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Association of Adjuvant Therapy with Improved Survival in Ampullary Cancer: A National Cohort Study

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Abstract

Background—There are limited data on the efficacy of adjuvant therapy in ampullary cancer. The aim of this study was to determine whether adjuvant therapy was associated with improved survival for patients with ampullary cancer.

Methods—From the National Cancer Database, we identified ampullary cancer patients who underwent resection between 2004–2013. We performed 1:1 propensity score matching, comparing patients who had postoperative observation to patients who received adjuvant chemotherapy (ACT) or adjuvant chemoradiotherapy (ACRT).

Results—We identified 4190 patients who fit our inclusion criteria; 63% had postoperative observation, 21% received ACT, and 16% underwent ACRT. In the matched cohorts, the use of ACT was associated with improved overall survival (HR = 0.82, 95% CI = 0.71 to 0.95). The median overall survival was 47.2 months for the ACT group and 35.5 months for the observation group. In a separate matched analysis, ACRT was also associated with improved survival (HR = 0.84, 95% CI = 0.72 to 0.98) as compared to observation. The median overall survival was 38.1 months for the ACRT group and 31.0 months for the observation group. The benefit was more pronounced in high risk patients, such as ones with higher T and N categories.

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Conclusions—In this retrospective study, the use of adjuvant therapy in ampullary cancer was associated with significantly improved overall survival. The benefit of adjuvant therapy for this disease should be confirmed in a more rigorous fashion via randomized controlled trials.

Keywords

Adjuvant therapy; ampullary cancer; ampullary carcinoma; chemotherapy; chemoradiation

Introduction

Five-year survival for resected ampullary cancer ranges from 38% to 68%.[1] While randomized controlled trials have demonstrated the efficacy of adjuvant therapy for pancreatic adenocarcinoma, which is the most common type of periampullary tumor, no such high-quality data exists for ampullary cancer. The results of clinical trials are inconclusive due to flawed methodology, and the only data supporting adjuvant therapy originates from single-institution studies with inherent limitations due to small sample sizes and the nature of a retrospective design. As a result, neither the National Comprehensive Cancer Network nor the European Society for Medical Oncology provide recommendations for the postoperative management of ampullary cancer.[2–7]

To evaluate the effects of adjuvant therapy for ampullary cancer, we used the National Cancer Database to perform a propensity-matched study comparing the overall survival of patients who had postoperative observation to patients who received adjuvant chemotherapy (ACT) or chemoradiotherapy (ACRT).

Materials and Methods

Database and Patient Population

This was a retrospective study using the National Cancer Database (NCDB). The NCDB is a national cancer registry that receives information from over 1500 Commission on Cancer–accredited cancer programs in the United States, and captures approximately 70% of cancer cases in the United States.[8]

We identified patients with ampullary malignancies (International Classification of Diseases for Oncology, third edition [ICD-O-3], topographical code C24.1) diagnosed between 2004 and 2013 who had surgical resection within 90 days of diagnosis. We included patients who were diagnosed with carcinoma and excluded all other histology types. We excluded patients who had metastatic disease, underwent palliative surgery, received neoadjuvant therapy, had macroscopic margin status, or had missing information (Supplementary Figure 1).

The following variables were abstracted: gender, age, ethnicity, insurance status, median household income of each patient's area of residence, Charlson/Deyo score, tumor grade, year of diagnosis, facility type, margin status, length of stay, 30-day readmission, 90-day mortality, pathological T (pT) and N (pN) categories based on the seventh edition of the American Joint Committee on Cancer TNM staging manual, and receipt of adjuvant therapy, which we divided into ACT and ACRT. We selected only patients who initiated adjuvant

therapy within 90 days following their surgery to exclude patients who had most likely received therapy for recurrence. We also abstracted follow-up and vital status data.

Statistical Analysis

In two separate analyses, we used propensity scores to match patients having postoperative observation to patients who received ACT or ACRT. We estimated the propensity score using a multivariable logistic regression model that included the following variables: gender, age, insurance status, median income of residence, Charlson/Deyo score, pT category, pN category, tumor grade, year of diagnosis, facility type, resection margin status, length of stay, and 30-day readmission. Patients in the two groups were then matched without replacement through a greedy 8-1 digit-matching algorithm.[9] We excluded patients who died within 90 days postoperatively to minimize the immortal time bias as patients who died in the immediate postoperative period would not receive adjuvant therapy.[10] The choice of the landmark time at 90 days corresponds to the postoperative time during which most of the surgery-related mortality occurs.[11, 12] Standardized differences between groups were assessed to establish whether adequate balance was achieved using a cutoff value ≥ 0.1 for imbalance.

Overall survival was estimated using Kaplan-Meier curves and compared with log-rank tests on the matched patient pairs. The hazard ratios were calculated using a Cox proportional hazards model. We evaluated the proportional hazards assumption by examining the Martingale residuals.

In this study, two-sided *P* values of ≤.05 were considered statistically significant. Analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC) and SPSS version 24.

Results

Baseline Characteristics of the Cohorts

We identified 4190 patients who met the inclusion criteria of the study; 63% (2651 patients) were observed after resection, 21% (870 patients) received ACT, and 16% (669 patients) underwent ACRT. Over the study time period, there was increased use of adjuvant therapy (Supplementary Figure 2). Notably, there was a shift away from ACRT in favor of ACT, which increased from 9% in 2004–2005 to 32% in 2012–2013, while ACRT utilization decreased from 20% in 2004–2005 to 12% in 2012–2013.

The baseline characteristics of the unmatched cohorts are presented in Table 1. Patients who received ACT or ACRT were more likely to have higher pT and pN categories, poorly/undifferentiated tumors, positive resection margins, and private insurance. They were younger, less likely to have comorbidities, had a lower mean length of stay after operation, and had a lower rate of 30-day readmission.

Survival Comparison of Observation Versus Adjuvant Chemotherapy

After 1:1 matching, we compared 768 patients who had observation to 768 patients who received ACT. The groups were well-balanced (Table 2). The median follow-up was 25.1

months for the observation group and 28.3 months for the ACT cohort. The receipt of ACT was associated with improved overall survival (HR = 0.82, 95% CI = 0.71 to 0.95; Figure 1). The median overall survival was 47.2 months for the ACT group and 35.5 months for the observation group. The 1-, 3-, and 5-year survival were 90%, 57%, and 44% for the ACT group and 85%, 49%, and 38% for the observation group. Subgroup analysis showed that the test of interaction was significant for T stage disease with T3/T4 disease benefiting more from the treatment compared to T1/T2 disease (Figure 2).

Survival Comparison of Observation Versus Adjuvant Chemoradiotherapy

After 1:1 matching, we compared 568 observation patients to 568 ACRT patients. The groups were well-balanced (Table 3). The median follow-up was 24.4 months for the observation group and 29.4 months for ACRT. The receipt of ACRT was associated with improved overall survival (HR = 0.84, 95% CI = 0.72 to 0.98; Figure 3). The median overall survival was 38.1 months for the ACRT group and 31.0 months for the observation group. The 1-, 3-, and 5-year survival were 88%, 51%, and 40% for the ACRT group and 83%, 45%, and 35% for the observation group. Subgroup analysis showed that the test of interaction was significant for nodal stage disease, with positive nodal disease benefiting more from the treatment compared to negative nodal disease (Figure 4).

Discussion

In this retrospective study of the NCDB, we found that adjuvant therapy is associated with improved overall survival for patients with ampullary cancers, and may be more effective for patients with tumors of higher T and N categories. Evidence supporting the use of adjuvant therapy for ampullary cancer has been equivocal. In previous large randomized clinical trials, ampullary cancers have been grouped with other periampullary tumors, making it difficult to ascertain the true benefit of adjuvant therapy for ampullary cancer patients. The ESPAC-3 trial randomized 434 patients with periampullary cancer to adjuvant chemotherapy or observation and showed no difference in overall survival between the groups.[13] A subgroup analysis of the 304 ampullary adenocarcinoma patients published in abstract form showed that the median survival of patients who received adjuvant therapy was 57 months as compared to 34 months for patients underwent observation. However, the difference did not reach statistical significance.[14] When only the 276 patients who received R0 resections were evaluated, the median survival was 58 months for patients who received adjuvant therapy and 45 months for patients who underwent observation, with a Cox proportional hazards of P = 0.057. However, since this was a subgroup analysis, the data has to be interpreted with appropriate caution. The EORTC 40891 trial that evaluated adjuvant chemoradiotherapy in 93 resected periampullary cancers also demonstrated no survival benefit.[15] However, detailed pathologic review that differentiated true ampullary cancers from other subtypes was not performed. Finally, a phase III randomized trial of a heterogeneous population of patients with pancreaticobiliary tumors compared adjuvant 5-fluorouracil and mitomycin-C to surgery alone and showed no survival improvement in the 48 patients with ampullary cancers.[16]

In contrast, several retrospective reports suggest that adjuvant therapy for ampullary cancer is associated with improved survival.[2–7] Most of these studies are single-institution reports limited by small sample size, uncontrolled analysis, and selection bias, making the interpretation of the results challenging. A meta-analysis of ten retrospective studies that included 3361 patients found adjuvant chemoradiation was associated with a lower risk of death (HR = 0.75; $P = .001$) compared to surgery alone.[17] This report was limited by the fact that all of the studies included were retrospective, some of which presented only unadjusted outcomes, and there was significant heterogeneity between the included studies.

The strength of our report is based on the large sample size of the NCDB that allowed us to mitigate biases that are inherent to all retrospective reviews. First, we were able to perform adjusted survival analyses controlling for various patient and tumor factors known to be associated with survival. Second, we generated large, well-balanced cohorts via propensity matching to diminish selection bias. Next, we decreased the effect of immortal time bias, which weakened many previous studies evaluating the use of adjuvant therapy, by excluding patients who died within the first 90 days. In addition, we matched patients based on length of stay and 30-day readmission as a surrogate for postoperative complications that may preclude the receipt of adjuvant therapy, as patients who have major postoperative complications requiring prolonged length of stay or readmissions in the early postoperative period are less likely to get adjuvant therapy.[18] Finally, we were able to analyze chemotherapy and chemoradiotherapy as separate variables because the NCDB does not indicate if chemotherapy used with radiation was a radiosensitizer or a full-course regimen. Finally, the NCDB gathers information from across the nation and thus provides information that is widely applicable.

Due to the lack of granular data in the NCDB, several important questions remain unaddressed by our study. First, we could not determine if adjuvant therapy was effective for both pancreaticobiliary and intestinal subtypes of ampullary cancer since detailed pathology information was not available. Previous studies have shown that pancreaticobiliary subtype tumors had more aggressive biology and worse outcomes compared to intestinal tumors.[19, 20] In an attempt to address this bias, we included tumor grade as a covariate in the analysis since pancreaticobiliary is more likely to be poorly differentiated.[21]

Second, we could not discern the chemotherapy regimens that were associated with improved survival. Going forward, ampullary cancer will likely be treated with a fluoropyrimidine-based regimen as extrapolated using data from other periampullary cancers. The ESPAC-4 study established 5-FU and gemcitabine as the standard of care for adjuvant therapy for pancreas cancer while the BILCAP trial, which was recently presented in abstract form, demonstrated that adjuvant capecitabine improved survival for biliary tract cancer patients.[22, 23] These results likely will be generalized to patients with pancreaticobiliary subtype while patients with intestinal subtype likely will be treated with FOLFOX, as based on the colon cancer treatment paradigm.

The role of radiation as an adjuvant modality for ampullary cancer will need to be clarified. The largest clinical trials evaluating adjuvant radiotherapy for periampullary and pancreatic malignancies, such as the EORTC trial and ESPAC-1, respectively, have shown no survival

benefit for radiation.[15, 24] In addition, the recent LAP07 study also showed that radiation provided no survival advantage in locally advanced pancreas cancer.[25] While we found that adjuvant chemoradiotherapy was associated with improved survival compared to observation alone, the lack of detailed chemotherapy information made it impossible to determine if the systemic component was a radiosensitizer or full-dose chemotherapy. Thus, the associated survival advantage may be due to the chemotherapy component.

Finally, we could not perform an intent-to-treat analysis since the NCDB does not determine which patients were selected *a priori* for adjuvant therapy. However, the inclusion of length of stay and readmission rate as covariate in our matching analysis, and the exclusion of patients who died within 90 days of resection, may mitigate this bias.

In conclusion, we found that the receipt of adjuvant therapy is associated with improved survival in patients with resected ampullary cancer in this propensity-matched, retrospective, hospital-based study. The benefits of therapy appeared to be especially valuable in patients with high risk disease such as ones with T3/T4 tumors and positive nodal involvement. Although our study is subject to the known limitations of a retrospective study, it provides treating physicians another source of data to use while discussing adjuvant therapy with their patients. Finally, our findings provide equipoise to study the role of adjuvant therapy in ampullary cancers in a randomized fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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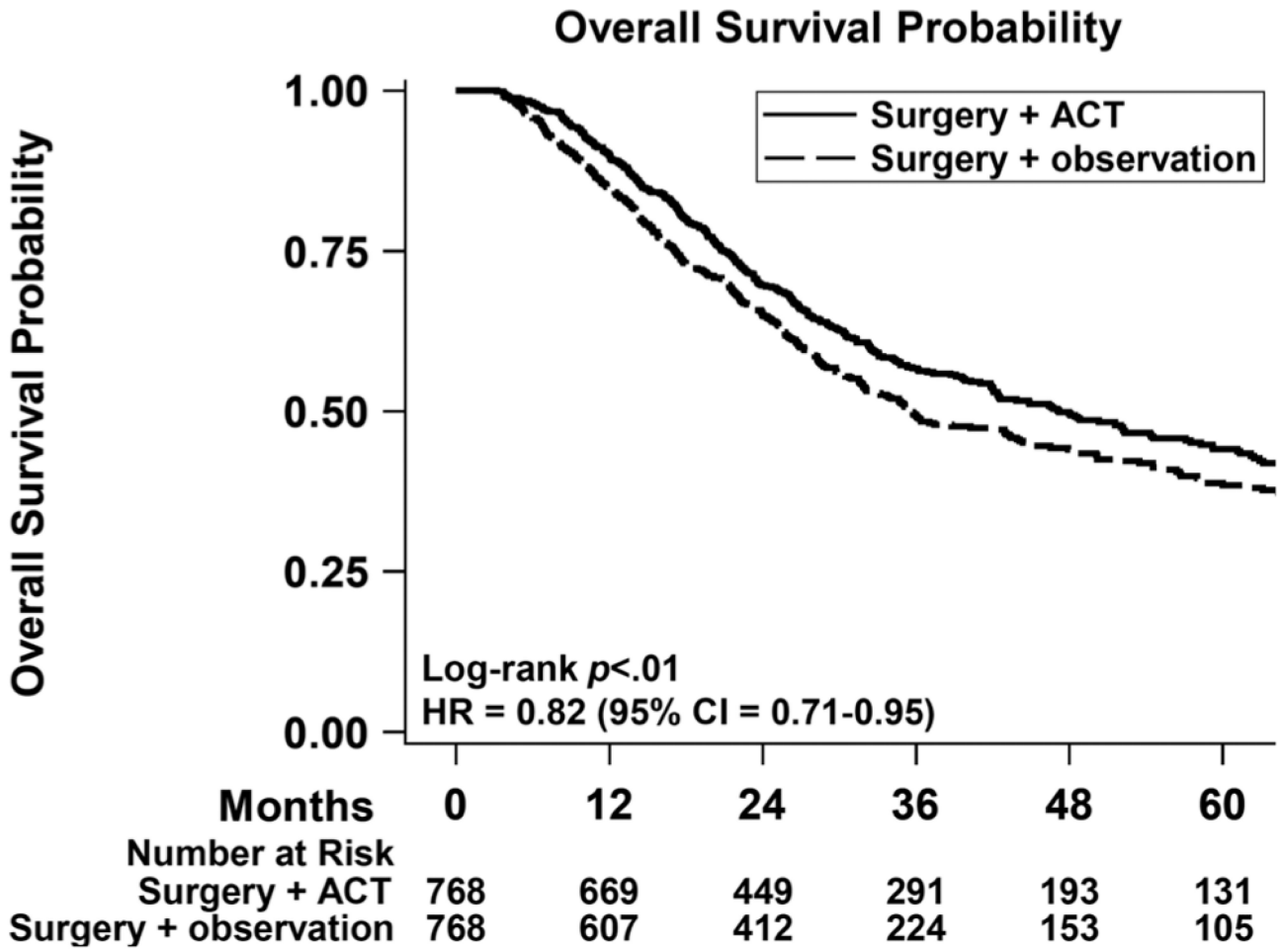


Treatment	Median survival in months (95% confidence interval)	1 year (%)	3 year (%)	5 year (%)
Surgery + observation	35.5 (30.2-40.7)	85	49	38
Surgery + ACT	47.2 (40.0-54.6)	90	57	44

Figure 1.

Overall survival of matched cohorts comparing patients who had surgery and observation versus surgery and adjuvant chemotherapy. ACT = adjuvant chemotherapy; CI = confidence interval; HR = hazard ratio.

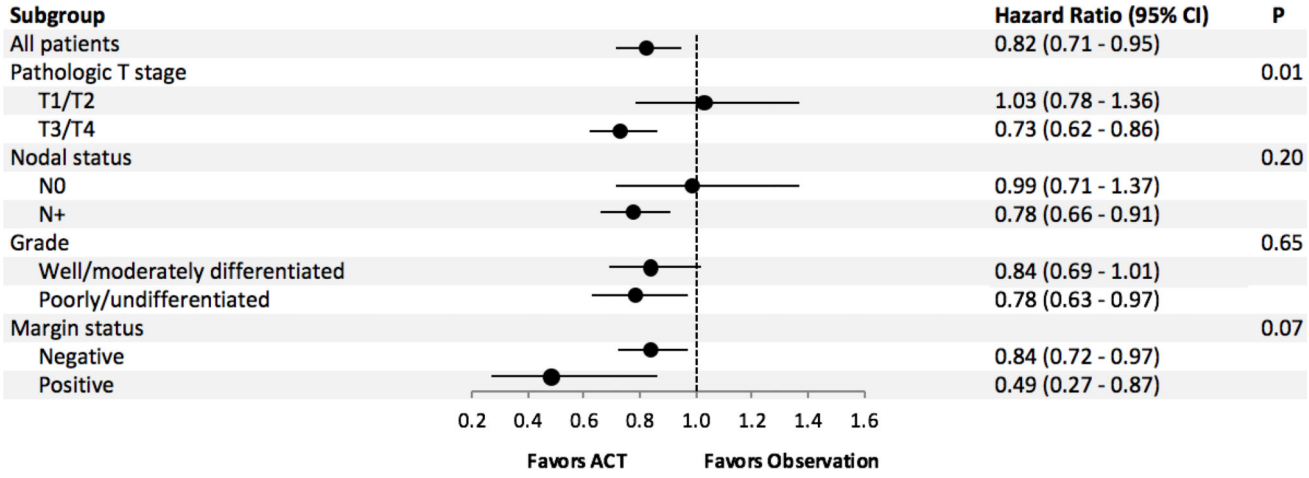
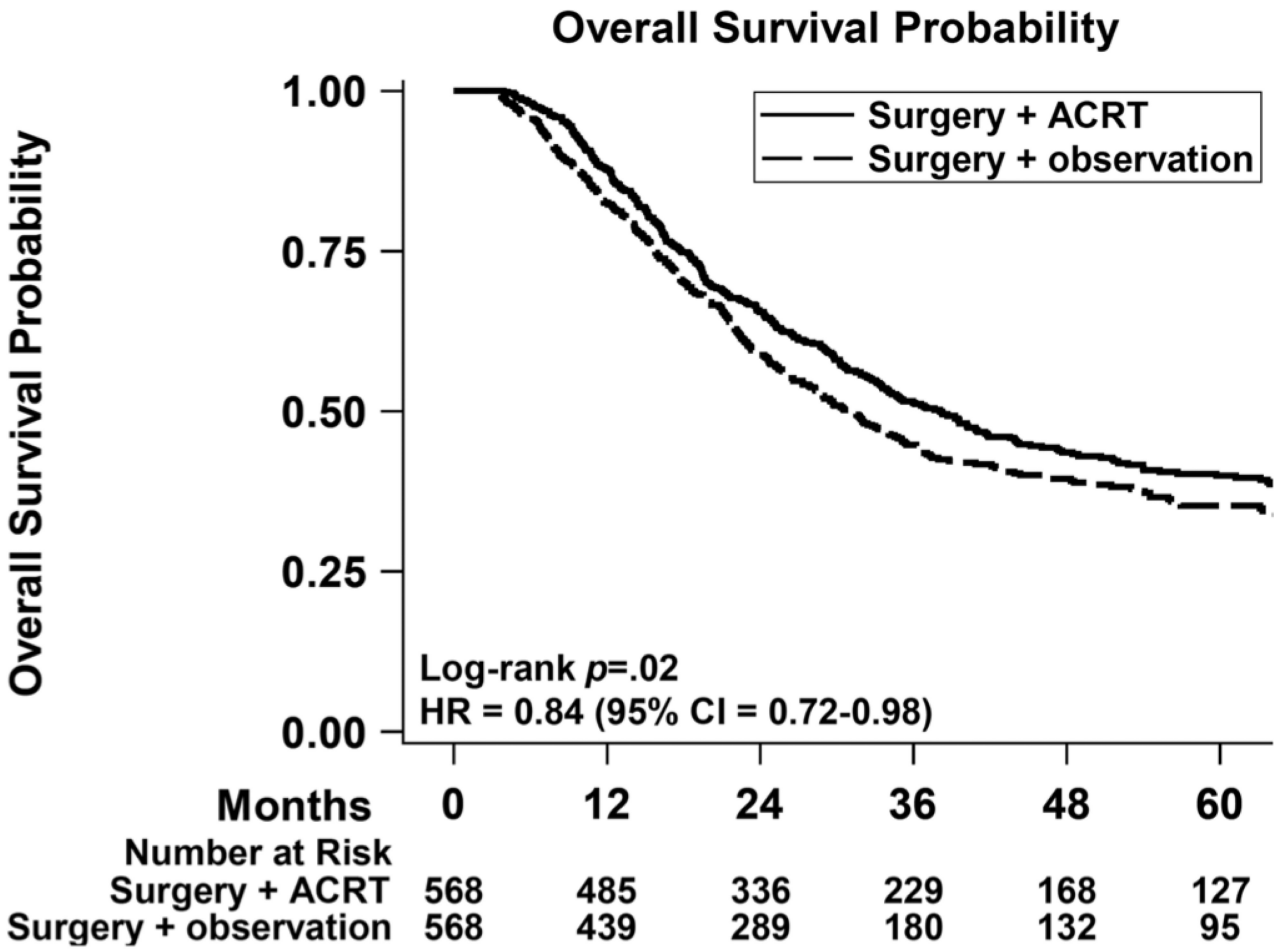


Figure 2.

Subgroup analysis of patients treated with adjuvant chemotherapy. ACT = adjuvant chemotherapy; CI = confidence interval.



Treatment	Median survival in months (95% confidence interval)	1 year (%)	3 year (%)	5 year (%)
Surgery + observation	31.0 (27.1-34.8)	83	45	35
Surgery + ACRT	38.1 (33.1-43.1)	88	51	40

Figure 3.

Overall survival of matched cohorts comparing patients who had surgery and observation versus surgery with adjuvant chemoradiotherapy. ACRT: adjuvant chemoradiotherapy; CI = confidence interval; HR = hazard ratio.

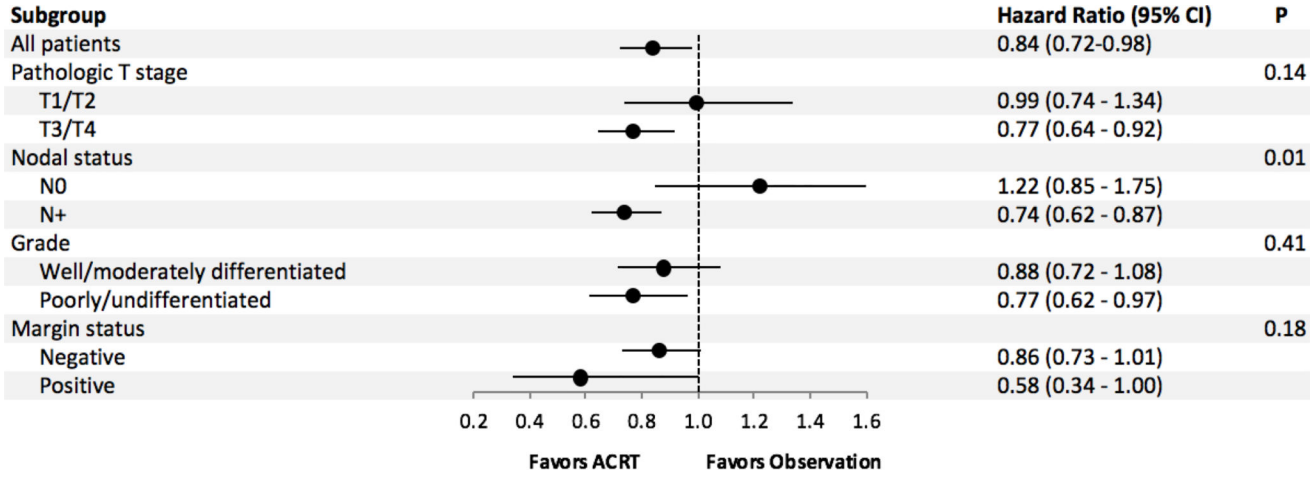


Figure 4.

Subgroup analysis of patients treated with adjuvant chemoradiotherapy. ACRT = adjuvant chemoradiotherapy; CI = confidence interval.

Table 1

Patient-, tumor-, and treatment-related factors of the entire cohort.

	Surgery + observation n (%)	Surgery + ACT n (%)	Surgery + ACRT n (%)	*P*
Number of patients	2651	870	669	
Gender				.16
Male	1480 (55.8)	504 (57.9)	355 (53.1)	
Female	1171 (44.2)	366 (42.1)	314 (46.9)	
Age (mean +/− SD years)	68.6 (10.6)	63.9 (10.3)	62.6 (9.9)	<.01
Ethnicity				.85
Non-Hispanic	2430 (91.6)	794 (91.3)	616 (92.1)	
Hispanic	221 (8.3)	76 (8.7)	53 (7.9)	
Insurance status				<.01
Not insured	101 (3.8)	41 (4.8)	24 (3.6)	
Private	857 (32.3)	403 (46.3)	325 (48.6)	
Medicaid	123 (4.6)	42 (4.8)	53 (7.9)	
Medicare	1538 (58.0)	380 (43.7)	257 (38.4)	
Other government	32 (0.8)	4 (0.5)	10 (1.5)	
Median income of residence				.02
Below median	1084 (40.9)	309 (35.5)	273 (40.8)	
Above median	1567 (59.1)	561 (64.5)	396 (59.2)	
Charlson/Deyo score				.04
0	1849 (69.7)	645 (74.1)	480 (71.8)	
≥1	802 (30.3)	225 (25.9)	189 (28.3)	
pT				<.01
1	570 (21.5)	64 (7.3)	43 (6.4)	
2	950 (35.8)	239 (27.5)	156 (23.3)	
3	665 (25.1)	314 (36.1)	250 (37.4)	
4	466 (17.6)	253 (29.1)	220 (32.9)	
pN				<.01
N0	1755 (66.2)	268 (30.8)	160 (23.9)	
N+	896 (33.8)	602 (69.2)	509 (76.1)	
Grade				<.01
Well/moderately differentiated	1910 (72.1)	523 (60.1)	388 (58.0)	
Poorly/undifferentiated	741 (27.9)	347 (39.9)	281 (42.0)	
Year				<.01
2004–2005	491 (18.5)	62 (7.1)	136 (20.3)	
2006–2007	506 (19.1)	104 (12.0)	133 (19.9)	
2008–2009	470(17.7)	162 (18.6)	129 (19.3)	
2010–2011	573 (21.6)	193 (22.2)	146 (21.8)	
2012–2013	611 (23.1)	349 (40.1)	125 (18.7)	
Facility type				<.01

	Surgery + observation n (%)	**Surgery + ACT n (%)**	**Surgery + ACRT n (%)**	***P***
Academic	1566 (59.1)	540 (62.1)	347 (51.9)	
Non-academic	1085 (40.9)	330 (37.9)	322 (48.1)	
Margin status				<.01
Negative	2584 (97.5)	829 (95.3)	614 (91.8)	
Positive	67 (2.5)	41 (4.7)	55 (8.2)	
Length of stay (mean +/− SD days)	14.8 (12.6)	10.8 (7.4)	11.0 (9.2)	<.01
30-day readmission				<.01
No	2350 (88.7)	816 (93.8)	628 (93.9)	
Yes	301 (11.4)	54 (6.2)	41 (6.1)	

ACRT = adjuvant chemoradiotherapy; ACT = adjuvant chemotherapy; SD = standard deviation.

Table 2

Patient-, tumor-, and treatment-related factors of patients who underwent surgery and observation matched to patients who underwent surgery and adjuvant chemotherapy.

	Surgery + observation n (%)	Surgery + ACT n (%)	*P*	S diff
Number of patients	768	768		
Gender			.96	<0.01
Male	440 (57.3)	439 (57.2)		
Female	328 (42.7)	329 (42.8)		
Age (mean +/− SD years)	65.0 (11.2)	64.9 (10.2)	.78	0.01
Ethnicity			.13	0.07
Non-Hispanic	712 (92.7)	696 (90.6)		
Hispanic	56 (7.3)	72 (9.4)		
Insurance status			.44	
Not insured	36 (4.7)	38 (5.0)		0.01
Private	318 (41.4)	328 (42.7)		0.02
Medicaid	41 (5.3)	28 (5.0)		0.02
Medicare	370 (48.2)	360 (46.9)		0.03
Other government	3 (0.4)	4 (0.5)		0.02
Median income of residence			.87	<0.01
Below median	282 (36.7)	285 (37.1)		
Above median	486 (63.3)	483 (62.9)		
Charlson/Deyo score			.69	0.02
0	551 (71.7)	558 (72.7)		
≥1	217 (28.3)	210 (27.3)		
pT			.53	
1	54 (7.0)	63 (8.2)	0.04	
2	234 (30.5)	224 (29.2)	0.03	
3	275 (35.8)	272 (35.4)	<0.01	
4	205 (26.7)	209 (27.2)	0.01	
pN+			.79	0.01
N0	262 (34.1)	266 (34.6)		
N+	506 (65.9)	502 (65.4)		
Grade			.96	<0.01
Well/moderately differentiated	478 (62.2)	477 (62.1)		
Poorly/undifferentiated	290 (37.8)	291 (37.9)		
Year			.92	
2004–2005	64 (8.3)	62 (8.1)		<0.01
2006–2007	105 (13.7)	98 (12.8)		0.03
2008–2009	148 (19.3)	146 (19.0)		<0.01
2010–2011	169 (22.0)	171 (22.3)		<0.01
2012–2013	282 (36.7)	291 (37.9)		0.02

	Surgery + observation n (%)	Surgery + ACT n (%)	*P*	S diff
Facility type			.72	0.09
Academic	472 (61.5)	465 (60.6)		
Non-academic	296 (38.5)	303 (39.4)		
Margin status			.90	<0.01
Negative	737 (96.0)	736 (95.8)		
Positive	31 (4.0)	32 (4.2)		
Length of stay (mean +/− SD days)	11.3 (7.7)	11.3 (7.6)	.89	<0.01
30-day readmission			.84	0.01
No	713 (92.8)	715 (93.1)		
Yes	55 (7.2)	53 (6.9)		

ACT = adjuvant chemotherapy; S diff = standardized differences; SD = standard deviation.

Table 3

Patient-, tumor-, and treatment-related factors of patients who underwent surgery and observation matched to patients who underwent surgery and adjuvant chemoradiotherapy.

	Surgery + observation n (%)	Surgery + ACRT n (%)	*P*	S diff
Number of patients	568	568		
Gender			.76	0.02
Male	301 (53.0)	306 (53.9)		
Female	267 (47.0)	262 (46.1)		
Age (mean +/− SD years)	63.9 (10.8)	63.9 (9.8)	.86	<0.01
Ethnicity			.91	<0.01
Non-Hispanic	525 (92.4)	524 (92.3)		
Hispanic	43 (7.6)	44 (7.7)		
Insurance status			.83	
Not insured	19 (3.4)	21 (3.7)		0.02
Private	245 (43.1)	252 (44.4)		0.02
Medicaid	36 (6.3)	40 (7.0)		0.03
Medicare	259 (45.6)	247 (43.5)		0.04
Other government	9 (1.6)	8 (1.4)		0.01
Median income of residence			.64	0.03
Below median	249 (43.8)	241 (42.4)		
Above median	319 (56.2)	327 (57.6)		
Charlson/Deyo score			.41	0.05
0	391 (68.8)	404 (71.1)		
≥1	177 (31.2)	164 (28.9)		
pT			.78	
1	38 (6.7)	42 (7.4)		0.03
2	146 (25.7)	151 (26.6)		0.02
3	220 (38.7)	200 (35.2)		0.07
4	164 (28.9)	175 (30.8)		0.04
pN			.33	0.04
N0	149 (26.2)	160 (28.2)		
N+	419 (73.8)	408 (71.8)		
Grade				
Well/moderately differentiated	336 (59.2)	341 (60.0)		
Poorly/undifferentiated	232 (40.9)	227 (40.0)		
Year			.62	
2004–2005	111 (19.5)	113 (19.9)		<0.01
2006–2007	118 (20.8)	110 (19.4)		0.04
2008–2009	91 (16.0)	108 (19.0)		0.08
2010–2011	121 (21.3)	124 (21.8)		0.01
2012–2013	127 (22.4)	113 (19.9)		0.06

	Surgery + observation n (%)	Surgery + ACRT n (%)	*P*	S diff
Facility type			>.99	<0.01
Academic	303 (53.4)	303 (53.4)		
Non-academic	265 (46.6)	265 (46.6)		
Margin status			.79	0.01
Negative	533 (93.8)	535 (94.2)		
Positive	35 (6.2)	33 (5.8)		
Length of stay (mean +/− SD days)	12.1 (8.7)	11.4 (9.7)	.08	0.09
30-day readmission			.91	<0.01
No	530 (93.3)	529 (93.1)		
Yes	38 (6.7)	39 (6.9)		

ACRT = adjuvant chemoradiotherapy; S diff = standardized differences; SD = standard deviation.