival for Patients Receiving Definitive Chemoradiotherapy

A tool predicting survival for patients unfit, unwilling, or of too advanced stage for surgery may not intuitively be of value—what decision is there to make when the planned treatment is already determined? However, when one considers the purpose of a nomogram and brings the information provided by such a tool into the larger clinical arena, it could advance all of the goals of a clinical prediction tool: aid in medical decision making, provide straightforward information for patients, supply baseline outcomes to aid in research protocol design, and potentially a baseline to compare against similar patients who did undergo CRT followed by surgery.

In contemplating the benefit of an esophageal preservation strategy for some patients based on their cCR and other appropriate variables, a predictive survival tool for those that have received definitive CRT would be immediately useful. Using their institutional clinical database including 257 patients undergoing definitive CRT Suzuki et al. (2012)

Fig. 4 Row 1 (points row) is the point assignment for each variable. Rows 2–6 correspond to the variables included in the model. For an individual patient, each variable is assigned a point value, which is determined by drawing a vertical line from the appropriate position on the variable row to the points row. Point scale nomogram adapted from Suzuki et al. (2012)

produced a nomogram predicting benefit from definitive CRT. Similarly to Ajani et al., discussed above, for predicting pCR, PET SUV was a significant predictor of outcome. However, here post treatment endoscopic biopsy was the strongest predictor of OS following treatment, as no pathologic staging data was available. Their final CI was 0.7 for predicting OS. Given the baseline complex medical history, making many of them inappropriate for operative intervention, OS analysis may be confounded by deaths due to non-oncologic etiologies (Fig. 4).

## 5.5 Predicting Perioperative Mortality

As part of a comprehensive strategy to correctly predict which patients will benefit from treatment, one must ultimately incorporate the potential mortality from treatment itself. Several nomograms for prediction of complications following esophagectomy have been published and are discussed below. As a general assertion one can say that these nomograms have been difficult to apply outside of their home institution due to the multifactorial etiology of the end outcomes, differing patient populations, operative techniques, and post operative management.

In 2006 Steyerberg et al. (2008) reported a predictive model for mortality following esophagectomy based on SEER-Medicare data from 1991 to 1996 and validated on several other cohorts. Perhaps due to the complex multifactorial nature of post operative outcomes, the Medicare database, and the low incidence of perioperative mortality the predictive power was low—a CI of 0.58 when externally validated.

Table 9 Score chart to estimate 30-day mortality after cancer-directed surgery for esophageal cancer

Characteristic	Score
Age, years	
50	−1
65	0
80	1
Comorbidity	
Pulmonary	1
Cardiovascular	1
Diabetes	1
Hepatic	1
Renal	1
Neoadjuvant therapy	
Radiotherapy	1.5
Chemoradiotherapy	1
Hospital volume, No. of esophagectomy/year	
Low (≤1)	0
Intermediate (1.1–2.5)	−0.5
High (≥2.6)	−1.5
Very high (±50)	−2

Sum score is obtained by adding scores. Intermediate scores for age can be approximated by linear interpolation. For example, age 72 corresponds to a score of +0.5. The formula to calculate the predicted probability of surgical mortality is P (mortality) $-1/[1 + \exp(2.41 - 0.32 \times \text{score})]$. Cancer. Adapted from Steyerberg et al. (2008)
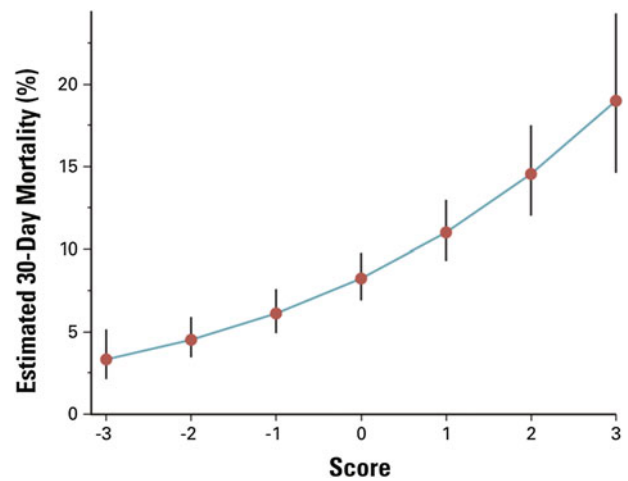
Fig. 6 Estimated surgical mortality in relation to the sum cumulative score that can be obtained from Table 9. The 95 % CIs are based on analysis of four cohorts, containing 3,592 patients undergoing surgery for esophageal cancer using the aforementioned scale and formula. Adapted from Steyerberg et al. (2008)

Table 9 below shows the variables considered in their nomogram with Fig. 5 graphically demonstrating the estimated 30-day perioperative mortality.

While the above model is not independently adequate for medical decision-making in its current state with a CI of 0.58, it provides a template for a more precise prediction tool. A more accurate, perhaps institution specific, prediction tool for perioperative mortality may be of use. Such a

Fig. 5 Adapted from Steyerberg et al. Score chart to estimate 30-day mortality after cancer-directed surgery for esophageal cancer

Characteristic	Score
Age, years	
50	−1
65	0
80	1
Comorbidity	
Pulmonary	1
Cardiovascular	1
Diabetes	1
Hepatic	1
Renal	1
Neoadjuvant therapy	
Radiotherapy	1.5
Chemoradiotherapy	1
Hospital volume; No. of esophagectomy/year	
Low (≤ 1)	0
Intermediate (1.1-2.5)	−0.5
High (≥ 2.6)	−1.5
Very high (± 50)	−2

tool could be of use in counseling high-risk patients with advanced stage to avoid esophagectomy based on a high estimate of postoperative mortality. Additionally, a perioperative mortality risk prediction tool may be used in conjunction with those predicting survival after cCR from chemoradiotherapy—identifying those patients most appropriate for esophageal salvage (Fig. 6).

6   Summary

While esophageal cancer continues to claim the lives of a significant number of those that it affects, aggressive trimodal treatment strategies within a targeted population has resulted in progressive increases in survival. However, neoadjuvant CRT followed by esophagectomy has the potential to provide significant survival benefit to patients whose tumor biology is responsive to CRT, despite advanced disease. However, the oncologic response to treatment is heterogenous across and within clinically stratified treatment groups. Accurately identifying those patients that will benefit from aggressive treatment, and sparing non-responders the risks associated with trimodality treatment will depend on novel utilization of existing prognostic tools and the development of additional assays.

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