Change in Chemotherapy During Concurrent Radiation Followed by Surgery After a Suboptimal Positron Emission Tomography Response to Induction Chemotherapy Improves Outcomes for Locally Advanced Esophageal Adenocarcinoma

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BACKGROUND: A positron emission tomography (PET) scan after induction chemotherapy before preoperative chemoradiation and surgery for esophageal adenocarcinoma predicts outcomes. Some patients with progression on PET after induction chemotherapy had long-term overall survival (OS) when they were changed to alternative chemotherapy during radiation.

METHODS: This study retrospectively reviewed esophageal adenocarcinoma patients who received induction chemotherapy and chemoradiation before planned surgery; all had undergone a PET scan before and after induction chemotherapy.

RESULTS: There were 201 patients, and 113 (56%) were PET responders (≥35% decrease in the maximum standardized uptake value of the tumor). All PET responders received the same chemotherapy during radiation, whereas 38 of the 88 PET nonresponders (43%) changed chemotherapy. Among the 152 patients who underwent surgery, the pathologic complete response rate was 15% for PET responders and 3% for PET nonresponders who did not change chemotherapy (P = .046). The median progression-free survival (PFS; 18.9 vs 10.0 months, P < .01) and OS (37 vs 25.3 months, P = .02) were significantly better for PET responders versus PET nonresponders who did not change chemotherapy. The median PFS for PET nonresponders who changed chemotherapy was 17.9 months, and it was superior to the median PFS for PET nonresponders who did not change chemotherapy (P = .01). For PET nonresponders, the 5-year OS rates were 37% for those who changed chemotherapy and 25% for those who did not change chemotherapy (P = .18).

CONCLUSIONS: A PET scan after induction chemotherapy predicts outcomes for locally advanced esophageal adenocarcinoma patients who undergo chemoradiation and surgery. The median PFS is improved, and trends toward improved OS appear possible in PET nonresponders who change chemotherapy during radiation. The fully accrued Cancer and Leukemia Group B 80803 study (NCT01333033) is evaluating this strategy.

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KEYWORDS: chemoradiation, chemotherapy, esophageal adenocarcinoma, induction, positron emission tomography (PET) scan.

INTRODUCTION

Esophageal cancer is a relatively uncommon but aggressive malignancy in the United States. Several phase 3 studies have now shown a clear benefit from additional therapy. A standard of care is preoperative chemoradiation for clinical stage III or lymph node–positive esophageal and gastroesophageal junction cancers on the basis of several phase 3 trials.

In a previous study of induction chemotherapy and concurrent chemoradiation followed by surgery that enrolled patients between 2002 and 2006, we demonstrated that changes in (18F)fluorodeoxyglucose ((18F)FDG) positron emission tomography (PET) after induction chemotherapy strongly predicted improved outcomes for patients with adenocarcinoma tumors. Specifically, patients whose tumor maximum standard uptake value (mSUV) decreased by ≥35% after induction chemotherapy had significantly improved pathologic complete response (pCR) rates, progression-free survival (PFS), and overall survival (OS) after chemoradiation and surgery in comparison with patients whose tumor mSUV...
decreased by <35%. In this study, 3 of 4 patients who had frank progression on PET scans after induction chemotherapy had long-term control of their disease when they were switched to alternative chemotherapy with radiation.

On the basis of the provocative results of this study, it has become our standard practice to change chemotherapy during concurrent radiation for patients assessed to be nonresponders to induction chemotherapy by PET scan. In our opinion, the dismal outcomes, including a median PFS of 7.7 months noted in the aforementioned study, which associated with continuing the same chemotherapy regimen with radiation for PET nonresponders justify this approach.

In this retrospective review, we evaluate the value of a PET scan after induction chemotherapy before chemoradiation in a larger cohort of adenocarcinoma patients. We assess the impact of changing chemotherapy during radiation in some patients with a suboptimal PET response after induction chemotherapy.

MATERIALS AND METHODS
This retrospective review was performed with patients treated at the Memorial Sloan Kettering Cancer Center. All patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma without distant metastases who had undergone induction chemotherapy and concurrent chemoradiation from 2002 through 2013 were identified through a comprehensive institutional database. Only those patients who met the following criteria were included in the analysis: 1) surgery was planned after chemoradiation, and 2) they underwent a PET scan at baseline and after induction chemotherapy and had FDG-avid tumors. Patients also underwent staging with computed tomography scans as well as endoscopic ultrasound. All pathology was reviewed and confirmed at the Memorial Sloan Kettering Cancer Center. A waiver of authorization to review these data was approved by the institutional review board.

We used a cutoff point of a 35% decrease in the standard uptake value (SUV) after induction chemotherapy for dichotomizing patients into 2 groups: PET responders (≥35%) and nonresponders (<35%). This cutoff was selected on the basis of our prior study, which in turn was guided by previous prospective validation by Ott et al. When differences in PFS and OS were analyzed through the use of the SUV cutoff, the starting date was the date of the follow-up PET scan. Survival was calculated from the date of follow-up PET to the time of death (for OS) or to the time of progression or death (for PFS), whichever occurred first. PFS and OS were analyzed with the Kaplan-Meier method. OS and PFS between groups were compared with the log-rank test. The Wilcoxon rank sum test and Fisher’s exact test were used to compare patient characteristics between the different groups.

A cumulative incidence function was used to estimate the incidence of first recurrence/progression, with death treated as a competing event. Gray’s test was used to compare the rates of recurrence/progression between the different groups. A competing risk regression method was used to further examine the incidence of recurrence/progression between the different groups after we had accounted for the effect of R0 surgery. Surgery was treated as a time-dependent covariate in the competing risk regression model.

All P values were based on 2-tailed statistical analysis and were determined with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Demographics
Two hundred one patients were identified, with the characteristics summarized in Table 1. The majority of the patients (82%) were male. The median age was 62 years (range, 23-88 years), and the median Karnofsky performance status was 90%. Nearly three-quarters of the patients had tumors that were uN1. There were no significant differences in baseline demographics between PET responders and nonresponders except that PET responders had more FDG-avid tumors than PET nonresponders (median SUV, 13.1 vs 7; P < .01).

Induction Chemotherapy
One hundred twenty-seven patients (63%) received induction chemotherapy with cisplatin/irinotecan (including 39 patients from our prior phase 2 study and 31 patients who received bevacizumab/cisplatin/irinotecan in a clinical study). The starting doses of chemotherapy ranged from 25 to 30 mg/m² for cisplatin and from 50 to 65 mg/m² for irinotecan on days 1 and 8 every 21 days for 2 cycles. Bevacizumab was administered at 7.5 mg/kg every 3 weeks. Cisplatin/irinotecan was the most commonly used regimen before mid-2010, when the results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) study were initially presented in abstract form. After that, most patients received carboplatin/paclitaxel. As such, 62 patients (31%) were treated with platinum/paclitaxel (60 with carboplatin and 2 with cisplatin). Doses ranged from an area under the curve of 1.5 to 2 for carboplatin and from 70 to
80 mg/m² for paclitaxel on days 1, 8, and 15 every 28 days for 1 cycle.

Seven patients (3.5%) received FOLFOX (ie, bolus and infusional 5-fluorouracil [5-FU], leucovorin, and oxaliplatin for 5 patients) or CapeOx (ie, capecitabine and oxaliplatin for 2 patients). The FOLFOX regimen was bolus 5-FU and leucovorin (300-400 mg/m²), infusional 5-FU (1000-1200 mg/m²/day for 46 hours), and oxaliplatin (65-85 mg/m²); each cycle was run every 14 days for 2 to 3 cycles. Capecitabine was administered at 1500 mg twice daily for 7 days with oxaliplatin at 70 mg/m² every 14 days for 2 to 3 cycles. Finally, 5 patients (2.5%) received treatment in a phase 1 study of docetaxel and irinotecan with or without cisplatin: 4 patients received docetaxel at 30 mg/m² and irinotecan at 50 mg/m², and 1 patient received this regimen with the addition of cisplatin at 25 mg/m². Therapy was administered on days 1 and 8 every 21 days for 2 cycles.

**PET Response After Induction Chemotherapy**

One hundred thirteen of the 201 patients (56%) had a ≥35% decrease in the mSUV of the primary tumor after induction chemotherapy. The induction chemotherapy regimens that PET responders and nonresponders received are listed in Table 1. There was a higher proportion of PET responders who received platinum/irinotecan regimens versus PET nonresponders (67% vs 58%, *P* = .02); similarly, 24% of PET responders received platinum/paclitaxel regimens, whereas 40% of PET nonresponders did.

**Chemotherapy Change With Radiation for PET Nonresponders**

All PET responders continued with the same regimen during radiation, which consisted of 28 fractions (1.8 Gy/fraction) administered over approximately 5.5 weeks (for a total of 50.4 Gy). In general, patients who received cisplatin/irinotecan with or without bevacizumab and docetaxel/irinotecan with or without cisplatin continued on the same dose/schedule with radiation. Patients who continued with platinum/paclitaxel during radiation typically continued with the same dose of cisplatin or carboplatin but had a dose reduction in paclitaxel from 70 to 50 mg/m², with the regimen administered weekly. Additional dose reductions, delays, and omissions were made on the basis of clinical parameters, including an absolute neutrophil count < 1,000/mL, a platelet count < 75,000/mL, and significant fatigue or dehydration from dysphagia/odynophagia.

Of the 88 PET nonresponders to induction chemotherapy, 50 (57%) continued with the same regimen during chemoradiation. Thirty-six of these patients received cisplatin/irinotecan with or without bevacizumab, 13 received platinum/paclitaxel, and 1 patient was treated with infusional 5-FU/oxaliplatin. Thirty-eight of the 88

### TABLE 1. Patient Characteristics

|                      | All Patients (n = 201) | PET Responders (n = 113) | PET Nonresponders (n = 88) | *P*
|----------------------|------------------------|--------------------------|---------------------------|------
| Age, median (range), y | 62 (23–88)             | 62 (23–82)               | 62.5 (33–88)              | .63  
| Sex, No. (%)          |                        |                          |                           | .71  
| Male                 | 164 (82)               | 91 (81)                  | 73 (83)                   |      
| Female               | 37 (18)                | 22 (19)                  | 15 (17)                   |      
| Karnofsky performance status, median (range), % | 90 (60–100) | 90 (70–100) | 90 (60–100) | .64  
| Baseline staging, No. (%) |                  |                          |                           | .38  
| uT2-3N0              | 39 (19)                | 22 (19)                  | 17 (19)                   |      
| uT1-2N+              | 14 (7)                 | 7 (6)                    | 7 (8)                     |      
| uT3-4N+              | 129 (64)               | 77 (68)                  | 52 (59)                   |      
| uT2-3Nx              | 10 (5)                 | 3 (3)                    | 7 (8)                     |      
| uTxN+                | 9 (4)                  | 4 (4)                    | 5 (6)                     |      
| Tumor location, No. (%) |                      |                          |                           | .84  
| Mid esophagus        | 4 (2)                  | 3 (3)                    | 1 (1)                     |      
| Distal esophagus     | 83 (41)                | 46 (41)                  | 37 (42)                   |      
| Gastroesophageal junction |              | 64 (56)                  | 50 (57)                   |      
| Baseline mSUV, median (range) | 10 (2.7–17.7) | 13.1 (3–37.4) | 7 (2.7–17.7) | <.01 
| Induction chemotherapy, No. (%) |                  |                          |                           | .02  
| Platinum/irinotecan ± bevacizumab | 127 (63) | 76 (67) | 51 (58) |      
| Platinum/paclitaxel  | 62 (31)                | 27 (24)                  | 35 (40)                   |      
| Docetaxel/irinotecan ± cisplatin | 5 (2)      | 5 (4)                   | –                         |      
| Fluoropyrimidine/oxaliplatin | 7 (3)      | 5 (4.4)                 | 2 (2)                     |      

Abbreviations: mSUV, maximum standard uptake value; PET, positron emission tomography.
PET nonresponders (43%) were changed to alternative chemotherapy during radiation as follows:

- Thirteen patients who were treated with induction cisplatin/irinotecan received fluoropyrimidine/paclitaxel with radiation. The fluoropyrimidine consisted of either 5-FU at 225 to 300 mg/m² for 96 to 120 hours or capecitabine at 825 mg/m² twice daily, Monday through Friday, for each week of radiation; paclitaxel was administered at 50 mg/m² weekly.

- Two patients who were treated with induction cisplatin/irinotecan received cisplatin/docetaxel. The doses were 20 to 25 mg/m² for cisplatin and 20 mg/m² for docetaxel weekly.

- Seventeen patients who were treated with induction carboplatin/paclitaxel were switched to fluoropyrimidine/oxaliplatin. Oxaliplatin was administered at 70 to 85 mg/m² every 14 days.

- Three patients who initially received carboplatin/paclitaxel were switched to capcitabine/mitomycin. Mitomycin was administered at 8 to 10 mg/m² during the first and fifth weeks of radiation.

- Two patients who received carboplatin/paclitaxel were switched to platinum/irinotecan.

- One patient who received FOLFOX during induction was changed to carboplatin/paclitaxel.

Pathologic Outcomes

Treatment outcomes are shown in Table 2. Although all patients were initially considered to be surgical candidates, 49 patients (24%) did not undergo surgery because of the development of metastatic disease (16%), subsequent determination of medical inoperability (6%), or refusal due to the achievement of a clinical complete response (2%). The proportions of patients who underwent surgery and were able to achieve R0 resections were similar in all 3 groups. In the subgroup of patients who underwent surgery, the pCR for PET responders was superior to that for PET nonresponders who did not change chemotherapy during radiation (15% vs 3%, \( P = .046 \)). The pCR rate for PET nonresponders who did not change chemotherapy was numerically inferior to the rate for nonresponders who did change chemotherapy with radiation (3% vs 10%) but this was not statistically significant (\( P = .32 \)).

Survival

As shown in Figure 1, the median PFS for PET responders (18.9 months; 95% confidence interval [CI], 13-35.4 months) was significantly superior to that for PET nonresponders who did not change chemotherapy (10 months; 95% CI, 7.2-12.7 months; \( P < .01 \)). The median PFS for PET nonresponders who changed chemotherapy during radiation (17.9 months; 95% CI, 9.1% to not reached) was similar to that for PET responders (\( P = .62 \)) and superior to that for the PET nonresponders who did not change therapy (\( P = .01 \)).

Similarly, the median OS for PET responders (37 months; 95% CI, 29-54 months) was significantly longer than that for PET nonresponders who did not change chemotherapy (25.3 months; 95% CI, 18-34.1 months; \( P = .02 \)). The median OS for PET nonresponders who changed chemotherapy during radiation (25.8 months; 95% CI, 16.6 months to not reached) was not different than that for PET nonresponders who did not change their chemotherapy (25.3 months; 95% CI, 18-34.1 months; \( P = .18 \)). The 3- and 5-year OS rates were 48% (95% CI, 31%-62%) and 37% (95% CI, 18%-55%) for PET nonresponders who changed chemotherapy during radiation and 35% (95% CI, 22%-48%) and 25% (95% CI, 14%-38%) for PET nonresponders who did not change chemotherapy, but this did not achieve statistical significance (\( P = .18 \)).
The cumulative incidence of progression/recurrence at 3 years was 53% (95% CI, 44%-63%) for PET responders and 72% (95% CI, 60%-85%) for the PET nonresponders who did not change chemotherapy during radiation, whereas the 3-year incidence was 43% (95% CI, 19%-50%) for PET responders who changed chemotherapy. Therefore, PET responders had a significantly lower incidence of disease progression/recurrence in comparison with PET nonresponders continued with the same chemotherapy or changed to an alternative regimen during concurrent radiation. PET indicates positron emission tomography.

DISCUSSION
The predictive value of PET scans in esophagogastric cancers has previously been demonstrated in numerous studies, which have shown that the degree of response detected by PET after preoperative chemoradiation or chemotherapy is highly correlated with the pathologic response at surgery and with patient survival.

The German MUNICON trial evaluated the strategy of taking patients with locally advanced gastroesophageal junction adenocarcinomas with a suboptimal PET response to 2 weeks of induction chemotherapy with 5-FU/cisplatin directly to surgery instead of continuing with presumably ineffective chemotherapy. Patients with a PET response (defined by the same ≥35% reduction in mSUV) continued with an additional 12 weeks of chemotherapy before surgery. This trial revealed significant improvements in the R0 resection rate (96% vs 74%, \(P = .002\)), major pathologic response rate (58% vs 0%, \(P = .001\)), median event-free survival (29.7 vs 14.1 months, \(P = .002\)), and median OS (median not reached vs 25.8 months, \(P = .015\)) for PET responders versus PET nonresponders. The outcome for PET nonresponders referred for immediate surgery was similar to the outcome for such patients in an earlier trial who completed 3 months of preoperative chemotherapy, and this indicates that nonresponding patients were not compromised by referral to immediate surgery. These results, therefore, support the early discontinuation of inactive preoperative chemotherapy in PET nonresponder patients.

Building on the results of the MUNICON trial, the MUNICON-2 trial attempted to improve outcomes for the PET nonresponders to the same regimen of preoperative 5-FU/cisplatin by treating them with salvage chemoradiation with cisplatin before surgery. Compared with the PET responders who completed 3 months of 5-FU/cisplatin before surgery, the PET nonresponders had inferior 2-year PFS (64% vs 33%, \(P = .035\)) and a trend toward inferior 2-year OS (71% vs 42%, \(P = .10\)). These results likely speak to the underlying unfavorable biology of the tumors of PET nonresponders but do not rule out the possibility that such patients could receive effective salvage therapy. In this trial, the chemotherapy administered with radiation was cisplatin, which had already been assessed to be associated with suboptimal outcomes by PET when it was administered as induction therapy but...
which was also administered at an unusual dose (6 mg/m² on days 1-5 and 8-12 of radiation). The radiotherapy was delivered in a nonstandard fashion with 1.6 Gy/fraction twice daily for a total dose of 32 Gy, which was also lower than the doses of preoperative chemoradiation used in the CROSS study (41.4 Gy) or in contemporary US studies (50.4 Gy). Therefore, the salvage regimen in this trial may not have been adequate to overcome the adverse biology of PET nonresponders.

In this large retrospective review, we further confirm the robust finding that a PET scan after induction chemotherapy is strongly predictive of outcomes. Specifically, PET responders to induction chemotherapy who continue on the same regimen during radiation have significantly superior pCR rates (15% vs 3%), median PFS (18.7 vs 9.7 months), and median OS (37 vs 25.2 months). These differences are very clinically significant and unfortunately highlight the dismal outcomes of PET nonresponders to initial chemotherapy who continue with the same regimen during radiation. Although PET responders to induction chemotherapy certainly fare better, their outcomes, in terms of a pCR rate of 15% and a 5-year survival rate of approximately 35%, are far from satisfactory and reflect the aggressiveness of this cancer even in this subgroup.

More importantly, the results of this study suggest that switching to alternative chemotherapy during radiation for PET nonresponders can improve outcomes. This strategy was initially based on anecdotal observations of 4 patients but is now further suggested on the basis of the outcomes of 38 patients. The median PFS of these PET nonresponders who switched chemotheraphy with radiation was significantly superior to the median PFS of the PET nonresponders who continued with the same regimen (18 vs 9.7 months). There was also a very meaningful reduction in 3-year cumulative incidence recurrence rates for the PET nonresponders who changed chemotherapy versus those who did not (43% vs 72%). There also appeared to be non-significant trends toward clinically relevant improvements in pCR rates (10% vs 3%) and long-term survival (5-year survival, 37% vs 25%). The lack of an OS benefit from changing chemotherapy in the PET nonresponders may be due to the relatively small patient numbers.

An interesting finding from this study is the fact that PET responders appeared to have more FDG-avid tumors than PET nonresponders (mSUV, 13.1 vs 7; P < .01). An analysis by Suzuki et al13 from The University of Texas MD Anderson Cancer Center suggested that a higher baseline SUV uptake in the primary tumor was associated with worse survival for patients treated with chemoradiation; these tumors were also associated with higher T and N stages. In conjunction with the fact that the T and N staging by endoscopy with ultrasound was not different between PET responders and nonresponders, these results suggest at a minimum that the PET responders did not have more favorable baseline factors.

Another notable finding is that there appeared to be a significant difference in the proportions of different induction chemotherapy regimens between PET responders and nonresponders. PET responders were more likely to have received platinum/irinotecan regimens, whereas PET nonresponders were more likely to have received platinum/paclitaxel regimens. Because of the nonrandomized nature of the induction chemotherapy regimens in this analysis, it is not possible to determine the superiority—by PET assessment—of any specific regimen. The major weakness of this large retrospective series is certainly that patients received different chemotherapy regimens.

However, although the pivotal Dutch CROSS study has established preoperative carboplatin/paclitaxel and radiation as a standard of care,5 it is not known whether this regimen is superior to other chemoradiation regimens. A limited comparison comes from the Eastern Cooperative Oncology Group 1201 study, which randomized 90 patients to radiation (45 Gy) with either cisplatin/irinotecan or cisplatin/paclitaxel before surgery.14,15 There was no significant difference in outcomes between the treatment arms, although there was a

### Table 3. Patterns of Recurrence

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>PET Responders (n = 113)</th>
<th>PET Nonresponders: No Chemotherapy Change (n = 50)</th>
<th>PET Nonresponders: Chemotherapy Change (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any site</td>
<td>63</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>Locoregional</td>
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<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Distant</td>
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<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Both</td>
<td>17</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: PET, positron emission tomography.
nonsignificant trend toward improved median OS in the cisplatin/irinotecan arm (35 vs 21 months).

The high pCR rate of 23% for adenocarcinoma patients in the CROSS study is also frequently cited to suggest its potential superiority to other chemoradiation regimens; it is certainly impressive when it is compared with the 15% pCR rate of PET responders in our review. However, pCR may not be as robust or reproducible an endpoint as has been consistently assumed. For example, in comparison with the 23% pCR rate in the CROSS trial, the aforementioned Eastern Cooperative Oncology Group 1201 study reported a 16% pCR rate for cisplatin/paclitaxel and radiation. Similarly, 2 US studies of 5-FU/oxaliplatin and radiation that treated 93 and 55 patients, respectively, reported different pCR rates of 28% and 11%.16,17

Our belief is that the major benefit of induction chemotherapy is that it permits an assessment by PET imaging before a commitment is made to the addition of radiation. Outside this specific context, there does not appear to be any benefit from additional chemotherapy before chemoradiation. The largest study to evaluate this approach is a randomized phase 2 study of 126 patients performed by Ajani et al.17 There was no improvement in the median OS for patients who received induction chemotherapy versus the chemoradiation-only patients (43.7 vs 45.6 months, \( P = .69 \)), and there was only a nonsignificant trend toward an improved pCR rate (22% vs 11%, \( P = .094 \)). These results mirror the recent findings of the UK OEO5 study, which did not show any improvement in survival outcomes with 6 weeks of preoperative chemotherapy versus 12 weeks for esophageal/gastroesophageal junction adenocarcinoma.18

Ultimately, this PET-directed strategy will require a prospective study to determine its benefit. To that end, the fully accrued Cancer and Leukemia Group B 200803 trial (NCT01333033) seeks to answer this question. Patients in this study were randomized to receive 6 weeks of induction carboplatin/paclitaxel or FOLFOX before reassessment by PET. PET responders (according to the same mSUV cutoff of \( \geq 35% \)) continued with the same regimen during radiation, whereas PET nonresponders were switched to the alternative regimen with radiation, all before surgery. The primary endpoint of the study is to improve the pCR rate of PET nonresponders from historical rates of 5% to 20%, whereas the secondary endpoints include survival outcomes. The study design may also provide an indirect comparison of both regimens by evaluating their PET response rates.

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**CONFLICT OF INTEREST DISCLOSURES**

The authors made no disclosures.

**AUTHOR CONTRIBUTIONS**

Geoffrey Y. Ku: Planning and performance of the study, responsibility for the overall content, detailed review, and comments on the manuscript. Anuja Kriplani: Planning and performance of the study, detailed review, and comments on the manuscript. Yelena Y. Janjigian: Detailed review and comments on the manuscript. David P. Kelsen: Detailed review and comments on the manuscript. Valerie W. Rusch: Detailed review and comments on the manuscript. Manjit Bains: Detailed review and comments on the manuscript. Joanne Chou: Statistical analyses, detailed review, and comments on the manuscript. Marinela Capanu: Statistical analyses, detailed review, and comments on the manuscript. Abraham J. Wu: Detailed review and comments on the manuscript. Karyn A. Goodman: Detailed review and comments on the manuscript. David H. Ilson: Detailed review and comments on the manuscript.

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