Title

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Improved survival with adjuvant chemotherapy in locally advanced rectal cancer patients treated with preoperative chemoradiation regardless of pathologic response☆

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A B S T R A C T

Objective: The aim of this study is to examine the effect of postoperative chemotherapy on survival in patients with stage II or III rectal adenocarcinoma who undergo neoadjuvant chemoradiation (CRT) and surgical resection.

Methods: A retrospective review of the National Cancer Database (NCDB) from 2006 to 2013 was performed. Cases were analyzed based on pathologic complete response (pCR) status and use of adjuvant therapy. The Kaplan-Meier method was used to estimate overall survival probabilities.
Results: 23,045 cases were identified, of which 5832 (25.31%) achieved pCR. In the pCR group, 1513 (25.9%) received adjuvant chemotherapy, and in the non-pCR group, 5966 (34.7%) received adjuvant therapy. In the pCR group, five-year survival probability was 87% (95% CI 84%–89%) with adjuvant therapy and 81% (95% CI 79%– 82%) without adjuvant therapy. In the non-pCR group, five-year survival probability was 78% (95% CI 76%–79%) with adjuvant therapy and 70% (95% CI 69%–71%) without adjuvant therapy. In the non-pCR and nodenegative subgroup (ypN-), five-year survival probability was 86% (95% CI 84%–88%) with adjuvant therapy and 76% (95% CI 74%–77%) without adjuvant therapy. In the non-pCR and node-positive subgroup (ypNþ), five-year survival probability was 67% (95% CI 65%–70%) with adjuvant therapy and 60% (95% CI 58%–63%) without adjuvant therapy.

Conclusions: Adjuvant chemotherapy in stage II or III rectal adenocarcinoma is associated with increased five-year survival probability regardless of pCR status. We observed similar survival outcomes among non-pCR ypNtreated with adjuvant chemotherapy compared with patients achieving pCR treated with adjuvant chemotherapy.

1. Introduction

Rectal cancer remains a prevalent disease within the United States, with an estimated 39,910 new diagnoses in 2017 [1]. Largely based on the work from the Swedish Rectal Cancer Trial [2], the Dutch Colorectal Cancer group [3] and the German Rectal Cancer Study Group [4], standard treatment for rectal cancer currently includes preoperative chemoradiation followed by surgical resection [5]. Because of the use of neoadjuvant chemoradiation, a significant portion of patients

will have down-staging noted on the pathologic evaluation, and many will have a pathologic complete response (pCR) [6,7]. pCR is defined as the complete absence of identifiable tumor on the pathologic specimen, and has been associated with improved overall survival. The current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend adjuvant chemotherapy in all Stage 2 and 3 patients [5]. These guidelines, however, do not specifically address the need for adjuvant chemotherapy in the setting of pCR. Studies examining the effect of adjuvant chemotherapy on overall survival in patients with pCR have yielded mixed results [8–10]. Therefore, the need for adjuvant chemotherapy among patients with pCR is not well known [11]. The purpose of this study was to examine the effect of adjuvant chemotherapy in patients with rectal adenocarcinoma who underwent neoadjuvant chemoradiation followed by surgical resection, using a large national database. Specifically, this study sought to compare the effect of adjuvant chemotherapy on overall survival between patients who achieve pCR and those who do not.

2. Methods

Database: The National Cancer Database (NCDB) is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. Established in 1989, the NCDB is a nationwide, facility-based, comprehensive clinical oncology data set which pulls hospital registry data that are collected in more than 1500 Commission on Cancer (CoC) accredited facilities. The NCDB currently captures 70% of all newly diagnosed malignancies in the United States annually [12]. Approval for the use of the NCDB was obtained from the Commission on Cancer of the American College of Surgeons and from the Institutional Review Board of the University of California, Irvine.

Participant selection and outcomes variables: A retrospective review of the NCDB was performed to identify patients with clinical stage 2 or 3 rectal adenocarcinoma from 2006 to 2013 who underwent pre-operative chemotherapy and radiation followed by complete surgical resection. Patients were identified using an International Classification of Disease for Oncology, Third Edition (ICD-O-3) topography code of C20.9 and an ICD-O-3 histology code of 814. The type of resection was identified using Facility Oncology Registry Data Standards (FORDS) codes 30–90. Patients were then categorized by whether they received adjuvant chemotherapy and whether they achieved pathologic complete response. Pathologic complete response (pCR) was defined as a pathologic T stage of 0 or X and a pathologic N stage or 0 or X. Overall survival was then calculated based on pathologic response and use of adjuvant chemotherapy. Patients with more than one primary malignancy, those who received post-operative radiation, those with stage 1 or stage 4 disease, or those lacking follow-up information were excluded from analysis.

Statistical Analysis: All data acquisition and statistical analyses were conducted using the Statistical Analysis System (SAS Institute Inc. SAS/ STAT Software, Version 9.4. Cary, NC, 2015) and the R Statistical Environment (R Foundation for Statistical Computing. Vienna, Austria, 2014). All-cause survival time was calculated in months from date of diagnosis to date of death, or if censored, the date of last contact. Survival time was considered to be right-censored if the patient was lost-to follow-up or alive at the end of the study period. Survival probabilities were estimated based on the Kaplan-Meier estimator [13,14]. The log-rank statistic was used to test for equality of survival outcomes when comparing key sub-populations based on therapeutic group and pathologic response. A Cox proportional hazards model was used to model

the hazard ratio for survival based on therapy and pathologic response. Two-tailed P-values were calculated and reported for all primary comparisons. Statistical significance was declared if $p < 0.05$.

3. Results

A total of 23,045 patients with clinical stage 2 or 3 rectal cancer cases reported in the NCDB study period 2006 to 2013 were evaluated. A total of 5832 patients (25.3%) achieved pCR. Among those that achieved pCR, 4319 (74.1%) received neoadjuvant therapy only and 1513 (25.9%) received both neoadjuvant and adjuvant therapy. Among those that did not achieve pCR, 11,247 (65.3%) received neoadjuvant therapy only and 5966 (34.7%) received both neoadjuvant and adjuvant therapy (Fig. 1). The difference in use of adjuvant chemotherapy was statistically significant with a $p < 0.0001$. Demographic data, stratified by pCR status and treatment status (use of adjuvant chemotherapy) is shown in Table 1.

Kaplan-Meier estimates of survival based on use of adjuvant therapy and pCR status are shown in Fig. 2. Patients with incomplete or insufficient follow up data were excluded from further survival analysis. The total number of patients included in the survival analysis are listed on Table 2 and Fig. 2.

The use of adjuvant chemotherapy and the achievement of pCR were both associated with increased overall survival ($p < 0.0001$).

Table 2 shows five-year survival (Probability) and 75th Percentile (Years) based on these Kaplan-Meier estimates. Among all patients, five-year survival probability was 0.80 (95% CI 0.79–0.81) with adjuvant therapy compared to 0.73 (95% CI 0.73–0.74) in patients who did not receive adjuvant therapy. Achieving pCR was associated with five-year survival probability of 0.82 (95% CI 0.81–0.83) compared to 0.73 (0.72–0.74) without pCR.

In the pCR group, five-year survival probability was 0.87 (95% CI 0.84–0.89) with adjuvant therapy and 0.81 (95% CI 0.79–0.82) without adjuvant therapy. In the non-pCR group, five-year survival probability was 0.78 (95% CI 0.76–0.79) with adjuvant therapy and 0.70 (95% CI 0.69–0.71) without adjuvant therapy.

In the non-pCR and node-negative subgroup (ypN-), five-year survival probability was 0.86 (95% CI 0.84–0.88) with adjuvant therapy and 0.76 (95% CI 0.74–0.77) without adjuvant therapy. In the non-pCR and node-positive subgroup (ypNþ), five-year survival probability was 0.67 (95% CI 0.65–0.70) with adjuvant therapy and 0.60 (95% CI 0.58–0.63) without adjuvant therapy.

Table 3 shows mortality hazard ratios (HR) based on pCR and adjuvant chemotherapy. Among all patients, those not treated with adjuvant chemotherapy had a HR of 1.35 (95% CI 1.23, 1.49), compared to those treated with adjuvant chemotherapy. Among all patients, those that achieved pCR had a HR of 0.61 (95% CI 0.55, 0.67), compared to those who did not achieve pCR. Among those that achieved pCR, those not treated with adjuvant chemotherapy had a HR of 1.36 (95% CI 1.14, 1.62), compared to those treated with adjuvant chemotherapy. Among those that did not achieve pCR, those not treated with adjuvant chemotherapy had a HR of 1.34 (95% CI 1.24, 1.46), compared to those treated with adjuvant chemotherapy.

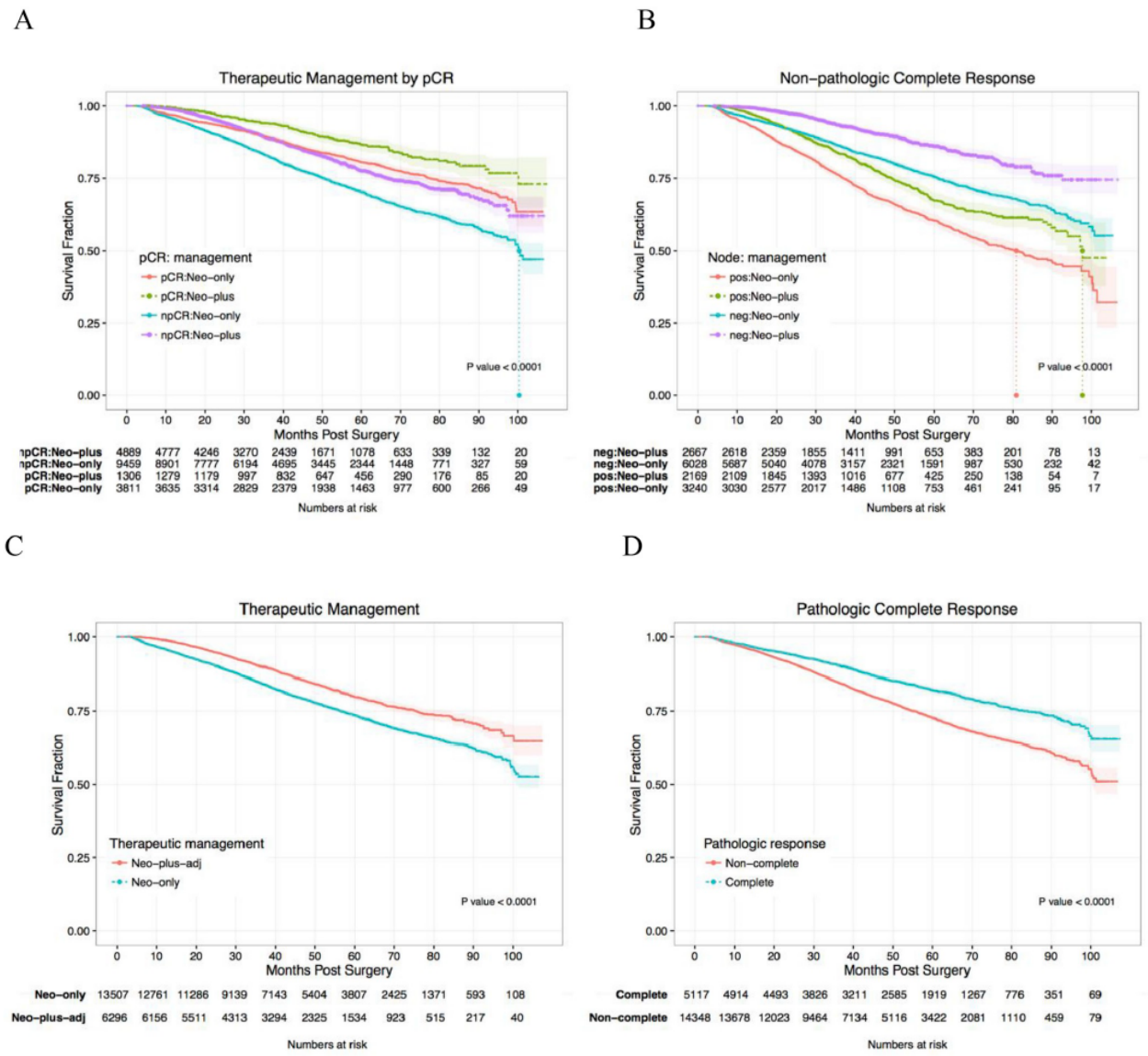

Fig. 2. Kaplan-Meier estimates of survival based on use of adjuvant therapy and pCR status.

4. Discussion

Neoadjuvant chemoradiation followed by total mesorectal excision and post-operative chemotherapy has become the standard management of locally advanced rectal cancer. The use of pre-operative chemo-radiation has led to a complete pathological response (pCR) in 20–40% of patients. Currently, there are no prospective studies that have examined the effect of adjuvant chemotherapy in patients with locally advanced rectal cancer who achieve pCR. Although the NCCN guidelines do not provide explicit recommendations for the use of adjuvant chemotherapy in patient who achieve pCR, the guidelines state that adjuvant chemotherapy be “strongly considered” in this population [5]. To our knowledge, the current study represents the largest and most current population-based analysis evaluating the effects of adjuvant chemotherapy in local-advanced rectal cancer. This study highlights a few important points: 1) the use of adjuvant

chemotherapy after neoadjuvant CRT national is overall quite low, 2) achieving pCR is associated with a decreased use of adjuvant chemotherapy, 3) the use of adjuvant chemotherapy is associated with improved overall 5-year survival both in patients that achieve pCR and those that do not, and 4) similar overall survival outcomes were observed between pCR patients who received adjuvant chemotherapy and non-pCR node-negative (non-pCR ypN-) patients who received adjuvant chemotherapy.

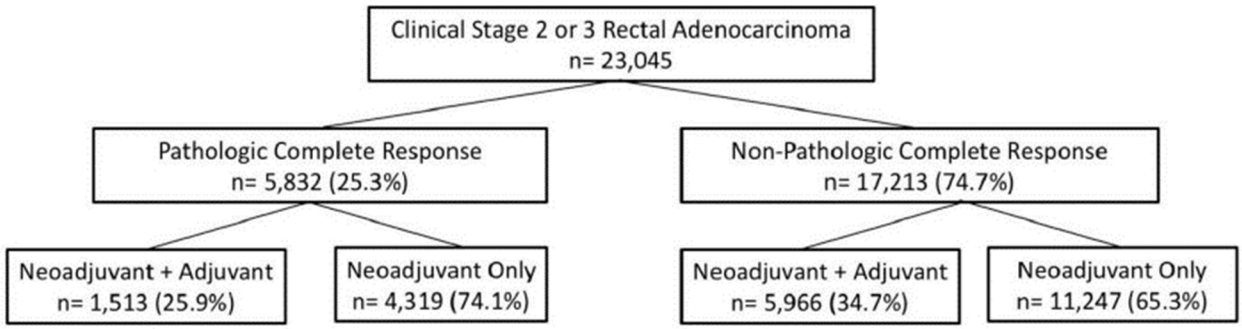

Fig. 1. Analysis of study patients by pCR status and use of adjuvant therapy

Table 1: Demographic data by pCR status and treatment status.

	Non-pCR		pCR	
	Neo + Adj (n = 5966)	Neo-only (n = 11,247)	Neo- + Adj (n = 1513)	Neo-only (n = 4319)
Age (years)	56.30 (11.23)	60.18 (12.32)	56.68 (11.06)	60.72 (12.30)
Male Sex	3710 (62%)	7084 (63%)	909 (60%)	2687 (62%)
Race				
White	5177 (87%)	9562 (85%)	1325 (88%)	3753 (87%)
Black	433 (7.3%)	995 (8.8%)	83 (5.5%)	330 (7.6%)
Other	356 (6%)	690 (6.1%)	105 (6.9%)	236 (5.5%)
Charlson/ Deyo	0.20 (0.47)	0.25 (0.52)	0.19 (0.45)	0.22 (0.50)

Neo + Adj = neoadjuvant chemoradiation and adjuvant chemotherapy.
Neo-only = neoadjuvant chemoradiation only.

In our study, a substantial portion of patients did not receive the recommended adjuvant chemotherapy, and achieving pCR was associated with a significantly lower rate of adjuvant chemotherapy: 25.9% in pCR patients versus 34.7% in non-pCR patients ($p < 0.0001$). These findings have been confirmed by multiple studies. In a study using the NCCN Colorectal Cancer Database, Khrizman et al. found that among patients with locally advanced rectal cancer treated at a specialized academic comprehensive cancer centers, 17% did not receive adjuvant chemotherapy. Increased age, decreased functional status, Medicaid insurance, presence of an ostomy, wound infection, and pCR were associated with not receiving adjuvant chemotherapy [15]. In a similar study using the SEER/Medicare database, Haynes et al. found that only 61.5% of patients with locally advanced rectal cancer received adjuvant chemotherapy, and pathologic

stage was the strongest predictor of adjuvant chemotherapy use [16]. However, that study did not identify patients with pCR. An older study of Veteran Affairs patients, performed before neoadjuvant chemoradiation was standard treatment, also demonstrated low rates of adjuvant chemotherapy use: 42.5% [17]. Our study demonstrates a decreased use of adjuvant therapy than these previous reports, which may reflect the broader population included by the NCDB. Because the NCDB captures approximately 70% of all cancer cases in the US, our findings may be a more accurate reflection of the national practice rather than the practice at specialized cancer centers. Although NCCN guidelines recommend the use of adjuvant chemotherapy in the setting of locally advanced rectal cancer, the data supporting this practice are limited and therefore somewhat controversial [5,18]. As previously noted, no randomized trial has focused on the use of adjuvant chemotherapy in patients with rectal cancer who achieve pCR. However, several randomized trials (EORTC 22921, CHRONICLE, PROCTOR-SCRIPT, I-CNR-RT, QUASAR) examining the use of adjuvant chemotherapy after neoadjuvant chemoradiation and surgical resection have failed to show an overall survival advantage with adjuvant chemotherapy [9,19–22]. The findings of our study are in contrast to these of previous reports: adjuvant chemotherapy is associated with improved overall survival among all patients with locally advanced rectal cancer including those with pCR, those with non-pCR ypNdisease and those with non-pCR ypN disease. There are a few possible explanations for these findings. The results of those five trials trended toward improved overall survival with the use of adjuvant therapy. However, all had relatively small sample sizes and therefore may have been unable to detect a 5% improvement in 5-year survival [23]. Furthermore, three of those trials (EORTC 22921, I-CTR-RT, QUASAR) began accrual in the early 1990s, and surgical technique has changed considerably since that time, specifically the broad use of total meso-rectal excision (TME). As an example, in the EORTC 22921 trial [24], a TME was performed in only 36.8% of patients. TME is currently considered standard and routine, which has dramatically improved local recurrence and survival rates [5,25].

Achieving pCR confers a survival advantage and can be of prognostic value in predicting overall survival [26,27]. This same finding was demonstrated in our study. Our data further showed that, even among patients who achieve pCR, adjuvant chemotherapy is associated with an additional survival benefit. Previous studies have demonstrated that patients who respond to neoadjuvant chemoradiation also have improved responses to adjuvant chemotherapy [24,28]. In a study by Janjan et al. examining survival among patients with locally advanced rectal cancer, the authors found that survival rates were higher among patients who responded to neoadjuvant treatment and received subsequent adjuvant chemotherapy, compared to those that received both neoadjuvant and adjuvant treatment but did not respond to the neo-adjuvant treatment. This finding led the authors to conclude that patients who respond to neoadjuvant therapy are most likely to respond to the same adjuvant therapy [28]. We can then extrapolate that the pCR patients in our study are the patients with favorable tumor biology who responded to neoadjuvant treatment, and it therefore make sense that the pCR patients would further benefit from adjuvant treatment. What was most revealing about our results is our finding that when treated with adjuvant chemotherapy, pCR patients and non-pCR ypNpatients have similar overall survival outcomes, with an approximate 86–87% 5-year survival probability. Cancer may exist not only at the primary tumor site but also as systemic micrometastatic disease. Our finding that adjuvant chemotherapy was associated with improved survival in all patients subsets may be explained by the fact that systemic chemo-therapy has the potential to treat micrometastatic disease that is not treat by local radiation or surgical resection [29]. Based on our results, the authors of this study

advocate for the use of adjuvant chemotherapy in locally advanced rectal cancer as it is associated with improved overall survival.

Two studies were recently published by Doss et al. and Polanco et al. using the NCDB to examine the effect of adjuvant chemotherapy in patients with rectal adenocarcinoma who achieve pCR [30,31]. Both studies demonstrated improved overall survival with the use of adjuvant chemotherapy in patients who achieve pCR. However, both studies defined pCR as pT0N0, excluding TXNX, resulting in a pCR rate of approximately 10%, much lower than previously published pCR rates. In pathology reports, the designation "X" means that the primary tumor cannot be assessed, meaning that the primary tumor is not present in the specimen, implying a complete response [32]. Therefore, the authors feel that the current study provides a more complete analysis of the effect of adjuvant chemotherapy among patients with pCR.

There are a few limitations to this study due to its retrospective the inherent biases within the database. As with all database studies, coding errors may exist and can affect the accuracy of the data. There are few demographic and comorbidity data collected within the NCDB database, which limits our ability to perform a risk-adjusted analysis. The NCDB does not capture disease recurrence which limits our ability to evaluate the effect of adjuvant therapy on disease free survival. Additionally, we noted that a significant portion of patients did not receive adjuvant chemotherapy, but it is not possible within this database to know why patients did or did not receive adjuvant therapy. Patient selection bias is unavoidable, and therefore the possibility that patients with complications that may increase recurrence risk such as anastomotic leak are less likely to receive adjuvant therapy is real, but conversely patients with adverse histologic features are more likely to receive adjuvant therapy and therefore would bias against our findings. Margin status was not assessed in this study, which may limit interpretation of results. However, this data is unlikely to change the results particularly in the patients with pCR who by definition should not have positive margins. The NCDB also does not provide details regarding preoperative staging methods (MRI or ultrasound) and adherence or completion of neoadjuvant or adjuvant treatment. Therefore, the data herein describes whether patients received any neoadjuvant or adjuvant treatment, rather than complete courses. Nevertheless, our study provides a comprehensive analysis of overall survival in patients with locally advanced rectal cancer.

5. Conclusions

The use of adjuvant chemotherapy in stage II or III rectal adenocarcinoma is associated with increased five-year survival probability regardless of pCR or nodal status. We observed similar survival outcomes among non-pCR ypNtreated with adjuvant chemotherapy compared with patients achieving pCR treated with adjuvant chemotherapy. Regardless of postoperative chemotherapy use, ypN disease was associated with poorer survival in rectal cancer. Acknowledging the limitations of the NCDB, our results reveal an improved survival with adjuvant chemotherapy among all locally advanced rectal cancer patients, reinforcing the importance of receiving adjuvant therapy in this setting.

Table 2: Kaplan-Meier estimates of five-year survival (Probability) and 75th percentile (Years).

	Probability (95% CI)	Years (95% CI)
Therapy		
Neoadjuvant only (n = 13,507)	0.73 (0.73, 0.74)	4.70 (4.54, 4.88)
Neoadjuvant + adjuvant (n = 6296)	0.80 (0.79, 0.81)	6.29 (5.85, 7.02)
Pathologic Response		
pCR (n = 5117)	0.82 (0.81, 0.83)	6.93 (6.44, 7.57)
non-pCR (n = 14,348)	0.73 (0.72, 0.74)	4.60 (4.44, 4.77)
pCR		
Neoadjuvant only (n = 3811)	0.81 (0.79, 0.82)	6.44 (6.03, 7.18)
Neoadjuvant + adjuvant (n = 1306)	0.87 (0.84, 0.89)	8.35 (7.64, ∞)
Non-pCR		
Neoadjuvant only (n = 9459)	0.70 (0.69, 0.71)	4.19 (4.06, 4.36)
Neoadjuvant + adjuvant (n = 4889)	0.78 (0.76, 0.79)	5.55 (5.24, 6.25)
Non-pCR – node negative		
Neoadjuvant only (n = 6028)	0.76 (0.74, 0.77)	5.08 (4.86, 5.37)
Neoadjuvant + adjuvant (n = 2667)	0.86 (0.84, 0.88)	7.72 (7.06, ∞)
Non-pCR – node positive		
Neoadjuvant only (n = 3240)	0.60 (0.58, 0.63)	3.08 (2.93, 3.26)
Neoadjuvant + adjuvant (n = 2169)	0.67 (0.65, 0.70)	4.09 (3.86, 4.43)

Table 3: Mortality hazard ratios.

	HR (95% CI)	P value
Therapy		
Neoadjuvant only	1.35 (1.23, 1.49)	<0.0001
Neoadjuvant + adjuvant (ref)		
M		
pCR	0.61 (0.55, 0.67)	<0.0001
non-pCR (ref)		
pCR		
Neoadjuvant only	1.36 (1.14, 1.62)	<0.0001
Neoadjuvant + adjuvant (ref)		
Non-pCR		
Neoadjuvant only	1.34 (1.24, 1.46)	<0.0001
Neoadjuvant + adjuvant (ref)		

Declaration of competing interest
There are no financial disclosures and no conflict of interest. No funding was received for this work.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.10.021.

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