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Adjuvant Therapy after Neoadjuvant Therapy for Esophageal Cancer: Who Needs It?

Type of Study: Multi-institution worldwide observational study

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Listed below are the contributions of the 10 authors who contributed substantially to this multi-departmental 2-institution study.

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2. Thomas W. Rice: Substantial contributions to the conception, design, data collection, and interpretation of the data. Also heavily involved in revising the paper.

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10. Hemant Ishwaran: Substantial contributions to the conception, design, and selection of statistical approach to the data, statistical analysis, and interpretation of the statistical results. Also heavily involved in drafting and revising the paper.

All authors have seen and given their final approval of the version being submitted for publication.

STRUCTURED ABSTRACT

Objective: We hypothesized that, on average, patients do not benefit from additional adjuvant therapy after neoadjuvant therapy for locally advanced esophageal cancer, although subsets of patients might. Therefore, we sought to identify profiles of patients predicted to receive the most survival benefit or greatest detriment from adding adjuvant therapy.

Summary Background Data: Although neoadjuvant therapy has become the treatment of choice for locally advanced esophageal cancer, the value of adding adjuvant therapy is unknown.

Methods: From 1970-2014, 22,123 patients were treated for esophageal cancer at 33 centers on 6 continents (Worldwide Esophageal Cancer Collaboration), of whom 7,731 with adenocarcinoma or squamous cell carcinoma received neoadjuvant therapy; 1,348 received additional adjuvant therapy. Random forests for survival and virtual-twin analyses were performed for all-cause mortality.

Results: Patients received a small survival benefit from adjuvant therapy (3.2±10 months over the subsequent 10 years for adenocarcinoma, 1.8±11 for squamous cell carcinoma). Consistent benefit occurred in ypT3-4 patients without nodal involvement and those with ypN2-3 disease. The small subset of patients receiving most benefit had high nodal burden, ypT4, and positive margins. Patients with ypT1-2N0 cancers had either no benefit or a detriment in survival. ~~The worst responders to neoadjuvant therapy had the best response to adjuvant therapy.~~

Conclusions: Adjuvant therapy after neoadjuvant therapy has value primarily for patients with more advanced esophageal cancer. Because the benefit is often small, patients considering adjuvant therapy should be counseled on benefits versus morbidity. Additionally, given that the

overall benefit was meaningful in a small number of patients, emerging modalities such as immunotherapy may hold more promise in the adjuvant setting.

INTRODUCTION

Although neoadjuvant therapy, in the form of either chemoradiotherapy or chemotherapy alone, for locally advanced cancer of the esophagus or esophagogastric junction is now standard of care,[1-6] the value of adjuvant therapy after neoadjuvant therapy is unclear. Several recent studies using easily accessible but limited databases such as the National Cancer Database and small multi-institutional clinical studies suggest that adjuvant therapy provides a survival benefit for patients with residual nodal disease.[7-9] Detailed analyses have thus far been lacking to examine and quantify the treatment effect in a granular fashion. Specifically, information about subsets of patients who benefit most from additional therapy and types of histopathology that are more sensitive to additional therapy have not been clearly identified.

In this study, we present our analysis of patients who did or did not receive adjuvant therapy after neoadjuvant therapy using the granular 6-continent Worldwide Esophageal Cancer Collaboration (WECC) database,[10] which was used to develop edition 8 cancer staging manuals.[11,12] Based on available studies, we hypothesized that most patients would receive no meaningful survival benefit from adjuvant therapy after neoadjuvant therapy, but some subsets might. Given the global nature of our database, the intent of this study was to examine the value of adjuvant therapy after neoadjuvant therapy generally, not to examine the effectiveness of any specific protocol.

To date, studies have used propensity-score methods that describe average treatment effect on the treated. Therefore, to compare survival after these two treatment strategies for individual patents, we used virtual-twin analysis, introduced in 2011 by Foster and colleagues.[13] As with propensity-score methods,[14] one first identifies patients likely to receive either therapy: "virtual equipoise." To compare survival with alternative therapies, each patient then serves as

his or her own control ("virtual twin") via calculations of risk-adjusted predicted survival for that patient with therapy received and again with therapy not received.

Thus, the objective of our study was to determine the individual benefit for patients within different cancer categories while accounting for the interplay of ypT and ypN categories for those undergoing adjuvant therapy after neoadjuvant therapy for adenocarcinoma and squamous cell carcinoma of the esophagus or esophagogastric junction.

METHODS

Patients and Therapies

From 1970 to 2014 at 33 WECC institutions (see Document, Supplemental Digital Content [SDC] 1, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, listing participating institutions and investigators), 22,123 consecutive patients had real-world clinical data available for epithelial cancers of the esophagus and esophagogastric junction as part of the effort to provide clinical,[10,15] pathologic,[16,17] and post-neoadjuvant staging data[18,19] for the 8th edition of the American Joint Commission on Cancer Staging Manual.[11] Of these, 7,731 had adenocarcinoma or squamous cell carcinoma and underwent neoadjuvant therapy (adenocarcinoma n=4,673, squamous cell carcinoma n=1,710) or neoadjuvant therapy followed by adjuvant therapy (adenocarcinoma n=1,013, squamous cell carcinoma n=335) (see Table, SDC 2, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, showing baseline and treatment data stratified by therapy).

Of the 5,686 patients with adenocarcinoma, 4,242 received chemoradiotherapy (75%), as did 1,372 (67%) of the 2,045 patients with squamous cell carcinoma (see Table, SDC 3,

Supplemental Digital Content 1, http://links.lww.com/SLA/E188, showing baseline and treatment data stratified by histopathologic type).

Data

This study used 36 variables representing patient demographics and comorbidities, cancer characteristics, cancer treatment, and time-related mortality (see Document, SDC 4, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, listing variables used in random forest analyses), with site and continent excluded to contain data dimensionality and reduce confounding with treatment.[10] These variables were obtained after local ethics-board approval of databases and data-use agreements with Cleveland Clinic. Data were requested in completely anonymized form using standard definitions. The Case Cancer Institutional Review Board of Case Western Reserve University and Cleveland Clinic Institutional Review Board approved the entire project and use of these data for research, with patient consent waived.

Missing data for independent variables were imputed using "on-the-fly" random forest imputation[20] implemented in the open-source randomForestSRC R-software package[21] under default settings.

In this paper, the terms upstaging and downstaging relate to change, positive or negative, from clinical (cTNM) to pathologic (ypTNM) categories.

Endpoint

The endpoint was all-cause mortality from first management decision after esophageal cancer diagnosis. Among all patients receiving neoadjuvant therapy with or without adjuvant therapy, median potential follow-up[22,23] was 8.2 years had there been no deaths, but considering deaths in this elderly population with a rapidly lethal cancer, median observed follow-up was 1.4 years. For patients receiving neoadjuvant therapy alone, 50% were followed >1.4 years, 25% >3.1

years, and 10% >5.8 years; for those receiving adjuvant therapy after neoadjuvant therapy, 50% were followed >1.3 years, 25% >2.4 years, and 10% >4.2 years.

Statistical Analysis

Analyses were conducted separately for adenocarcinoma and squamous cell carcinoma. For these cancers, the initial therapy decision is whether or not to use neoadjuvant therapy; addition of adjuvant therapy is a decision made after pathologic characteristics of the cancer (yp) are determined. Adjuvant therapy after neoadjuvant therapy is, therefore, the focus of this study. The primary objective of the analysis is to identify patients for whom addition of adjuvant therapy to neoadjuvant therapy is predicted to be beneficial, makes no difference, or is harmful based on difference in survival time. This was accomplished in four analytic steps:

1. Eligibility: We identified patients deemed eligible for both strategies based on observed clinical practice across the world (see Document, SDC 5, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, describing patient eligibility (overlap) for virtual-twin analysis).[24] Although theoretically all patients in this study could have received neoadjuvant therapy with or without adjuvant therapy, patients who exhibited a complete pathologic response generally did not receive additional adjuvant therapy, and those with deeply invasive ypT and residual ypN generally did; comparison of survival for these patients was considered unfair, and therefore they were excluded from any further analysis (see Table, SDC 6, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, describing characteristics of patients with adenocarcinoma deemed eligible or not for both therapies and Table, SDC 7, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, describing characteristics of such patients with squamous cell carcinoma). Those deemed eligible to receive either therapy were included in the final analysis. This data-driven strategy is similar to that used in

propensity-score–based analyses.[14]

2. Survival analysis: We performed multivariable survival analyses for patients found eligible for both neoadjuvant therapy alone and adjuvant therapy after neoadjuvant therapy. The analysis was performed using random survival forests virtual-twin interaction (RSF-VT-I), which incorporated interaction terms for all clinical and cancer variables with the two treatment strategies (see Document, SDC 8, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, describing details of the survival analysis using random survival forests virtual-twin analysis).[21,25] This differs from comparisons based on propensity-matched pairs of patients: virtual twins are, by definition, exact matches.
3. Virtual-twin survival predictions: From the survival analysis, we generated two predicted survival curves for each patient, one for the actual treatment received and one for the counterfactual treatment.[13,25] This was accomplished using the identical patient data, but substituting the counterfactual therapy for the actual therapy received.
4. Gain or loss of lifetime: We calculated the area under each pair of survival curves for each patient from initial therapy to 10 years—a measure of length of life within those 10 years called Restricted Mean Survival Time [RMST])—and took the difference.[26,27] Difference in RMST between survival curves for pairs of therapies estimated the amount of survival time gained (positive number) or lost (negative number) by being treated with neoadjuvant therapy alone or with adjuvant therapy after neoadjuvant
5. therapy. From this difference, we identified the cancer profile of those benefiting or not benefiting from adjuvant therapy.

RESULTS

Therapy Eligibility (Virtual Equipoise)

Among patients with pure adenocarcinoma, 3,563 (63%) were deemed eligible for neoadjuvant therapy with or without adjuvant therapy (Table 1). They constituted the study group for adenocarcinoma (see Table, SDC 9, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, showing baseline characteristics of patients eligible for both therapies, stratified by histopathologic cell type). Among patients with squamous cell carcinoma, 808 (40%) were deemed eligible for neoadjuvant therapy with or without adjuvant therapy (see Table 1). They constituted the study group for squamous cell carcinoma (see Table, SDC 9, Supplemental Digital Content 1, http://links.lww.com/SLA/E188).

As an example, within the group of patients with adenocarcinoma deemed to have a low probability of receiving adjuvant therapy after neoadjuvant therapy, 1.2% actually received it (see Table, SDC 6, Supplemental Digital Content 1, http://links.lww.com/SLA/E188). Similarly, within the group deemed to have a high probability of receiving adjuvant therapy, 89% actually received it after neoadjuvant therapy.

Survival Analysis (Virtual-Twin Analysis)

Adenocarcinoma

Patients undergoing adjuvant therapy after neoadjuvant therapy for adenocarcinoma had a small overall survival benefit (mean 3.2±10 months). Survival with adjuvant therapy was slightly better in more than 50% of patients when they had persistent node- positive disease at resection (ypN+) (Figure 1 and Figure, SDC 10, Supplemental Digital Content 2, http://links.lww.com/SLA/E189 showing survival of patients undergoing neoadjuvant therapy for adenocarcinoma of the esophagus according to ypT, lymph node category (ypN0 vs. ypN+), and

receipt (esop/neo/adj) or not (esop/neo) of adjuvant therapy after neoadjuvant therapy). In node-negative (ypN0) patients, a benefit was seen only for more invasive cancers (ypT3 or ypT4). Of the ypT1-2N0 patients, more than 50% had no survival benefit or a slight decrement in survival after adjuvant therapy. When the interplay between ypT and ypN was further investigated, gain in life due to adjuvant therapy increased with increasing nodal involvement (Figure 2).

The benefit of therapy for nodal involvement was tempered, however, by ypT category: For patients with a large number of positive nodes, adjuvant therapy was more beneficial for less invasive cancers (Table 2). As an example, patients with a ypT2N3 cancer had a 5.6-month survival benefit, but those with a ypT3N3 cancer had only a 1.9-month survival benefit. Nevertheless, most patients with ypN2-3 cancer had longer survival when receiving adjuvant therapy than those who did not. Most of that benefit was derived from cancers having four or more positive lymph nodes. For patients with ypN1 cancers, the pattern of gain in lifetime was inconsistent across ypT categories.

Squamous cell carcinoma

The pattern of gain or loss in lifetime described for adenocarcinoma was similar for patients with squamous cell cancer. There was also a small overall survival benefit for patients undergoing adjuvant therapy after neoadjuvant therapy (1.8±11 months). Adjuvant therapy was associated with slightly greater survival in more than 50% of patients who had persistent node-positive disease (see Figure 1 and Figure, SDC 11, Supplemental Digital Content 3, http://links.lww.com/SLA/E190 showing survival of patients undergoing neoadjuvant therapy for squamous cell carcinoma of the esophagus according to ypT, lymph node category [ypN0 vs. ypN+], and receipt [esop/neo/adj] or not [esop/neo] of adjuvant therapy after neoadjuvant therapy). Patients with ypN2-3 disease after neoadjuvant therapy benefited from adjuvant therapy (see Table

2). For patients with ypN1 cancer, benefit was inconsistent until ypT3-4 (see Figure 2). Gain in lifetime was generally absent or negative for node-negative patients (ypN0), except for those with ypT4N0 cancer, in whom there was a 4.7-month survival benefit with addition of adjuvant therapy. Similarly, there was no substantial benefit for patients with ypT0 cancer regardless of residual nodal disease burden.

Survival benefit by patient and cancer characteristics

Patients who benefited most from adjuvant therapy after neoadjuvant therapy had more residual disease than those who had the most detriment (Tables 3 and 4). Their mean gain in lifetime was 22±6.0 months for adenocarcinoma and 23±8.1 months for squamous cell carcinoma. Patients with the greatest survival benefit had a higher frequency of nodal disease and nodal upstaging and greater frequency of ypT4 and positive margins. In general, patients predicted to derive the most benefit from adjuvant therapy also had a greater disease burden after neoadjuvant therapy. Patients with low burden of disease had a detriment to survival. This pattern was similar for adenocarcinoma (see Tables 2 and 3 and Table, SDC 12, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, showing complete clinical cancer categories to augment Table 3) and squamous cell carcinoma (see Tables 2 and 4 and Table, SDC 13, Supplemental Digital Content 1, http://links.lww.com/SLA/E188, showing complete clinical cancer categories to augment Table 4).

DISCUSSION

Principal Findings

The survival benefit overall for patients receiving adjuvant therapy after neoadjuvant therapy for esophageal cancer was small and variable. The findings were mostly consistent for adenocarcinoma and squamous cell cancers, with some notable differences. Survival benefit is now quantified for

each TNM category in adenocarcinoma and squamous cell carcinoma (see Table 2). Generally, patients with ypT0-2N0-1 cancers

had either no benefit or worse survival from addition of adjuvant therapy; patients with ypT3-4N0 or ypN2-3 cancers received a slight survival benefit. The small subset of patients who received the most benefit tended to have a higher frequency of nodal disease and nodal upstaging and greater frequency of ypT4 category and positive margins.

Context and Review of the Literature

Since the CROSS (ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study) trial,[1] which demonstrated improved survival with addition of chemoradiotherapy to surgery, neoadjuvant therapy has been the standard of care for locally advanced esophageal cancer. Even with this aggressive treatment regimen, however, less than half of patients survived beyond 5 years.[1] Similarly, in patients who underwent induction chemotherapy alone with FLOT, median survival was only 50 months.[6] Although use of chemotherapy alone versus chemoradiotherapy is hotly debated,[3] the need for some type of neoadjuvant therapy is rarely in question for locally advanced esophageal and esophagogastric cancers. This poor outcome provided the impetus for clinicians to explore the use of adjuvant therapy after neoadjuvant therapy. But does adjuvant therapy improve survival? There are no randomized trials to answer this question; the evidence either comes from retrospective database studies or is extrapolated from data in neoadjuvant therapy trials such as CROSS and FLOT4.[1,6]

Burt and colleagues[7] attempted to answer this question using the National Cancer Database and found no survival benefit from adjuvant therapy after neoadjuvant therapy. However, there was a subset of patients with residual nodal disease whose survival was longer. A later study by Samson and colleagues[8] using the same database identified a similar survival

benefit with residual nodal disease across all N categories. Further, a retrospective cohort study of 209 patients from 9 institutions receiving adjuvant therapy after neoadjuvant therapy demonstrated a mortality reduction of 24%.[9] However, despite starting with a large data set, the number of patients receiving adjuvant therapy after neoadjuvant therapy was small and insufficient to examine such things as the interplay between ypT and ypN categories or to identify subgroups that benefit, have no benefit, or are potentially harmed by additional adjuvant therapy. In general, to date, we do not have enough information to know which subgroups of patients benefit from therapy and which groups, when treated with adjuvant therapy after neoadjuvant therapy, take on the morbidity of the treatment without benefit.

In our study, we found an overall treatment benefit associated with adjuvant therapy after neoadjuvant therapy, but the survival benefit was small—1.8 to 3.2 months. Given the minor effect of adjuvant therapy, the variable prognosis after neoadjuvant therapy, and the morbidity associated with additional postoperative therapy, we attempted to identify subgroups of patients for whom additional therapy may be clinically beneficial, as well as patients unlikely to derive a clinical benefit. As noted in the previously discussed studies, patients with persistence of nodal disease demonstrated the greatest benefit, particularly those with ypN2-3 disease. However, the interplay between ypT and ypN categories is more complex than the effect of either variable alone on survival. As expected, patients with ypT3-4 cancers also had a benefit. Currently, most oncologists would view node-positive patients as a homogeneous cohort. However, with a granular database, we saw that the survival benefit occurred mainly in patients who had four or more positive nodes.

Patients who seem to benefit most (more than 22 months of lifetime gained) had a significant residual disease burden after neoadjuvant therapy. These data support targeting this

patient population for future studies of conventional therapy. Patients with a persistent but lower burden of disease should be spared the morbidity of adjuvant therapy. Given that overall survival with this disease is poor, trials of emerging therapies, such as immunotherapy, may hold more promise in the adjuvant setting than conventional therapy.[28,29] In a recently published large, randomized, open-label, phase III trial (CheckMate 649) of first-line nivolumab plus chemotherapy versus chemotherapy alone for metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma, overall survival differed by only 3.3 months (combined positive score ≥5), curiously similar to the 3.2-month overall benefit we found in our adenocarcinoma group.[30]

In another recently published large, randomized, double-blind placebo-controlled trial (CheckMate 577), Kelly and colleagues[31] examined the role of adjuvant nivolumab in completely resected esophageal cancer patients with residual disease in the resection specimen. They found the median disease-free survival in the nivolumab arm to be 22.4 months, compared with 11.0 months. Although survival data have not yet been reported, this magnitude of difference is encouraging. Should a similar benefit be demonstrated in overall survival, immunotherapy may be an alternative to the limited benefit seen in conventional adjuvant therapy after neoadjuvant therapy.

An interesting finding of this study that has rarely been discussed in the literature is the detrimental survival value of adjuvant therapy in some subsets of patients. The high rate of cancer recurrence despite even a complete response has been used as a rationale for adjuvant therapy after neoadjuvant therapy. We have found that most patients with ypN0 disease had not only no improvement but a predicted detriment to survival, except those in advanced ypT categories.

Traditionally, cancer staging has focused on prognostication. However, medical informatics has now reached a state that should allow us to maximize survival by making personalized treatment decisions based on more variables than the traditional four anatomic cancer categories: T, N, M, and grade. Precision-care analysis is the individualization of treatment decisions to improve outcomes, even among apparently homogeneous populations.[32,33] A recent study from this same WECC database has shown that such a survival analysis, which incorporated patient and cancer characteristics, identified an optimal treatment that potentially could have improved survival by an average of 7% over the actual therapy received. As such, our future understanding of prognostication will likely need to transcend the "classic" variables.

Strengths and Limitations

The strength of this study resides in the quality of the data, which were heavily audited to ensure accuracy and completeness as they were collected to create the 8th edition of the American Joint Commission on Cancer Staging Manual chapter on esophageal and esophagogastric junction cancer. The other obvious strength is the large number of patients who had adjuvant therapy after neoadjuvant therapy compared with any previous study, as well as a large number of variables from a global (not North America specific) cohort of patients. Furthermore, the virtual-twin model was used to generate a survival curve for each therapy (with and without adjuvant therapy) for each patient, allowing us to estimate gain or loss of lifetime for even the smallest of subsets within this cohort of patients. Although it has become customary to approach an analysis such as this using propensity-score methods,[14] the biologically plausible interplay of depth of tumor invasion (T) and nodal involvement (N) due to the unique lymphatic drainage of the esophagus[34-37] led us to use nonparametric random forest methods, accounting for the interplay

of T and N. In addition, propensity-score methods tend to focus on average treatment effect on the treated rather than the more informative individual treatment effect.[13,25]

In regard to limitations, the data used in this analysis were obtained from observational institutional databases worldwide, and there was practice pattern variability. Esophageal cancer is a rare disease, and patients submitted to WECC from around the world included those treated as far back as 1970. However, the majority of patients submitted and deemed eligible for comparison of survival were treated from 2000 through 2013 (see Figure, SDC 14, Supplemental Digital Content 4, http://links.lww.com/SLA/E191 which shows the distribution of dates of treatment of patients deemed eligible for both neoadjuvant therapy only and neoadjuvant therapy and adjuvant therapy). The WECC database does not have specifics of chemotherapy, radiotherapy, and chemoradiotherapy regimens and doses. However, the goal of this study was to examine the value of adjuvant therapy after neoadjuvant therapy in a real-world setting, not the effectiveness of specific protocols. The endpoint was all-cause mortality from initial treatment for this rapidly lethal disease. This likely included a few non-cancer deaths, but it is a reliable endpoint when adjusted for patient demographics and comorbidities[38,39] and is the basis for cancer staging.[40,41] However, the fact that all patients underwent surgical treatment after neoadjuvant therapy, and all patients receiving adjuvant therapy had to survive past time zero—the point at time of first management—introduces a small immortality bias for which we cannot account. We did not have morbidity information to evaluate treatment toxicity, although hospital mortality was low.[10] The inherent limitations of clinical staging in determining upstaging and downstaging are affected by local clinical and pathologic staging protocols among institutions.

Conclusions and Relevance

Adjuvant therapy after neoadjuvant therapy has an overall positive survival benefit primarily for patients with persistent nodal disease or deeper tumors without nodal involvement. Because the benefit is often small, patients considering adjuvant therapy should be counseled on the benefits versus morbidity. Additionally, given that the overall benefit was meaningful in a small number of patients, further investigations into emerging modalities such as immunotherapy may hold promise.

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Figure 1: Box and whiskers plot of gain (positive) or detriment (negative) in lifetime within 10 years by adding adjuvant therapy after neoadjuvant therapy according to ypT along horizontal axis, and ypN0 and ypN+ along right-hand edge for adenocarcinoma (left) and squamous cell carcinoma (right). Solid bar is median, box encloses the 25th and 75th percentiles of values, whiskers are 1.5 times the interquartile range, and filled circles are values beyond this. Box width is proportional to sample size. When median (solid bar) is above zero there is a gain in lifetime, and when below zero a detriment in lifetime, for that ypT category.

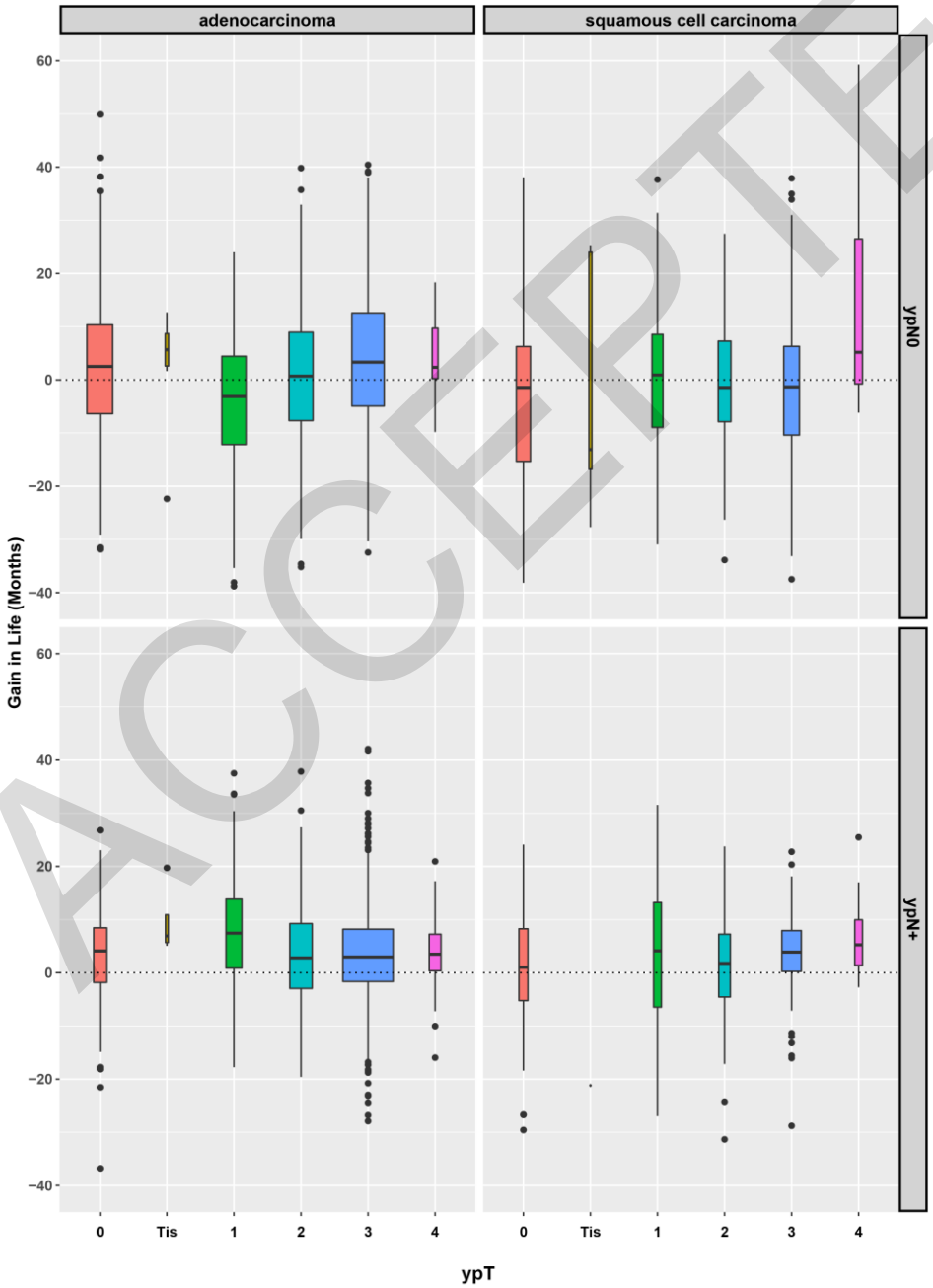

Figure 2: Box and whiskers plot of gain (positive) or detriment (negative) in lifetime within 10 years by adding adjuvant therapy after neoadjuvant therapy according to ypT category along horizontal axis, and number of cancer-positive lymph nodes (right-hand edge) for adenocarcinoma (left) and squamous cell carcinoma (right). Format is as in Figure 1.

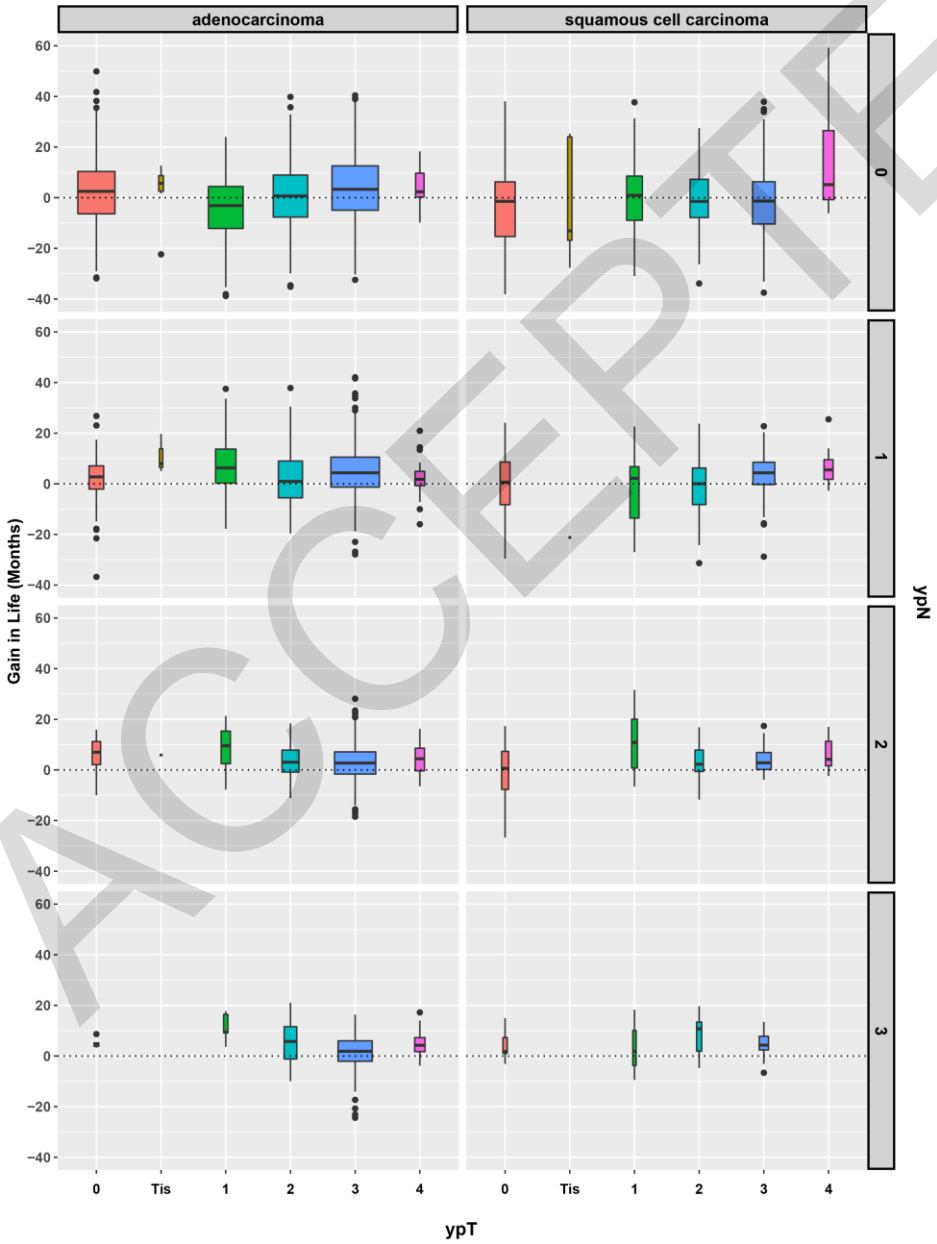

Table 1. Cancer characteristics of patients deemed eligible for neoadjuvant therapy only or adjuvant therapy after neoadjuvant therapy, stratified by pure histopathologic cell type

	Neoadjuvant Therapy Only				Adjuvant after Neoadjuvant Therapy			
	Adenocarcinoma (N=2777)		Squamous Cell Carcinoma (N=601)		Adenocarcinoma (N=786)		Squamous Cell Carcinoma (N=207)	
Category	n[a]	No. (%)	n[a]	No. (%)	n[a]	No. (%)	n[a]	No. (%)
Pathologic T	2575		586		708		206	
0		367 (14)		127 (22)		70 (9.9)		24 (12)
Tis		9 (0.35)		4 (0.68)		1 (0.14)		2 (0.97)
1		371 (14)		73 (12)		69 (9.7)		27 (13)
2		475 (18)		117 (20)		108 (15)		43 (21)
3		1283 (50)		223 (38)		437 (62)		91 (44)
4		70 (2.7)		42 (7.2)		23 (3.2)		19 (9.2)
X		202		15		78		1
Pathologic N	2572		556		739		200	
0		1302 (51)		323 (58)		291 (39)		107 (54)
1		585 (23)		136 (24)		174 (24)		55 (28)
2		412 (16)		77 (14)		165 (22)		30 (15)
3		273 (11)		20 (3.6)		109 (15)		8 (4.0)
X		205		45		47		7
Pathologic ypM1	2777	207 (7.5)	601	67 (11)	786	72 (9.2)	207	24 (12)
Complete response (ypT0N0M0)	2561	296 (12)	585	88 (15)	705	57 (8.1)	206	18 (8.7)
Resection margin	2777		601		786		207	
0		2486 (90)		516 (86)		704 (90)		189 (91)
1		188 (6.8)		67 (11)		75 (9.5)		15 (7.2)
2		103 (3.7)		18 (3.0)		7 (0.89)		3 (1.4)

a. Patients with data available.

Table 2. Median months of life gained (positive values) or lost (negative values) over 10 years from adjuvant therapy after neoadjuvant therapy for adenocarcinoma and squamous cell cancer of the esophagus

Depth of Invasion	ypN0 RMS	ypN+ RMS	ypN1 RMS	ypN2 RMS	ypN3 RMS
Adenocarcinoma					
ypT0	2.5	4.2	2.8	7.0	4.9
ypTis	—	—	—	—	—
ypT1	-3.3	7.5	6.3	9.6	9.5
ypT2	0.5	2.8	0.94	3.0	5.6
ypT3	3.3	3.0	4.3	2.8	1.9
ypT4	4.6	3.5	1.8	4.4	4.2
Squamous cell carcinoma					
ypT0	-1.5	1.1	0.65	0.59	
ypTis	—	—	—	—	—
ypT1	0.92	4.9	4.1		
ypT2	-1.5	1.9	0.05	2.2	
ypT3	-1.3	3.9	4.7	2.4	4.0
ypT4	4.7	5.2	5.5	4.2	

Note: Groups with <10 patients are not depicted in this table.

Key: RMS, restricted mean survival difference within 10 years; ypN+, node-positive disease.

Table 3. Gain or loss of lifetime over 10 years by adjuvant therapy after neoadjuvant therapy according to cancer characteristics in patients with adenocarcinoma of the esophagus

	>16 months (N=354)		-2 to 8 months (N=1,476)		< -11 months (N=359)		
Characteristic	n[a]	No. (%)	n[a]	No. (%)	n[a]	No. (%)	P
Gain or loss (months)		22±6.0		2.9±2.8		-18±6.3	
Pathologic T category	330		1351		334		<.0001
0		51 (15)		150 (11)		57 (17)	
Tis		1 (0.30)		6 (0.44)		1 (0.30)	
1		36 (11)		146 (11)		90 (27)	
2		62 (19)		207 (15)		83 (25)	
3		175 (53)		783 (58)		102 (31)	
4		5 (1.5)		59 (4.4)		1 (0.30)	
Difference in T category	251		1162		300		<.0001
Upstaged 4		0 (0)		1 (0.09)		1 (0.33)	
Upstaged 3		0 (0)		2 (0.17)		0 (0)	
Upstaged 2		6 (2.4)		24 (2.1)		4 (1.3)	
Upstaged 1		25 (10)		128 (11)		25 (8.3)	
Unchanged		126 (50)		597 (51)		96 (32)	
Downstaged 1		47 (19)		188 (16)		80 (27)	
Downstaged 2		19 (7.6)		92 (7.9)		52 (17)	
Downstaged 3		3 (1.2)		38 (3.3)		11 (3.7)	
Downstaged 4		24 (9.6)		84 (7.2)		30 (10)	
Downstaged 5		1 (0.40)		8 (0.69)		1 (0.33)	
Pathologic ypN+	350	143 (41)	1467	958 (65)	359	75 (21)	<.0001
Pathologic N stage	328		1358		355		<.0001
0		207 (63)		509 (37)		284 (80)	
1		85 (26)		313 (23)		48 (14)	
2		26 (7.9)		314 (23)		15 (4.2)	
3		10 (3.0)		222 (16)		8 (2.3)	
Difference in N stage	68		431		160		<.0001
Upstaged 3		7 (10)		53 (12)		3 (1.9)	
Upstaged 2		8 (12)		76 (18)		6 (3.8)	
Upstaged 1		20 (29)		84 (19)		8 (5.0)	
Unchanged		23 (34)		194 (45)		131 (82)	
Downstaged 1		8 (12)		19 (4.4)		10 (6.3)	
Downstaged 2		2 (2.9)		5 (1.2)		2 (1.3)	

Complete response (ypT0N0M0)	326	46 (14)	1344	109 (8.1)	334	51 (15)	.0002
Resection margin	354		1476		359		<.0001
0		335 (95)		1273 (86)		341 (95)	
1		13 (3.7)		144 (9.8)		14 (3.9)	
2		6 (1.7)		59 (4.0)		4 (1.1)	

a. Patients with data available.

Table 4. Gain or loss of lifetime over 10 years by adjuvant therapy after neoadjuvant therapy according to cancer characteristics in patients with squamous cell cancer of the esophagus

	>15 months (N=80)		-3 to 7 months (N=327)		< -15 months (N=88)		
Characteristic	n[a]	No. (%)	n[a]	No. (%)	n[a]	No. (%)	P
Gain or loss (months)		23±8.1		2.0±2.8		-22±7.0	
Pathologic T category	79		319		86		<.0001
0		14 (18)		50 (16)		34 (40)	
Tis		2 (2.5)		0 (0)		3 (3.5)	
1		13 (16)		28 (8.8)		12 (14)	
2		16 (20)		58 (18)		13 (15)	
3		21 (27)		149 (47)		24 (28)	
4		13 (16)		34 (11)		0 (0)	
Difference in T category	71		254		71		<.0001
Upstaged 3		2 (2.8)		2 (0.79)		0 (0)	
Upstaged 2		2 (2.8)		6 (2.4)		0 (0)	
Upstaged 1		11 (15)		42 (17)		0 (0)	
Unchanged		26 (37)		96 (38)		20 (28)	
Downstaged 1		7 (9.9)		51 (20)		11 (15)	
Downstaged 2		8 (11)		18 (7.1)		9 (13)	
Downstaged 3		3 (4.2)		12 (4.7)		6 (8.5)	
Downstaged 4		11 (15)		22 (8.7)		25 (35)	
Downstaged 5		1 (1.4)		5 (2.0)		0 (0)	
Pathologic ypN+	80	27 (34)	325	183 (56)	88	18 (20)	<.0001
Pathologic N category	80		294		87		<.0001
0		53 (66)		142 (48)		70 (80)	
1		17 (21)		79 (27)		15 (17)	
2		8 (10)		62 (21)		2 (2.3)	
3		2 (2.5)		11 (3.7)		0 (0)	
Difference in N category	51		146		29		.0001
Upstaged 3		1 (2.0)		6 (4.1)		0 (0)	
Upstaged 2		4 (7.8)		19 (13)		1 (3.4)	
Upstaged 1		5 (9.8)		39 (27)		3 (10)	
Unchanged		27 (53)		68 (47)		25 (86)	
Downstaged 1		14 (27)		12 (8.2)		0 (0)	
Downstaged 2		0 (0)		2 (1.4)		0 (0)	
Complete response (ypT0N0M0)	79	10 (13)	318	35 (11)	86	28 (33)	<.0001

Resection margin	80	327	88	.003
0	69 (86)	268 (82)	87 (99)	
1	9 (11)	47 (14)	1 (1.1)	
2	2 (2.5)	12 (3.7)	0 (0)	

a. Patients with data available.