Actionable Locoregional Relapses after Therapy of Localized Esophageal Cancer: Insights from a Large Cohort

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Keywords

Esophageal cancer · Localized esophageal cancer · Actionable locoregional relapse

Abstract

Objective: The goal of surveillance after therapy of localized esophageal cancer (LEC) is to identify actionable relapses amenable to salvage; however, the current surveillance algorithms are not optimized. We report on a large cohort of LEC patients with actionable locoregional relapses (LRRs).

Methods: Between 2000 and 2013, 127 (denominator = 752)

patients with actionable LRR were identified. Histologic/cytologic confirmation was the gold standard. All surveillance tools (imaging, endoscopy, fine needle aspiration) were assessed. **Results:** Most patients were men (89%), had adenocarcinoma (79%), and had no new symptoms (72%) when diagnosed with LRR. In trimodality patients, endoscopic confirmation of positron emission tomography-computed tomography-suspected LRR occurred in only 44%, and 56% required additional tools (e.g., fine needle aspiration). Alternatively, in bimodality patients, endoscopy confirmed LRRs in 81%. Trimodality patients had a higher risk of subsequent LRR/distant metastases after the first LRR than the bimodal-

ity patients ($p = 0.03$). In all patients, 78% of the subsequent relapses were distant. For patients who were salvaged, survival was significantly prolonged (50.6 vs. 25.1 months, $p < 0.01$). **Conclusions:** Patients live longer after successful salvage of the LRR than if salvage is not possible. After LRR, patients have a high risk of subsequent distant metastasis and whether the second relapse is local or distant, survival is uniformly poor.

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Introduction

Esophageal cancer (EC) (originating from the esophagus or the gastroesophageal junction) is the eighth most common malignancy worldwide [1, 2]. In North America and the Western world, the incidence of esophageal squamous cell carcinoma has been decreasing; however, the incidence of adenocarcinoma has been steadily climbing over the past four decades [3–5]. In North America, the two most commonly prescribed therapies for localized EC (LEC) are either chemoradiotherapy followed by surgery (trimodality therapy [TMT]) [6, 7], or definitive chemoradiotherapy (bimodality therapy [BMT]) [6, 8]. The decision between TMT and BMT is influenced by multiple factors, which have been discussed previously [9–11]. Although it has previously been shown that the locoregional relapse (LRR) rate is low after TMT [12–16], it is considerably higher after BMT [9, 10, 17]. We recently reported that only 2% of 518 patients treated with TMT benefited from surveillance/salvage strategies [12], bringing into question their usefulness in this setting. Alternatively, in the BMT group, approximately 8% of all patients (or 36% of patients with LRR alone) benefited from salvage therapy, indicating that at least in this setting surveillance may play an important role [17].

The goal of surveillance after local therapy (TMT or BMT) is to salvage patients with actionable LRR; however, the benefits of current surveillance strategies are not well documented. We report on the largest cohort of LEC patients with actionable LRR to date [12, 17]. The purpose of this study was to document the value of imaging (positron emission tomography-computed tomography [PET-CT], magnetic resonance imaging, or computed tomography [CT]), endoscopy, and onset of new symptoms in detecting potentially salvageable LRRs and to determine the outcomes of salvaged patients with those of patients who cannot be salvaged.

Patients and Methods

Patient Selection

We analyzed patients from our prospectively maintained database on EC at the Department of Gastrointestinal Medical Oncology at the University of Texas M.D. Anderson Cancer Center to find consecutive patients who, between 2000 and 2013, had histologically confirmed EC and successfully completed BMT or TMT. BMT patients who underwent planned surgery or salvage surgery within 6 months after chemoradiotherapy were excluded to avoid bias because that group could be construed as TMT for whom surgery is delayed for one reason or another. All patients had baseline and postchemoradiation staging that included imaging studies and esophagogastroduodenoscopy (EGD) with biopsies. Endoscopic ultrasonography was performed in each patient at baseline. Imaging studies included chest and abdomen CT and/or PET-CT. PET-CT was preferred; however, CT was done when insurance coverage for PET could not be obtained. Before proceeding with therapy, each patient was evaluated by physicians from appropriate disciplines and then discussed by the multidisciplinary team (consisting of radiologists, gastroenterologists, thoracic surgeons, radiation oncologists, pathologists, nutritionists, geneticists [when appropriate], and medical oncologists). Clinical staging was based on the American Joint Committee on Cancer (AJCC) classification, 6th edition [18] and pathologic staging was based on the AJCC classification, 7th edition [19]. The institutional review board approved this analysis.

Therapy

We have described TMT and BMT previously [12, 17]. TMT consisted of chemoradiation, followed by preoperative restaging 5–6 weeks after its completion. Finally, all patients had an esophagectomy (surgical technique at the discretion of the operating surgeon). BMT consisted of radiation (50.4 Gy in 28 fractions) and concurrent chemotherapy (most patients received a fluoropyrimidine with a platinum or taxane). Patients who developed LRR alone were rediscussed in our multidisciplinary conference so that a consensus could be developed for salvage strategy.

Surveillance after Therapy

Each patient was generally surveyed by the following surveillance strategy: patient visits were performed every 3 months for the first year, then every 6 months for 2 additional years, and then once a year for at least 5 years. An imaging study (CT or PET-CT) and blood tests were performed at each visit. Endoscopic evaluation for relapse was performed every 6 months in the first 18 months and then once a year. BMT patients underwent EGD and multiple biopsies plus CT or PET-CT at their first visit (5 and 8 weeks after completion of BMT).

First and second relapses, distant metastases (with or without LRR), or LRR alone were documented. Patients who had LRR with distant metastases at first occurrence were excluded from this analysis since they were not subjected to a salvage strategy. Patients with LRR for whom salvage therapy was attempted were carefully monitored for outcome. Chemoradiotherapy was the preferred approach for salvage (if the LRR occurred outside the prior field of radiation), and surgery salvage was the last choice.

LRRs and distant metastases were recorded and tabulated. We also documented whether the LRR was discovered by imaging, whether there were new symptoms, and whether positive imaging

Table 1. Patient characteristics

<i>Initial treatment</i>		New symptom of locoregional relapse	
Age	64 (27–91)	No	92 (72%)
Sex		Yes	35 (28%)
Female	14 (11%)	Outside routine surveillance ^b	
Male	113 (89%)	No	108 (85%)
Initial surgery		Yes	19 (15%)
No	86 (67.7%)	Failure suspected by imaging study	
Yes	41 (32.3%)	No	33 (26%)
T stage		Yes	94 (74%)
T1	2 (1.6%)	Failure suspected by PET-CT	
T2	7 (5.5%)	No	24 (18.9%)
T3	110 (86.6%)	Yes	86 (67.7%)
T4	4 (3.1%)	NA	17 (13.4%)
TX	4 (3.2%)	Failure suspected by contrast CT	
N stage		No	24 (18.9%)
N0	40 (31.5%)	Yes	43 (33.9%)
N1	83 (65.4%)	NA	60 (47.2%)
NX	4 (3.2%)	Failure suspected by MRI	
M stage		Yes	2 (1.6%)
M0	122 (96.1%)	NA	125 (98.4%)
M1a	5 (3.9%)		
<i>Relapse</i>		<p>Values are presented as median (range) or <i>n</i> (%). CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography. ^a 15% (<i>n</i> = 19) of patients did not have pathologic confirmation of recurrence. Of these 19 patients, 13 had no evidence of malignancy in the diagnostic biopsies (all biopsies were triggered by abnormalities on imaging). The remaining 6 had abnormal imaging suspicious of relapse; however, all were in poor general condition (i.e., not candidates for salvage or palliation), therefore, after discussions in the multidisciplinary conference, it was elected not to pursue histologic confirmation. All these 6 patients received only best supportive care. ^b Outside clinical visits scheduled for routine surveillance.</p>	
Pathology at relapse			
No	19 (15%) ^a		
Yes	108 (85%)		
Relapse location			
Luminal/regional	11 (8.7%)		
Luminal	85 (67.0%)		
Regional	31 (24.3%)		
Intervention after relapse			
Chemoradiotherapy	17 (13.4%)		
Surgery	47 (37%)		
Palliative care	59 (46.5%)		
Unknown	4 (3.0%)		

was confirmed by positive endoscopy. The survival follow-up was carried out through our institution's tumor registry, electronic medical records, and/or the Social Security database.

Statistical Analysis

Continuous variables were summarized using median and range. Categorical variables were tabulated by frequency and percentage. The Fisher exact test was used to assess the association between treatment strategy (BMT versus TMT) and whether or not the diagnosis was confirmed by endoscopy. The probabilities of overall survival (OS), OS since relapse, and failure time were estimated using the Kaplan-Meier method. The OS was defined as the time from the time of diagnosis (initial diagnosis of EC) until death or last follow-up. For the second relapse patients, the OS was the time from the relapse until death or last follow-up. The failure time was defined as the time from either surgery date or end of radiation/chemotherapy date to local failure date (all patients in this cohort had experienced local failure). The log-rank test was used to compare subgroups of patients. Statistical significance was defined as $p < 0.05$. Sensitivity and specificity were computed based

on the cross-tabulated results for each measurement versus the gold standard, i.e., the pathologic biopsy. Sensitivity measures the proportion of true positives which are correctly identified as such, and specificity measures the proportion of true negatives which are correctly identified as such.

Results

The clinical characteristics of the 127 patients included in this study are listed in Table 1. During the time period 2000–2013, a total of 752 patients with EC or gastroesophageal junction cancer were treated with BMT or TMT. Briefly, for the 127 patients, the median age was 64 years (range 27–90 years). The majority of the patients were men (89%), had adenocarcinoma (79%), had their LRR identified through surveillance (85%), and most had

Table 2. Summary of sensitivity and specificity for TMT and BMT patients

	Sample size	Sensitivity	Specificity
<i>TMT patients</i>			
Image + outside surveillance + new symptom	41	30/33 = 0.91	0/8 = 0.00
Image: PET-CT/CT/MRI	41	28/33 = 0.85	0/8 = 0.00
Contrast CT	21	12/17 = 0.71	0/4 = 0.00
PET-CT	33	25/27 = 0.93	0/6 = 0.00
Outside surveillance	41	6/33 = 0.18	6/8 = 0.75
New symptom	41	10/33 = 0.3	5/8 = 0.63
PET-CT + CT + outside surveillance + new symptom	41	30/33 = 0.91	0/8 = 0.00
<i>BMT patients</i>			
Image + outside surveillance + new symptom	86	53/75 = 0.71	0/11 = 0.00
Image: PET-CT/CT/MRI	86	47/75 = 0.63	0/11 = 0.00
Contrast CT	46	24/42 = 0.57	1/4 = 0.25
PET-CT	77	45/67 = 0.67	0/10 = 0.00
Outside surveillance	86	9/75 = 0.12	9/11 = 0.82
New symptom	86	19/75 = 0.25	8/11 = 0.73
PET-CT + CT + outside surveillance + new symptom	86	54/75 = 0.72	0/11 = 0.00

BMT, bimodality therapy; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; TMT, trimodality therapy.

Fig. 1. Kaplan-Meier estimates for OS (in months) from initial diagnosis, stratified by TMT (surgery = yes) and BMT (surgery = no) status. BMT, bimodality therapy; OS, overall survival; TMT, trimodality therapy.

no new symptoms (72%). Fifteen percent ($n = 19$) of patients did not have pathologic confirmation of recurrence. Of these 19 patients, 13 had no evidence of malignancy in the diagnostic biopsies (all biopsies were triggered by abnormalities on imaging). The remaining 6

patients had abnormal imaging suspicious of relapse; however, all 6 patients were in poor general condition (i.e., not candidates for salvage or palliation), therefore, after discussions in the multidisciplinary conference, it was elected not to pursue histologic confirmation. All these 6 patients received only best supportive care. The median survival follow-up for these patients ($n = 127$) was 80.7 months (95% CI 69.5–98.4). The median OS for TMT patients was 42.3 months (95% CI 33.0–55.2), while that of BMT patients was 36.4 months (95% CI 28.5–46.8) ($p = 0.64$) (Fig. 1).

Utility of Imaging in Detecting Relapse

For the 127 patients with LRRs treated with BMT or TMT, the sensitivity of PET-CT, combined with the presence of new symptoms and discovery outside routine surveillance, was 78%, while the sensitivity of PET-CT alone was 74%. PET-CT information was available for 110 patients (86.8%).

For the 41 LRRs after TMT, the sensitivity of PET-CT alone was 93% (Table 2, upper part). In TMT patients with a positive PET-CT for LRR, only 44% had LRR confirmed by endoscopy, and 56% of LRRs were confirmed by additional testing (e.g., fine needle aspiration, etc.). Alternatively, in BMT patients, endoscopy confirmed LRR in 81% ($n = 85$, 1 patient not evaluable; online suppl. Table 1) (for all online suppl. material, see www.elsevier.com/locate/bscr).

Fig. 2. **a** Kaplan-Meier estimates of OS from initial diagnosis by first salvage (salvage versus no salvage) in BMT and TMT patients. Salvage was defined as definitive chemoradiation (dose >41.4 Gy) or surgery. **b** Kaplan-Meier estimates of OS from initial diagnosis by first salvage in TMT patients. **c** Kaplan-Meier estimates of OS from initial diagnosis by first salvage in BMT patients. BMT, bi-modality therapy; OS, overall survival; TMT, trimodality therapy.

karger.com/doi/10.1159/000486720). In the BMT patients the sensitivity of PET-CT was only 67% (Table 2, lower part).

Benefit of Surveillance in Terms of Salvageable Patient Survival

A total of 127 patients with first LRR alone were stratified by whether they could undergo definitive salvage (i.e., surgery or chemoradiotherapy with radiation of at least 41 Gy). We found that 64 patients could undergo definitive salvage while 63 did not. Of the 63 patients who did not receive definitive therapy, 24 received chemotherapy alone, 32 received no intervention after initial relapse and were followed until further progression, 1 patient received radiation alone, and 6 patients were lost to follow-up. The reasons for not undergoing salvage are as follows:

7 patients declined salvage, 17 patients (all with in-field recurrence) had technically unresectable relapses, 9 patients had distant metastases, 22 patients (all with in-field recurrences) had poor medical condition precluding surgery, and in 8 patients we were unable to determine the exact reason for not proceeding with salvage. The median OS for salvaged patients was 50.6 months (95% CI 43.5–69.3) versus 25.1 months (95% CI 19.5–36.4) for those who could not be salvaged ($p < 0.01$) (Fig. 2a). The patients were further subclassified by whether they initially received BMT or TMT. Of the patients initially treated with TMT, 20 were able to undergo salvage therapy while 21 were not. The median OS of those who did was 50.6 months (95% CI 40.5–NA) versus 31.9 months (95% CI 19.5–58.4) for those who did not ($p = 0.02$) (Fig. 2b). Patients initially treated with BMT also benefited from sal-

Fig. 3. a TMT patients who had PET-CT imaging and in whom histology was confirmed by biopsy versus those who were not confirmed by biopsy. **b** BMT patients who had PET-CT imaging and in whom histology was confirmed by biopsy versus those who were not confirmed by biopsy. BMT, bimodality therapy; EGD, esophagogastroduodenoscopy; FNA, fine needle aspiration; PET, positron emission tomography; PET-CT, positron emission tomography-computed tomography; TMT, trimodality therapy.

vage, with a median OS of 50.5 months (95% CI 42.8–101.5) versus 21.1 months (95% CI 16.8–39.7) ($p = 0.001$) (Fig. 2c).

Second Relapses and Outcomes after Second Relapse

After treatment for LRR, 73 patients experienced a second relapse, including 57 distant relapses and 16 LRRs. TMT patients were at higher risk of subsequent (e.g., distant) relapse after LRR had been documented (80%) than were BMT patients (58%) ($p = 0.03$). Seventy-eight percent of the relapses were distant.

Of the 127 patients, 85 (67%) had their diagnosis confirmed by endoscopy, 36 (28%) did not, and 6 (5%) had no available data and were therefore not evaluable. BMT patients were more likely to have their LRR confirmed by endoscopy (81%) than were TMT patients (44%; $p \leq 0.01$; see online suppl. Table 1). Of the TMT patients, 56% re-

quired additional procedures (most commonly fine needle aspiration) to confirm the diagnosis. Of the BMT patients with PET-CT-positive failures, 15 patients had a negative endoscopy while 39 patients were confirmed by positive endoscopy. Importantly, 22 patients had a negative PET-CT, but a proven LRR by endoscopy. Alternatively, in TMT patients, only 2 patients with a negative PET-CT had an LRR confirmed by endoscopy (Fig. 3a, b).

The median follow-up for TMT patients after second relapse was 20.6 months, while that of BMT patients was 39.5 months. Of the 56 patients who had distant relapses, 28 were treated with chemotherapy, 1 with chemoradiation, and 1 with palliative radiation, while 26 patients received best supportive care alone, most commonly because of poor medical condition. Interestingly, whether patients had LRR or distant relapse, the OS of both groups was poor ($p = 0.36$). The OS was similar irrespective of

whether they were initially treated by BMT or TMT ($p = 0.76$).

In BMT patients, 99% of relapses (LRRs and/or distant relapses) occurred within 36 months of therapy, while in TMT patients, 90% of relapses occurred within 36 months of surgery. When assessing failure-free-survival (in months) stratified by BMT or TMT status, patients treated with BMT had a shorter median time to relapse (6.1 months) than TMT patients (16.1 months) ($p = 0.001$) (see online suppl. Fig. 1).

Discussion

Little is known about the usefulness of methods for surveillance after local therapy (either TMT or BMT) in EC. However, surveillance is routinely performed in the Western world, despite a lack of data as to its benefits. Since there has never been a prospective study analyzing the conservative versus aggressive surveillance approach, there are considerable variations in the current algorithms [12]. The benefit of a surveillance strategy is that it may provide a survival advantage for patients with LRR alone by allowing successful salvage. In this report, we show that salvage is an effective strategy for both TMT and BMT patients. This leaves us with more questions than answers, as our position has been to de-emphasize aggressive surveillance particularly in TMT patients who are least likely to benefit because they experience relatively few salvageable LRRs.

In other malignancies, some data exist about the benefits of surveillance strategies after definitive therapy. Although the evidence is limited, surveillance mammography appears to be associated with a reduction in mortality among women of all ages [20–22]. Conflicting with these data, one large study included 1,310 patients and compared intensive versus conservative (clinically indicated testing only) follow-up of curatively treated stage I–III breast cancer. That study showed no difference in time to detection of recurrence, OS, or quality of life assessments at any interval between the stage-matched cohorts [23]. Multiple randomized trials and separate meta-analyses support a modest but significant OS benefit for intensive posttreatment surveillance following potentially curative resection of colorectal cancer [24–27]. However, the best surveillance strategy to achieve such a benefit has not been defined because the strategies within trials varied significantly. There are also no randomized trials that have defined the optimal follow-up strategy for men following their initial treatment for localized pros-

tate cancer. The natural history of prostate cancer following a prostate-specific antigen relapse does not necessarily predict the development of metastases or death [28, 29]. Although long-term outcomes are better with early treatment for a prostate-specific antigen-only recurrence, these results may reflect the natural history of the disease and do not necessarily reflect a benefit from therapy. In conclusion, in all of these settings, the benefits of surveillance in terms of absolute values are relatively small if they exist at all. Finally, although clear data exist that screening programs can improve outcomes, surveillance is only beneficial if recurrence is detected at a point where a more effective treatment is available [30]. This should lead us to question many surveillance programs, particularly in the context of the American Society of Clinical Oncology framework, to assess the value of cancer treatment options [31].

Our group has recently demonstrated that the rate of LRR in TMT patients with EC is low (~5%) [12]. More importantly, less than 2% of TMT population who had salvage therapy survived more than 2 years, bringing into question the value of surveillance of this population. However, in a BMT cohort, 23% of patients develop LRR alone, and of those 36% were able to undergo salvage surgery [17]. To the best of our knowledge, no other group has reported on the results of salvage in EC patients.

Of the total population ($n = 752$), only 17% of patients experienced potentially salvageable LRRs. Interestingly, approximately 50% of patients treated with both TMT and BMT were able to undergo definitive salvage and lived significantly longer than those who could not have salvage. As expected, LRRs were more frequent after BMT than after TMT ($p < 0.001$), highlighting the role surgery plays in the local control of EC.

Assessing all patients who had LRR (Fig. 1), the outcomes were poor regardless of whether they had been initially treated with TMT or BMT, with long-term survivors making up only ~20% of the population. TMT patients were at higher risk of subsequent (e.g., distant) relapse after LRR salvage than BMT patients ($p = 0.03$); in all patients, 78% of the relapses were distant. Since most relapses occurred within 36 months of local therapy, surveillance after 36 months may be less productive.

Our analysis has the following limitations: it is retrospective in nature; it involves a single-institution experience; the total denominator, although it is the largest reported, is still relatively small; and the data emerged from a relatively aggressive surveillance strategy. However, our analysis has the following strengths: it provides the first evidence, to our knowledge, of the value of individual sur-

veillance methods (i.e., endoscopy versus imaging) in terms of definitive diagnosis of LRR; and our data suggest that PET-CT is more likely to detect LRRs than endoscopy in TMT patients. However, in BMT patients, endoscopy is more valuable than PET-CT for documenting LRRs. At least 3 years of surveillance seem appropriate. However, even after salvage, distant relapses are common.

These intriguing data remain preliminary, but in combination with our other reports, they can serve as a basis to propose a large multicenter randomized controlled trial of surveillance in EC. The standard arm would be an aggressive surveillance strategy, meaning patient visits every 3 months for the first year, then every 6 months for 2 additional years, and then once a year for up to 5 years. At each visit, an imaging study (PET-CT) and blood tests would be performed. Endoscopic evaluation (in BMT patients only) for relapse would be performed every 6 months in the first 18 months and then once a year. The control arm would consist of no surveillance imaging, however patients would be seen for history and physical examination every 6 months, with tests ordered depending on symptoms experienced. Only symptomatic intervention would be allowed in the control arm. The pri-

mary objective of such a study would surround issues of salvage, cost, and quality of life.

In conclusion, the benefit of surveillance for the entire LEC population remains a quandary and should be the subject of prospective research. However, patients who can have salvage do benefit in terms of OS. LRR is an ominous sign for subsequent development of distant metastases.

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Disclosure Statement

The authors have no conflict of interest to declare.

References

- 1 Jemal A, et al: Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- 2 Ferlay J, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–2917.
- 3 Brown LM, Devesa SS, Chow WH: Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008;100:1184–1187.
- 4 Pohl H, Welch HG: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:142–146.
- 5 Engel LS, et al: Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst* 2003;95:1404–1413.
- 6 Ajani JA, et al: Esophageal and esophagogastric junction cancers. *J Natl Compr Canc Netw* 2011;9:830–887.
- 7 van Hagen P, et al: Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–2084.
- 8 Cooper JS, 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;281:1623–1627.
- 9 Welsh J, et al: Failure patterns in patients with esophageal cancer treated with definitive chemoradiation. *Cancer* 2012;118:2632–2640.
- 10 Amini A, et al: Factors associated with local-regional failure after definitive chemoradiation for locally advanced esophageal cancer. *Ann Surg Oncol* 2014;21:306–314.
- 11 Suzuki A, 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;24:2854–2859.
- 12 Sudo K, et al: Locoregional failure rate after preoperative chemoradiation of esophageal adenocarcinoma and the outcomes of salvage strategies. *J Clin Oncol* 2013;31:4306–4310.
- 13 Oppedijk V, et al: Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;32:385–391.
- 14 Bekkar S, et al: The impact of preoperative radiochemotherapy on survival in advanced esophagogastric junction signet ring cell adenocarcinoma. *Ann Thorac Surg* 2014;97:303–310.
- 15 Mariette C, Robb WB, Piessen G: Reply to letter: “The role of surgery for patients with a complete clinical response after chemoradiation for esophageal cancer.” *Ann Surg* 2015;262:e101–e102.
- 16 Dorth JA, et al: Patterns of recurrence after trimodality therapy for esophageal cancer. *Cancer* 2014;120:2099–2105.
- 17 Sudo K, et al: Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. *J Clin Oncol* 2014;32:3400–3405.
- 18 Greene FL, Page DL, Fleming ID, et al (eds): *AJCC Cancer Staging Manual*, 6th edition. New York, Springer, 2002.
- 19 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds): *AJCC Cancer Staging Manual*, 7th edition. New York, Springer, 2010.
- 20 Lash TL, et al: Mammography surveillance and mortality in older breast cancer survivors. *J Clin Oncol* 2007;25:3001–3006.
- 21 Lash TL, Fox MP, Silliman RA: Reduced mortality rate associated with annual mammograms after breast cancer therapy. *Breast J* 2006;12:2–6.

- 22 Schootman M, et al: Surveillance mammography and the risk of death among elderly breast cancer patients. *Breast Cancer Res Treat* 2008; 111:489–496.
- 23 Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. *JAMA* 1994;271:1587–1592.
- 24 Pietra N, et al: Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. *Dis Colon Rectum* 1998;41:1127–1133.
- 25 Wang T, et al: The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective, randomized clinical study. *Gastrointest Endosc* 2009;69 (3 Pt 2):609–615.
- 26 Rodriguez-Moranta F, et al: Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. *J Clin Oncol* 2006;24:386–393.
- 27 Pita-Fernandez S, et al: Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. *Ann Oncol* 2015;26:644–656.
- 28 Freedland SJ, et al: Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294:433–439.
- 29 Antonarakis ES, et al: The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int* 2012;109:32–39.
- 30 Furman MJ, et al: Rational follow-up after curative cancer resection. *J Clin Oncol* 2013;31: 1130–1133.
- 31 Schnipper LE, et al: American Society of Clinical Oncology Statement: a conceptual framework to assess the value of cancer treatment options. *J Clin Oncol* 2015;33:2563–2577.