Review Article

Clinical tools to predict outcomes in patients with esophageal cancer treated with definitive chemoradiation: are we there yet?

Abraham J. Wu, Karyn A. Goodman

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

Correspondence to: Abraham Wu, MD. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 22, New York, NY 10065, USA. Email: wua@mskcc.org.

Abstract: Definitive chemoradiation (CRT) is a well-established treatment for esophageal cancer, but disease recurrence is common and many patients do not achieve initial remission with CRT alone. Predictors of outcome with CRT are needed to guide prognosis and further treatment decisions, in particular the need for post-CRT surgery. We review the role of baseline clinical factors, such as histology and tumor bulk, in predicting response to CRT. Post-CRT assessments, particularly PET imaging, may provide further information about the likelihood of complete response and survival, but the predictive power of clinical assessments remains limited. Emerging research on biomarkers holds promise for more tailored and accurate prediction of outcome with definitive CRT.

Keywords: Esophageal cancer; radiotherapy; chemoradiation (CRT); response prediction

Submitted Sep 04, 2014. Accepted for publication Oct 29, 2014.
doi: 10.3978/j.issn.2078-6891.2014.099
View this article at: http://dx.doi.org/10.3978/j.issn.2078-6891.2014.099

Introduction

Radiotherapy, when delivered with concurrent radiosensitizing chemotherapy, is a potentially curative treatment for nonmetastatic esophageal cancer. The seminal RTOG 8501 trial demonstrated that approximately one in four patients treated with concurrent chemoradiation (CRT) become long-term survivors. This was in contrast to patients treated with radiation alone, among whom there were no long-term survivors (1,2). Unfortunately, most patients treated with definitive CRT still experience disease recurrence, prompting many efforts to improve outcomes by intensifying CRT or adding additional treatment modalities, particularly surgery.

In many cases, the pattern of failure is local. The local progression rate in RTOG 8501 exceeded 50%, reflecting not only local relapse but also local persistence of disease in many patients. Efforts to improve the local control rate by increasing radiation dose have so far been unsuccessful (3,4). Higher radiation doses may not improve the therapeutic ratio in definitive CRT, given that acute toxicities of CRT are significant even with the moderate doses of RT currently used. Nonetheless, the optimal radiotherapy dose for patients treated with CRT alone is still unknown and depending on the primary tumor site and histology, patients may be treated with doses ranging from 5,000 to 6,600 cGy. Improved predictors of outcome after definitive CRT are urgently needed to better individualize therapy and identify patients who may benefit from dose intensification and those in whom moderate doses are adequate.

For patients with resectable disease, trimodality therapy with surgery after CRT is often favored. Since CRT achieves pathologic complete response (pCR) in only 20-30% of patients, surgery mitigates against the possibility of persistent tumor leading to local progression or distant metastatic spread (5). Two randomized trials of CRT with or without surgery demonstrated reduced local recurrence with trimodality therapy (6,7). However, these trials failed to demonstrate an improvement in survival with surgery, likely due to an increase in treatment-related mortality.

Despite the lack of a demonstrable survival advantage, it stands to reason that some patients with esophageal cancer benefit from surgery after CRT. Non-responders to CRT have residual viable malignancy that would be eradicated by

surgical resection, making surgery a curative intervention if occult systemic spread has not yet occurred. Conversely, for the substantial minority of patients who achieve complete pathologic response to CRT, surgical resection likely adds nothing to the probability of cure, while exposing the patient to the significant risks and morbidities of a major operation. For these reasons, the ability to predict whether CRT alone will be curative for a given patient would be immensely valuable.

Many factors have been examined as potential predictors of CRT response, which can be broadly divided into two categories: (I) potential predictors based on pre-treatment patient or tumor characteristics; and (II) potential predictors based on diagnostic tests or tumor characteristics during or immediately after CRT.

Pre-CRT predictors

Besides stage, the most important differentiating factor in the treatment and prognostication of esophageal cancer is histology. The literature establishing efficacy of definitive CRT is almost entirely limited to squamous cell carcinoma (SCC), which comprised the vast majority of patients in the RTOG 8501 trial, as well as the two major trials of CRT with or without surgical resection referenced above. There are few prospective data on definitive CRT for AC, which now represents the predominant form in the Western world. Multiple lines of evidence suggest that SCC is more likely to respond to definitive CRT than AC. For example, a matched-pair analysis of CRT in SCC *vs.* AC showed significantly greater rates of clinical complete response (cCR) in SCC (8).

pCR rates have been shown to correlate with outcome (9), and pCR rates in studies of preoperative CRT are a reasonable proxy for the expected outcome of definitive CRT in these patients. In the landmark CROSS trial, which compared pre-operative carboplatin and paclitaxel with concurrent radiotherapy to a dose of 4,140 cGy versus surgery alone, the rate of pCR was significantly greater for SCC than for AC (49% *vs.* 23%, P=0.008), though preoperative CRT proved beneficial for both subtypes (5). Investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) have also shown, based on analysis of post-CRT esophagectomy specimens, that the pCR rate is significantly greater in SCC than AC (10). The presence of signet ring cell features and high tumor grade may further diminish the probability of response to CRT in AC (11-13).

Because outcomes with definitive CRT are better established in SCC, some clinicians are more likely to defer surgery after CRT for SCC than for AC, when a cCR has been achieved. It is reasoned that SCC patients with cCR are more likely to have a pCR and therefore, potentially be cured without requiring surgery. Among patients with cCR to CRT, SCC histology was independently associated with improved disease-free survival an analysis by MD Anderson Cancer Center (MDACC) (13). However, a significant number of SCC patients with cCR may have microscopic residual disease, leaving open the question of whether surgery should nevertheless be pursued in cCR patients who can safely undergo resection (14).

One option that has been evaluated to balance the potential risks of surgery after definitive CRT with the need to address residual disease is the use of surgical salvage. This approach allows the opportunity to improve locoregional control while reserving surgical resection only for patients with residual or recurrent locoregional disease. The RTOG reported reasonably good results with definitive CRT in a small single-arm trial of selective surgical salvage in a cohort with mostly adenocarcinoma (AC) (15). Nonetheless, this option relies on the ability to distinguish between responders and non-responders to CRT.

Besides histology, baseline tumor bulk and extent is commonly hypothesized to predict outcome with definitive CRT. Indeed, the MDACC group found that node-positive status and T3/T4 disease correlated with worse disease-free survival after definitive CRT (13). Investigators from Taiwan reported that increasing pre-treatment tumor depth, as well as increased length, predicted for local recurrence after CRT (16). Along with T and N stage, lymph node size was found to be independently prognostic in SCC patients undergoing definitive CRT by Japanese investigators (17). It is logical that patients with a greater baseline disease burden remain at higher risk for relapse even if cCR to CRT is achieved, but a validated threshold for recommending further treatment such as surgery has not yet been established.

FDG-PET imaging, which has proven value in detecting occult metastatic disease in esophageal cancer, has also been investigated as a predictor for CRT efficacy. The intensity of FDG uptake correlates with tumor metabolic activity and may therefore predict biologic behavior and treatment responsiveness. Numerous studies have examined the prognostic value of baseline maximum standardized uptake value (SUV_{max}) in patients with esophageal cancer, with most showing a correlation between SUV_{max} and outcome (18). However, whether baseline SUV_{max} is an independent

prognostic factor in the context of treatment with CRT is less clear. For example, Rizk *et al.* identified a lower baseline SUV_{max} as a positive prognostic factor for patients undergoing surgery alone, but SUV_{max} no longer predicted survival when applied to patients undergoing preoperative CRT (19,20). In fact, patients with SUV_{max} >4.5 were more likely to achieve pCR after CRT, suggesting that higher baseline FDG avidity is actually a positive predictive factor for success with definitive CRT. However, an analysis by Suzuki *et al.* in definitive CRT patients reached the opposite conclusion, in that higher baseline SUV_{max} correlated with worse overall survival (21). A more recent analysis from this group indicated that patients with baseline SUV_{max} <6 fare equally well with CRT alone as with trimodality therapy, and this finding awaits validation in other cohorts and in the prospective setting (22).

Post-CRT predictors

Even if narrowly defined in terms of stage, histology, and metabolic activity as described above, it seems unlikely that pre-treatment clinical categorization alone can identify a population of esophageal cancer patients with reliably predictable outcome after CRT. Post-CRT assessments of tumor burden, since they attempt to measure CRT effectiveness directly, may be a more robust predictor of long-term outcome in a given patient. Positive identification of viable malignancy after CRT (such as with biopsy) essentially proves that definitive CRT will not be curative for that patient. However, it is much more difficult to show that the absence of detectable malignancy after CRT translates to cure, because of the inherent challenge of ruling out microscopic disease. The only way to prove that pCR has been achieved is to resect the tumor and subject the specimen to histologic analysis, but this obviously defeats the purpose of determining whether surgery is therapeutically beneficial in the first place.

The most commonly accepted method of establishing CRT response is endoscopic biopsy. Unsurprisingly, a negative post-CRT biopsy is correlated with a significantly better outcome than a positive biopsy, since the negative result at least holds some promise of an actual pCR (23). However, multiple studies have shown that most patients with a negative post-CRT biopsy have residual tumor cells in the esophagectomy specimen. As a result, the negative predictive value of endoscopic biopsy is only on the order of 30% (23-26). Whether surgery improves aggregate survival in such patients by removing persistent foci of disease remains unproven, based on the randomized studies of CRT with or without surgery discussed earlier. Regardless, it is clear that sampling error significantly limits the predictive power of post-CRT biopsy. The accuracy of restaging endoscopic ultrasound in the post-CRT setting is also quite poor (27).

Whether post-CRT PET can distinguish complete from incomplete responders has been extensively investigated. In a provocative study from Wake Forest University, investigators found that a complete metabolic response was the strongest prognostic factor for survival in patients treated with definitive CRT, and suggested that surgery may only be necessary for metabolic nonresponders (28). Investigators at MDACC reported that definitive CRT achieved equivalent survival to trimodality therapy only if a significant post-CRT metabolic response had been achieved similarly suggesting that persistent FDG-avidity is a useful determinant of whether surgery is needed (29).

Multiple groups have now reported strong correlation between post-CRT metabolic response and outcomes, both with respect to pCR and survival (30-34). However, some groups have also reported no significant or clinically useful association between residual FDG avidity and pCR (35,36). A review of multiple studies of PET response after induction chemotherapy or CRT attempted to synthesize these disparate results. Drawing overall conclusions from these retrospective studies was limited by inherent differences in patient characteristics and FDG-PET techniques, but it was concluded that residual FDG avidity likely has predictive value (18). Assessment of PET response after CRT appears to be less reliable than after chemotherapy alone, as persistent FDG-avidity from radiation esophagitis is typically indistinguishable from active malignancy.

FDG-PET has particular promise in evaluating response to chemotherapy in patients with esophageal AC. A seminal prospective trial from Germany showed that after starting induction chemotherapy, early response assessment with PET could predict whether significant pathologic response would be achieved (37). Reduction in the SUV_{max} of >35% from baseline to the scan performed 2 weeks into chemotherapy was associated with improved disease-free survival. A prospective trial at MSKCC of induction chemotherapy followed by preoperative CRT indicated that PET response after the induction chemotherapy phase correlated with pCR after CRT (38). Because it is clear (from RTOG 8501) that definitive radiotherapy can achieve cure only with effective chemotherapy, PET

response after induction chemotherapy may be a useful predictor of outcome with definitive CRT. A strategy of utilizing post-induction chemotherapy PET to direct the choice of radiosensitizing chemotherapy is now being tested prospectively in the CALGB 80803 trial, and may further validate post-induction chemotherapy PET response as a useful predictor of outcome with CRT.

Combining multiple clinical factors could improve predictive power compared to any single factor. Ajani *et al.* constructed a model to predict pCR after CRT, based on multivariate analysis of multiple demographic and clinical factors (12). They found that gender, tumor grade, baseline T-stage, post-treatment SUV_{max}, and post-treatment biopsy status were independently associated with pCR and incorporated these factors into a nomogram. A high nomogram score after CRT would predict a >60% chance of pCR upon surgery. The authors acknowledged that this model requires validation before clinical use. Even if validated, it is debatable whether a model that accurately predicts pCR in approximately two out of three patients would be sufficient to make a significant treatment decision such as surgery.

Biomarkers and future directions

Though clinical parameters and PET assessments have value in predicting response to definitive CRT, it is unlikely that any of those tools will be reliable enough to ensure that CRT alone maximizes survival for a given patient, or that surgery would definitely improve outcome. An alternative, potentially more promising approach is to identify biomarkers to predict the likelihood of response to CRT.

Numerous genetic biomarkers have been reported to have association with CRT response, including NF-κB (39), p53 (40), ERCC1 (41), BRCA1 (42), and ALDH-1 (43), among others. DNA-repair (44) and apoptosis-related protein expression levels (45) have also been proposed as predictors of CRT response. Several groups have constructed multiple-gene expression profiles to discriminate CRT responders from non-responders (46,47).

Other areas of recent investigation include the correlation of micro-RNA expression and CRT outcomes. Ko *et al.* reported that complete responders to CRT had different miRNA expression profiles than nonresponders (48). Skinner *et al.* have subsequently developed an miRNA expression model to predict pCR after neoadjuvant CRT (49). Serum biomarkers such as protein complement levels (50), and interleukin-6 levels (51), have also been correlated with CRT response. A Dutch group recently reported that cancer stem cell markers might have predictive value in the treatment of esophageal cancer with radiotherapy (52).

Whether any of these or other candidate biomarkers will be validated in a larger population remains to be seen, and much translational work remains to be done before any such biomarker is shown to be sufficiently robust to enter routine clinical use and direct treatment decisions. However, significant improvements in the ability to predict CRT response will likely come from these avenues of investigation.

Conclusions

At this time, available clinical tools do not permit the clinician to predict confidently whether definitive CRT will lead to cure, or even to a pCR. However, significant though imperfect correlations between numerous factors and CRT outcome have been identified. Baseline clinical factors, most notably histologic subtype and possibly SUV_{max}, correlate with the probability of pCR. Additional predictive value may be obtained by incorporating post-CRT assessments, such as biopsy and PET. Positive post-CRT biopsy is an indication that CRT alone has been insufficient and surgery likely beneficial. A negative post-CRT PET combined with negative biopsy suggests that favorable outcome may be achieved without surgery, but whether surgery should routinely be omitted in this circumstance remains debatable due to the substantial risk of persistent microscopic disease. Even if biopsy and PET imaging are not sensitive enough at this time to identify residual microscopic disease after CRT, they have added value for many patients with esophageal cancer in whom surgery may be a high-risk procedure, by helping to guide expectant management and follow-up recommendations. Emerging data on molecular biomarkers are likely to improve predictive ability, but it is uncertain which biomarkers will prove most helpful, and when such tools will be available and validated for clinical decision-making.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer:

long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623-7.
2. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-8.
3. Gaspar LE, Winter K, Kocha WI, et al. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. Cancer 2000;88:988-95.
4. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-74.
5. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
6. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-8.
7. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310-7.
8. Tougeron D, Di Fiore F, Hamidou H, et al. Response to definitive chemoradiotherapy and survival in patients with an oesophageal adenocarcinoma versus squamous cell carcinoma: a matched-pair analysis. Oncology 2007;73:328-34.
9. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol 2005;23:4330-7.
10. Rizk NP, Seshan VE, Bains MS, et al. Prognostic factors after combined modality treatment of squamous cell carcinoma of the esophagus. J Thorac Oncol 2007;2:1117-1123.
11. Patel VR, Hofstetter WL, Correa AM, et al. Signet ring cells in esophageal adenocarcinoma predict poor response to preoperative chemoradiation. Ann Thorac Surg 2014;98:1064-71.
12. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. Ann Oncol 2012;23:2638-42.
13. Amini A, Ajani J, Komaki R, et al. Factors associated with local-regional failure after definitive chemoradiation for locally advanced esophageal cancer. Ann Surg Oncol 2014;21:306-14.
14. Molena D, Sun HH, Badr AS, et al. Clinical tools do not predict pathological complete response in patients with esophageal squamous cell cancer treated with definitive chemoradiotherapy. Dis Esophagus 2014;27:355-9.
15. Swisher SG, Winter KA, Komaki RU, et al. A Phase II study of a paclitaxel-based chemoradiation regimen with selective surgical salvage for resectable locoregionally advanced esophageal cancer: initial reporting of RTOG 0246. Int J Radiat Oncol Biol Phys 2012;82:1967-72.
16. Chao YK, Tseng CK, Wen YW, et al. Using pretreatment tumor depth and length to select esophageal squamous cell carcinoma patients for nonoperative treatment after neoadjuvant chemoradiotherapy. Ann Surg Oncol 2013;20:3000-8.
17. Nomura M, Shitara K, Kodaira T, et al. Recursive partitioning analysis for new classification of patients with esophageal cancer treated by chemoradiotherapy. Int J Radiat Oncol Biol Phys 2012;84:786-92.
18. Omloo JM, van Heijl M, Hoekstra OS, et al. FDG-PET parameters as prognostic factor in esophageal cancer patients: a review. Ann Surg Oncol 2011;18:3338-52.
19. Rizk N, Downey RJ, Akhurst T, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography standardized uptake values predict survival after esophageal adenocarcinoma resection. Ann Thorac Surg 2006;81:1076-81.
20. Rizk NP, Tang L, Adusumilli PS, et al. Predictive value of initial pet-suvmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. J Thorac Oncol 2009;4:875-879.
21. Suzuki A, Xiao L, Hayashi Y, et al. Prognostic significance of baseline positron emission tomography and importance of clinical complete response in patients with esophageal or gastroesophageal junction cancer treated with definitive chemoradiotherapy. Cancer 2011;117:4823-33.
22. Suzuki A, Xiao L, Taketa T, et al. Results of the baseline positron emission tomography can customize therapy of localized esophageal adenocarcinoma patients who achieve a clinical complete response after chemoradiation. Ann Oncol 2013;24:2854-9.
23. Miyata H, Yamasaki M, Takiguchi S, et al. Prognostic value of endoscopic biopsy findings after induction chemoradiotherapy with and without surgery for esophageal cancer. Ann Surg 2011;253:279-84.

24. Peng HQ, Halsey K, Sun CC, et al. Clinical utility of postchemoradiation endoscopic brush cytology and biopsy in predicting residual esophageal adenocarcinoma. Cancer 2009;117:463-72.
25. Sarkaria IS, Rizk NP, Bains MS, et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. Ann Surg 2009;249:764-7.
26. Yang Q, Cleary KR, Yao JC, et al. Significance of post-chemoradiation biopsy in predicting residual esophageal carcinoma in the surgical specimen. Dis Esophagus 2004;17:38-43.
27. Griffin JM, Reed CE, Denlinger CE. Utility of restaging endoscopic ultrasound after neoadjuvant therapy for esophageal cancer. Ann Thorac Surg 2012;93:1855-9; discussion 1860.
28. Monjazeb AM, Riedlinger G, Aklilu M, et al. Outcomes of patients with esophageal cancer staged with [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol 2010;28:4714-21.
29. Murthy SB, Patnana SV, Xiao L, et al. The standardized uptake value of 18-fluorodeoxyglucose positron emission tomography after chemoradiation and clinical outcome in patients with localized gastroesophageal carcinoma. Oncology 2010;78:316-22.
30. Flamen P, Van Cutsem E, Lerut A, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol 2002;13:361-8.
31. Javeri H, Xiao L, Rohren E, et al. The higher the decrease in the standardized uptake value of positron emission tomography after chemoradiation, the better the survival of patients with gastroesophageal adenocarcinoma. Cancer 2009;115:5184-92.
32. Jayachandran P, Pai RK, Quon A, et al. Postchemoradiotherapy positron emission tomography predicts pathologic response and survival in patients with esophageal cancer. Int J Radiat Oncol Biol Phys 2012;84:471-7.
33. Kim MK, Ryu JS, Kim SB, et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer 2007;43:1385-91.
34. Swisher SG, Erasmus J, Maish M, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer 2004;101:1776-85.
35. Piessen G, Petyt G, Duhamel A, et al. Ineffectiveness of ^{18}F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg 2013;258:66-76.
36. Vallböhmer D, Hölscher AH, Dietlein M, et al. [18F]-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg 2009;250:888-94.
37. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007;8:797-805.
38. Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer. Cancer 2012;118:2820-7.
39. Izzo JG, Malhotra U, Wu TT, et al. Association of activated transcription factor nuclear factor kappab with chemoradiation resistance and poor outcome in esophageal carcinoma. J Clin Oncol 2006;24:748-54.
40. Makino T, Yamasaki M, Miyata H, et al. p53 Mutation status predicts pathological response to chemoradiotherapy in locally advanced esophageal cancer. Ann Surg Oncol 2010;17:804-11.
41. Brabender J, Vallböhmer D, Grimminger P, et al. ERCC1 RNA expression in peripheral blood predicts minor histopathological response to neoadjuvant radio-chemotherapy in patients with locally advanced cancer of the esophagus. J Gastrointest Surg 2008;12:1815-21.
42. Gao Y, Zhu J, Zhang X, et al. BRCA1 mRNA expression as a predictive and prognostic marker in advanced esophageal squamous cell carcinoma treated with cisplatin- or docetaxel-based chemotherapy/chemoradiotherapy. PLoS One 2013;8:e52589.
43. Ajani JA, Wang X, Song S, et al. ALDH-1 expression levels predict response or resistance to preoperative chemoradiation in resectable esophageal cancer patients. Mol Oncol 2014;8:142-9.
44. Alexander BM, Wang XZ, Niemierko A, et al. DNA repair biomarkers predict response to neoadjuvant chemoradiotherapy in esophageal cancer. Int J Radiat Oncol Biol Phys 2012;83:164-71.
45. Chen Y, Wang Y, Song H, et al. Expression profile of apoptosis-related genes potentially explains early

recurrence after definitive chemoradiation in esophageal squamous cell carcinoma. Tumour Biol 2014;35:4339-46.
46. Duong C, Greenawalt DM, Kowalczyk A, et al. Pretreatment gene expression profiles can be used to predict response to neoadjuvant chemoradiotherapy in esophageal cancer. Ann Surg Oncol 2007;14:3602-9.
47. Wen J, Yang H, Liu MZ, et al. Gene expression analysis of pretreatment biopsies predicts the pathological response of esophageal squamous cell carcinomas to neo-chemoradiotherapy. Ann Oncol 2014;25:1769-74.
48. Ko MA, Zehong G, Virtanen C, et al. MicroRNA expression profiling of esophageal cancer before and after induction chemoradiotherapy. Ann Thorac Surg 2012;94:1094-102; discussion 1102-3.
49. Skinner HD, Lee JH, Bhutani MS, et al. A validated miRNA profile predicts response to therapy in esophageal adenocarcinoma. Cancer 2014. [Epub ahead of print].
50. Maher SG, McDowell DT, Collins BC, et al. Serum proteomic profiling reveals that pretreatment complement protein levels are predictive of esophageal cancer patient response to neoadjuvant chemoradiation. Ann Surg 2011;254:809-16; discussion 816-7.
51. Makuuchi Y, Honda K, Osaka Y, et al. Soluble interleukin-6 receptor is a serum biomarker for the response of esophageal carcinoma to neoadjuvant chemoradiotherapy. Cancer Sci 2013;104:1045-51.
52. Smit JK, Faber H, Niemantsverdriet M, et al. Prediction of response to radiotherapy in the treatment of esophageal cancer using stem cell markers. Radiother Oncol 2013;107:434-41.

Cite this article as: Wu AJ, Goodman KA. Clinical tools to predict outcomes in patients with esophageal cancer treated with definitive chemoradiation: are we there yet? J Gastrointest Oncol 2015;6(1):53-59. doi: 10.3978/j.issn.2078-6891.2014.099

