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# Impact of residual nodal involvement after complete tumor response in patients undergoing neoadjuvant (chemo)radiotherapy for rectal cancer

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ABSTRACT

*Background:* The management of patients with a complete clinical response after neoadjuvant therapy for rectal adenocarcinoma is controversial. Those who advocate for resection point out the inaccuracy of N-staging with current imaging modalities. The objective of this study is to determine the impact of residual nodal involvement after complete tumor regression after neoadjuvant (chemo)radiotherapy.

*Methods:* The 2004 to 2014 National Cancer Database was queried for patients undergoing proctectomy for nonmetastatic rectal adenocarcinoma who had received neoadjuvant (chemo)radiotherapy and with ypT0 on final pathology. Patients were grouped based on pathologic nodal stage: ypT0N- and ypT0N+. The main outcome was 5-year overall survival.

*Results:* There were 5,156 patients with ypT0N- and 527 with ypT0N+. Mean lymph node harvest was similar (ypT0N- 12.2 nodes [standard deviation 9.1] vs ypT0N+ 11.6 nodes [standard deviation 10.3]; $P = .086$). Patients with ypT0N+ were more likely to have had clinically involved nodes ($P < .001$) and earlier clinical T-stage ($P = .002$). Overall survival at 5 years was less for patients with ypT0N+ (80% vs 86%, log-rank $P = .014$). ypT0N+ was independently associated with worse overall survival (hazard ratio 1.74, 95% confidence interval 1.33–2.28).

*Conclusion:* Residual nodal involvement despite complete tumor regression was associated with worse 5-year overall survival compared to complete pathologic response. Additional therapy should be considered in the presence of complete clinical tumor regression after neoadjuvant (chemo)radiotherapy.


## Introduction

The standard of care for locally advanced rectal cancer is neoadjuvant chemoradiation followed by total mesorectal excision (TME).[1] TME, however, is associated with a substantial postoperative morbidity and mortality, and long-term complications including defecatory, sexual, and urinary dysfunctions, which can persist, if present.[2] Organ preservation in carefully selected cases, that is, watchful waiting for patients with a clinical complete response and local excision for patients with small residual tumors, may offer more favorable functional outcomes, but the oncologic adequacy of these emerging management strategies remains controversial.[3]

One of the main disadvantages of organ preservation compared with TME is the lack of definitive nodal staging. Residual positive mesorectal lymph nodes can lead to local recurrence and distant metastases with worse oncologic outcomes.[4] Also, patients who need systemic chemotherapy based on nodal status potentially can be missed and undertreated.

Therefore, those who advocate for radical surgery in the context of an apparent clinical complete response justify this approach based on the inaccuracy of nodal restaging with current locoregional imaging modalities and the potential negative effect of residual nodal disease.[5] The incidence of residual nodal involvement in the context of a complete luminal tumor response, however, is

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not well characterized. Furthermore, the prognosis of patients with ypT0N+ disease is poorly described.

Therefore, the objective of this study was to determine the impact of residual nodal involvement after complete tumor regression after neoadjuvant (chemo)radiotherapy in patients with rectal adenocarcinoma.

## Methods

### *Data source and study population*

The National Cancer Database (NCDB) is a cancer registry sponsored by the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. Each year, greater than 1 million new cancer cases are entered into this database, which corresponds to approximately 70% of all new cancer cases from 1,500 hospitals.[6] All hospitals accredited by the CoC are required to enter all new cancer cases into the NCDB. Yearly data-quality reviews are performed to ensure its validity and quality.[7] For this study, we queried the rectal cancer participant user file for the period from 2004 to 2014. Patients with a documented pretreatment clinical stage of at least cT1N0 who subsequently received (chemo)radiotherapy followed by proctectomy and with ypT0 on final pathology were included. Patients were further excluded if they had metastatic disease at diagnosis, in situ disease, or cTX at initial diagnosis; if no resection was performed; or for histology other than rectal adenocarcinoma. Variable definitions can be found at http://ncdbpuf.facs.org/node/259. Patient characteristics included age, sex, race and ethnicity, comorbidities, insurance status, median household income, population density and education distribution of the patient's ZIP code, and distance traveled to the reporting institution. Patient comorbidities were defined according to the Deyo classification of the Charlson Comorbidity Index.[8] The NCDB does not provide more detailed information on specific comorbidities, body mass index, or postoperative morbidity. Hospital characteristics included hospital type and facility location. Facility is defined as per the CoC accreditation criteria, which is based on total number of new cancer diagnoses, diagnostic and treatment services, research participation, and resident training. Hospital location is based on US census information. Annual hospital volume was divided based on the number of rectal cancer cases per year, and then hospitals were divided into low-volume (fewer than 10 resections), mid-volume (10–30 resections), and high-volume (>30 resections) status. Pretreatment tumor-related variables included clinical T and N stages and preoperative serum carcinoembryonic antigen level. Carcinoembryonic antigen level was only included in the NCDB after 2010. Treatment-related variables included the type of neoadjuvant therapy regimen, interval from the end of radiotherapy to operation, primary operative procedure, lymph node yield (total number of harvested and positive nodes), adjuvant systemic therapy, and vital status at last contact. Patients were divided into 2 groups based on the presence of nodal metastases on final pathology: ypT0N- and ypT0N+. The NCDB does not provide any information on local recurrence or metastatic disease and their treatment(s).

### *Outcomes and statistical analysis*

The main outcome measure was 5-year overall survival. Oncologic outcomes were defined using overall survival (OS) because the NCDB does not record local recurrence or metastatic disease, and therefore disease-free survival could not be reported.[9] Data are represented as *n* (%) for categorical variables and mean ± standard deviation for continuous variables. Univariate analyses were performed using a Student *t* test for continuous variables and the $\chi^2$ test for categorical variables. Kaplan-Meier curves were used to describe OS, and log-rank tests were used to compare the cumulative survival distributions. Treating institutions were categorized according to annual number of rectal resections: low-volume (less than 10 rectal resections/y), mid-volume (10–30 rectal resections/y), and high-volume (greater than 30 rectal resections/y) centers. Multilevel regression analyses were performed using Cox proportional hazard models to determine the independent effect of residual nodal involvement on overall 5-year survival using institution as the higher-order variable. Interactions between nodal involvement and initial clinical stage at diagnosis and adjuvant treatment were also tested. We performed different models expressing residual nodal involvement as ypT0N- versus ypT0N+ and as ypT0N0 versus ypT0N1 versus ypT0N2. Further sensitivity analyses were performed by excluding clinical stage I disease because the delivery of neoadjuvant therapy in these patients is not standard of care. All analyses were performed using STATA 15.1 (StataCorp, College Station, TX).

## Results

A total of 5,683 patients were eligible and included in this study, of whom 5,156 (90.7%) were ypT0N- and 527 (9.3%) were ypT0N+ in final pathology. Among those with ypT0N+, 409 patients (77.6%) were ypN1 and 118 (22.4%) were ypN2. Patient and facility characteristics are shown in Table I, and tumor and treatment characteristics are shown in Table II. Patients with ypT0N- were somewhat older than patients with ypT0N+ (60.2 ± 12.1 years vs 58.8 ± 12.4 years; $P = .008$); however, this difference was not clinically significant. There were no differences in any other baseline characteristics, including sex, comorbidities, ethnicity, insurance status, and treatment at a high-volume center (>30 rectal resections/y) (Table I).

There were differences in preoperative clinical T- and N-stages. There were 370 (6.5%) patients with clinical stage I disease in this study cohort. Patients with ypT0N+ were more likely to have clinically involved nodes (55% vs 43%, $P < .001$) and earlier clinical T-stage (cT1-2: 29% vs 22%, $P = .002$) compared with ypT0N-. The mean lymph node harvest was similar in both groups (ypT0N- 12.2 ± 9.1 vs ypT1N+ 11.6 ± 10.3 nodes; $P = .086$) as was the mean interval from end of radiotherapy to operation (ypT0N- 61.3 ± 26.7 vs ypT0N+ 62.0 ± 34.2 days; $P = .601$) and mean follow-up (ypT0N- 51.1 +/= 29.5) vs 49.7 ± 28.3 months; $P = .365$). Patients with residual nodal involvement were more likely to receive adjuvant chemotherapy (33% vs 49%, $P < .001$).

On survival analysis, final pathology of ypT0N+ was associated with a lesser overall cumulative survival at 5 years compared with ypT0N- (80% vs 86%, log-rank $P = .014$), despite a greater proportion of these patients receiving adjuvant chemotherapy (Fig 1). There were no differences in 5-year OS when stratified by clinical stage, regardless of the pathologic nodal status (Fig 2). Results of the multiple survival regression analyses are shown in Table III. After adjusting for age, comorbidities, facility characteristics, insurance status, clinical stage, grade, lymph node harvest, and adjuvant systemic therapy, ypT0N+ was independently associated with worse OS (HR 1.86, 95% CI 1.44–2.41). The alternative method demonstrated similar results. There were no significant changes in both models if patients with clinical stage I disease were excluded (data not shown).

## Discussion

An important proportion of patients may exhibit a clinical complete response after neoadjuvant treatment for locally advanced rectal cancer.[10] The management of these patients is controversial. Although luminal response can be determined

**Table I**
Patient and facility characteristics

| | ypT0N0 (n = 5156) | ypT0N+ (n = 527) | *P* value |
|---|---|---|---|
| Mean age, years (SD) | 60.3 (12.1) | 58.2 (12.0) | <.001 |
| Male | 3,082 (59.8%) | 316 (60.0%) | .931 |
| Race/ethnicity | | | .787 |
| White | 4,514 (87.6%) | 458 (86.9%) | |
| Black | 344 (6.7%) | 41 (7.8%) | |
| Hispanic | 211 (4.1%) | 20 (3.8%) | |
| Other/unknown | 86 (1.7%) | 8 (1.5%) | |
| Charlson-Deyo score | | | .231 |
| 0 | 4,096 (79.4%) | 432 (82.0%) | |
| 1 | 856 (16.6%) | 81 (15.4%) | |
| 2 | 204 (4.0%) | 13 (2.6%) | |
| Insurance | | | .068 |
| No insurance | 141 (2.7%) | 19 (3.6%) | |
| Private insurance | 2,743 (53.2%) | 306 (58.1%) | |
| Medicare/Medicaid | 2,224 (43.1%) | 197 (37.4%) | |
| Unknown/missing | 48 (1.0%) | 5 (1.0%) | |
| Median household income | | | .042 |
| <$38,000 | 769 (14.9%) | 66 (12.5%) | |
| $38,000-$47,999 | 1,147 (22.3%) | 136 (25.8%) | |
| $48,000-$62,999 | 1,437 (27.9%) | 123 (23.3%) | |
| $63,000+ | 1,760 (34.1%) | 196 (37.2%) | |
| Missing | 43 (0.8%) | 6 (1.1%) | |
| Without high-school degree | | | <.001 |
| ≥21% | 778 (15.1%) | 74 (14.0%) | |
| 13%–20.9% | 1,279 (24.8%) | 135 (25.6%) | |
| 7%-12.9% | 1,703 (33.0%) | 175 (33.2%) | |
| <7% | 1,354 (26.3%) | 137 (26.0%) | |
| Missing | 42 (0.8%) | 6 (1.1%) | |
| Distance traveled | | | .558 |
| <30 miles | 3,895 (75.5%) | 385 (73.1%) | |
| 30–60 miles | 652 (12.6%) | 71 (13.5%) | |
| 60–100 miles | 297 (5.8%) | 37 (7.0%) | |
| >100 miles | 312 (6.1%) | 34 (6.4%) | |
| Facility type | | | .177 |
| Community | 330 (6.7%) | 30 (6.1%) | |
| Comprehensive | 2,073 (42.0%) | 193 (39.2%) | |
| Academic/research | 1,944 (39.4%) | 219 (44.4%) | |
| Integrated | 589 (11.9%) | 51 (10.3%) | |
| Population density | | | .508 |
| Metro | 4,139 (80.3%) | 437 (82.9%) | |
| Urban | 804 (15.6%) | 71 (13.5%) | |
| Rural | 90 (1.8%) | 7 (1.3%) | |
| Unknown | 123 (2.4%) | 12 (2.3%) | |
| Yearly center volume | | | .330 |
| 1–10 cases | 337 (6.5%) | 32 (6.1%) | |
| 11–30 cases | 1,742 (33.8%) | 195 (37.0%) | |
| >30 cases | 3,077 (59.7%) | 300 (56.9%) | |

directly by endoscopy with or without local excision, nodal status cannot be determined reliably by clinical means. The present study demonstrates that even in the setting of a complete tumor regression (ypT0), the incidence of nodal involvement is high: 9.3%. Previous studies reported rates between 6% and 17%.[11,12] This ratio is less compared with other gastrointestinal malignancies like pancreatic cancer; however, it becomes clinically relevant when a nonoperative management strategy is to be pursued because this treatment approach would be a deviation from standard of care as of today. The need for more accurate imaging modalities is more pronounced to identify the patients who may or may not gain survival benefit from subsequent resection.

A watch-and-wait strategy is emerging as a potential management strategy for patients who demonstrate a clinical complete response after neoadjuvant (chemo)radiotherapy. The study by Habr-Gama et al on clinical complete response pioneered a novel discussion and gave rise to the concept of the organ preservation in rectal cancer.[10] The OnCoRe project showed similar OS between the watch-and-wait strategy and resection; however, the local regrowth rate was 38% in 3 years in the watch-and-wait group and 5% of regrowth was in the submucosa or mesorectum with a normal mucosa.[13] An increasing percentage of patients prefer to pursue organ preservation strategies even if the risk of recurrence may be greater than with resection owing to adverse functional outcomes associated with TME.[14] This is a rightful demand; however, a balance needs to be struck between oncologic and functional outcomes. The diagnosis of a clinical complete response is also subject to some uncertainty because the nodal status cannot be determined accurately based on current imaging modalities. Magnetic resonance imaging (MRI) and positron emission tomography have limited accuracy in nodal staging—for both initial staging and restaging after neoadjuvant treatment.[15,16] This uncertainty may lead to potential undertreatment in an important percentage of cases. There are currently 12 active clinical trials worldwide that aim to compare clinical outcomes of resective surgery versus organ preservation in rectal cancer by either the watch-and-wait approach or local excision (https://clinicaltrials.gov/ct2/results?cond=Rectal+Cancer&term=organ+preservation&cntry=&state=&city=&dist=). We expect to have a clearer understanding of the safety and feasibility of these approaches as the results from prospective trials become available.

**Table II**
Tumor and treatment characteristics

| | ypT0N0 (n = 5156) | ypT0N+ (n = 527) | *P* value |
|---|---|---|---|
| Clinical T-stage | | | <.001 |
| cT1 | 221 (4.3%) | 34 (6.4%) | |
| cT2 | 596 (11.5%) | 78 (14.8%) | |
| cT3 | 4,120 (79.9%) | 385 (73.1%) | |
| cT4 | 219 (4.3%) | 50 (5.7%) | |
| Clinical N-stage | | | <.001 |
| cN0 | 2,362 (45.8%) | 167 (31.7%) | |
| cN1 | 2317 (44.9%) | 290 (55.0%) | |
| cN2 | 223 (4.3%) | 38 (7.2%) | |
| cN+, NOS | 254 (4.9%) | 32 (6.1%) | |
| Clinical stage | | | <.001 |
| cStage I | 330 (6.4%) | 40 (7.6%) | |
| cStage II | 2,032 (39.4%) | 127 (24.1%) | |
| cStage III | 2,794 (54.2%) | 360 (68.3%) | |
| Preoperative serumCEA*, ng/dL (SD) | 6.5 (14.8) | 6.6 (15.5) | .968 |
| Neoadjuvant therapy regimen | | | .045 |
| Long-course chemoradiotherapy | 4,479 (86.9%) | 458 (86.9%) | |
| Long-course radiotherapy only | 61 (1.2%) | 3 (0.6%) | |
| Short-course radiotherapy | 19 (0.4%) | 6 (1.1%) | |
| Incomplete or other treatment regimen | 597 (11.6%) | 60 (11.4%) | |
| Mean interval from end of radiotherapy to resection, days (SD) | 61.3 (26.7) | 62.0 (34.2) | .601 |
| Operative procedure | | | .279 |
| Partial proctectomy | 3,182 (61.7%) | 338 (64.1%) | |
| Total proctectomy | 1,860 (36.1%) | 174 (33.0%) | |
| Proctectomy NOS | 114 (2.2%) | 15 (2.9%) | |
| Mean lymph node harvest, nodes (SD) | 12.2 (9.1) | 11.6 (10.3) | .086 |
| Adjuvant systemic therapy delivered | 1696 (33%) | 257 (49%) | <.001 |
| Mean follow-up, months (SD) | 51.1 (29.5) | 49.7 (28.3) | .365 |

*CEA*, carcinoembryonic antigen; *SD*, standard deviation.
* Only available from 2010 onward.

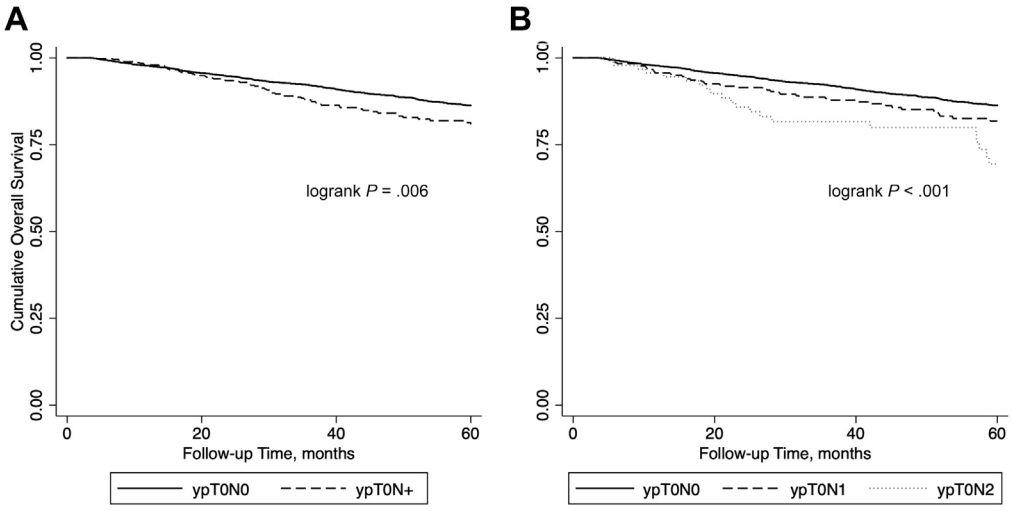


**Fig 1.** Comparison of 5-year overall survival (OS) curves between patients with complete tumor response and different N-stage on final pathology. (*A*) ypT0N0 versus ypT0N+. (*B*) ypT0N0 versus ypT0N1 versus ypT0N2.

In the present study, we demonstrated that even though the primary rectal tumor regresses completely after neoadjuvant treatment (ypT0), persistence of nodal involvement is high. The presence of nodal involvement in both clinical and pathologic staging translates into worse clinical outcomes. Patients with involved clinical lymph nodes are more likely to have persistent nodal disease. Also, multivariate survival regression analyses demonstrated that the hazard ratio increases with more advanced pathologic nodal stage. Residual nodal disease may increase the risk of not only local recurrence but also distant metastasis.[17] Although the guidelines of the National Comprehensive Cancer Network for rectal cancer treatment recommend adjuvant chemotherapy after resection for initially locally advanced tumors,[18] this rate was not greater than 50% in either group. This finding may be due to several factors, including patient age, preexisting medical comorbidities, or postoperative complications after TME. The reason for omitting adjuvant chemotherapy, however, is not recorded in the NCDB, and thus it is unclear whether the delivery of adjuvant systemic therapy would have increased OS in these patients; however, Dossa et al[19] showed that patients who initially had nodal disease and achieved a pathologic complete response after neoadjuvant treatment still benefit from adjuvant chemotherapy.

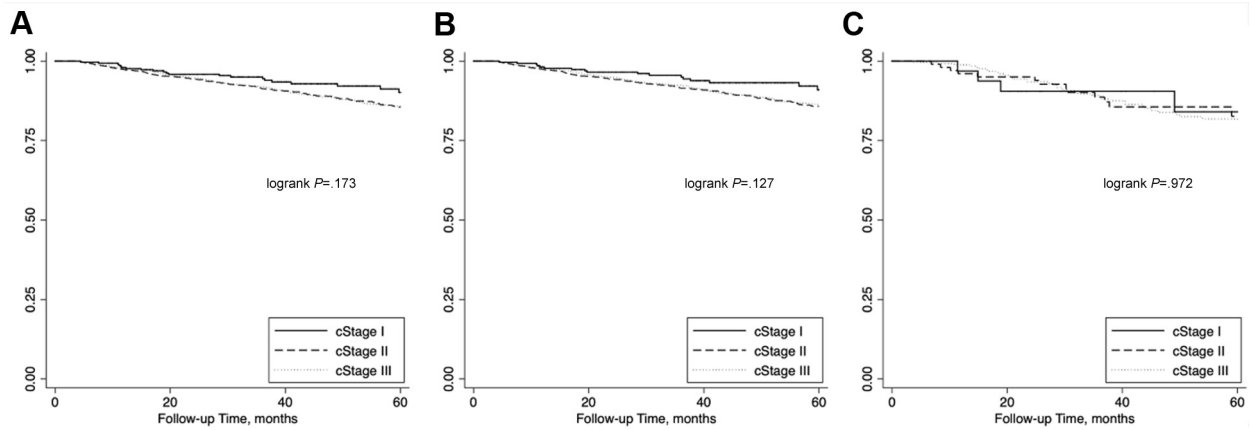


**Fig 2.** Comparison of 5-year overall survival (OS) curves by clinical stage in (*A*) the overall ypT0 cohort; (*B*) patients with ypT0N0; and (*C*) patients with ypT0N+ disease.

**Table III**
Results of multiple regression analyses

| | Model 1 | Model 2 |
|---|---|---|
| | HR (95% CI) | |
| ypT0N+ (vs ypT0N0) | 1.86 (1.44–2.41) | – |
| ypN status | | |
| ypN0 (ref.) | – | – |
| ypN1 | – | 1.75 (1.25–2.45) |
| ypN2 | – | 2.93 (1.92–4.49) |
| Age, per year increase | 1.05 (1.03–1.06) | 1.04 (1.03–1.06) |
| Male sex | 1.46 (1.22–1.77) | 1.36 (1.14–1.64) |
| Charlson/Deyo score | | |
| 0 (ref.) | – | – |
| 1 | 1.21 (0.96–1.52) | 1.40 (1.11–1.75) |
| 2 | 2.58 (1.93–3.46) | 2.44 (1.82–3.26) |
| Insurance status | | |
| No insurance (ref.) | – | – |
| Private insurance | 0.44 (0.27–0.72) | 0.49 (0.29–0.82) |
| Medicare/Medicaid | 0.51 (0.31–0.86) | 0.59 (0.34–1.00) |
| Unknown/missing | 0.41 (0.12–1.47) | 0.84 (0.28–2.48) |
| Ethnicity | | |
| White (ref.) | – | – |
| Black | 1.44 (1.03–2.02) | 1.23 (0.85–1.77) |
| Hispanic | 1.19 (0.77–1.84) | 1.01 (0.64–1.60) |
| Other/unknown | 1.12 (0.54–2.32) | 0.96 (0.44–2.13) |
| Operative procedure | | |
| Partial proctectomy (ref.) | – | – |
| Total proctectomy | 1.23 (1.02–1.47) | 1.11 (0.93–1.34) |
| Proctectomy NOS | 0.48 (1.19–1.17) | 0.63 (0.30–1.35) |
| Lymph node harvest, per node increase | 0.98 (0.97–0.99) | 0.97 (0.96–0.99) |
| Adjuvant systemic therapy | 0.72 (0.59–0.88) | 0.76 (0.61–0.94) |
| Clinical stage | | |
| cStage I (ref.) | – | – |
| cStage II | 1.43 (0.90–2.24) | 1.40 (0.92–2.21) |
| cStage III | 1.54 (0.98–2.40) | 1.44 (0.97–2.15) |

Furthermore, despite the significantly greater rate of adjuvant treatment in the patients with ypT0N+ disease, the OS at 5 years was still less than in the patients with ypT0N0 disease. This observation is consistent with several other studies emphasizing the prognostic value of nodal status after neoadjuvant treatment[20] and suggests that current protocols may not be adequate for patients with nodal disease. These patients may require a more aggressive approach. There is evidence that addition of systemic chemotherapy after chemoradiotherapy in the neoadjuvant setting is associated with a greater rate of pathologic complete response compared with chemoradiotherapy alone.[21] Another approach suggested by the GRECCAR 2 study is local excision after neoadjuvant treatment and to tailor the treatment accordingly.[22] This approach enables obtaining a pathologic T-stage, which translates into a better risk assessment. Local excision after neoadjuvant chemoradiation has similar survival outcomes compared with radical resection in T2N0 rectal cancer.[23] Organ preservation can still be pursued for these patients.

Clinical response to neoadjuvant (chemo)radiation is heterogeneous. Why nodal involvement persists despite total tumor response in some patients is not known. Scattering of tumor cells may give a false impression of tumor regression.[24] Furthermore, eradication of the primary tumor from mucosa and submucosa may not always correspond to a pathologic complete response. Residual cancer cells have been shown to remain in various layers of the bowel wall as well as in lymph

nodes.[25] Whether ypT0N+ disease signifies a different tumor biology compared with those with ypT0N0 remains unanswered and requires further research. If, however, this is the case, patients with residual nodal involvement may potentially benefit from a different chemotherapy regimen. Additionally, residual nodal involvement is independently associated with worse OS, even in the setting of definitive pathologic staging and a greater rate of adjuvant chemotherapy. This fact brings the effectiveness of a watch-and-wait approach into question. Although not resecting the rectum spares patients the potential operative morbidity and mortality, it comes at a cost of not having a definitive pathologic staging. It may be necessary to do more than wait as we watch the patient. When organ preservation is the aim, additional therapy should be considered in the presence of complete tumor regression after neoadjuvant (chemo) radiotherapy.

The results of this study should be interpreted in view of several limitations. The main limitation of the present study is extrapolating patients who had resection and with a final pathology of either ypT0N0 or ypT0N+ to patients with a clinical complete response without such a complete resection. Unfortunately, post-neoadjuvant endoscopic findings or MRI results of the patients were not available. We do not know why resection was performed instead of watch and wait—whether it was patients' choice or there was another reason for subsequent resection. Additionally, clinical information of patients who developed a clinical complete response and without subsequent resection was also not available. This situation may affect the external validity of the study, because this group may be different in terms of oncologic characteristics and operative risk compared to the population of current study. It is not known if there was a difference between clinical responses of 2 groups after neoadjuvant (chemo)radiotherapy. Although the NCDB contains data regarding the tumor regression grade on final pathology, the other criteria that are necessary to define a complete clinical luminal response are not known. This can be particularly important to identify, if any, response patterns associated with persistent nodal disease. We also did not have detailed data on the various chemoradiotherapy regimens that may have affected the clinical response, such as appropriateness, dosing, tolerance, and completion of a full treatment course. The NCDB does not include data on recurrence and their treatment(s)[9]; therefore, we could not study and report recurrence rate and disease-free survival. Local recurrence would be of special interest owing to its association with nodal disease. Finally, it is not known how many patients did not undergo resection after achieving a complete clinical response and the accuracy of preoperative clinical staging depending on the imaging modality that was used (endorectal ultrasonography versus MRI).

In conclusion, our data show that in the setting of a complete tumoral regression after neoadjuvant (chemo)radiation for rectal cancer, mesorectal lymph nodes may not have been cleared of tumor completely. Although this represents a small group of patients, 5-year OS is statistically less than patients with a pathologic response despite a greater rate of adjuvant systemic treatment. These data suggest the possible need for additional therapy, possibly with a different regimen in the presence of complete clinical tumor regression after neoadjuvant (chemo) radiotherapy.

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None.

## Conflict of interest/Disclosure

Dr. Nassif is a consultant for Mallinckrodt and for Applied Medical. Dr. Albert is consultant and stock options from Applied Medical, and a consultant for Stryker, KCI, and Conmed. Dr. Monson is a consultant for Medtronic and Twistle. Dr. Lee is the recipient of an investigator-initiated research grant from Johnson & Johnson. Drs. Erkan, Mendez, Trepanier, and Kelly have no conflict of interest or financial ties to disclose.

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# Discussion


**Dr Paula M. Termuhlen** (Duluth, MN): First, I want to thank you for being very timely in getting me your manuscript, giving me a chance to take a nice look at it.

As surgeons, we recognize that the procedures we perform on patients can have significant life-changing effects that occur in the effort to eradicate disease. As our multidisciplinary treatments for cancer increase the number of cancer survivors, we are asked to consider how to limit the impact of our treatments and improve their quality of life in the post-treatment phase. The advocacy of patients and our willingness to listen to their life experiences has inspired us to dig deeper into understanding the extent of treatment each patient may need and the impact those treatments have on their lives.

In this presentation, Dr. Erkan and his colleagues have taken a look at outcomes of patients with residual nodal involvement after complete tumor response who required neoadjuvant chemoradiation for rectal cancer at a time when patients likely ask, "Why do I need surgery if my cancer appears to be gone?" They used the strength of the NCDB to examine the outcomes of these patients who have had complete clinical responses to neoadjuvant treatment. The power of their work is in helping us to stratify which patients may benefit most from comprehensive surgery, and who may need different therapeutic interventions due to residual disease.

I have the following questions for you regarding your work:

While I realize you can't obtain information on disease-free survival, which is a limitation of the NCDB, were you able to look at subsets of patients and, in particular, those with pretreatment staging of T3N0 disease? If so, this seems to be a potential group to consider for observation after complete clinical response based on your multivariate analysis that patients with advanced N-stage disease are more likely to have residual nodal disease post-treatment.

There is at least 1 observational trial in progress in Europe, the RESARCH trial. Are you aware of any trials that are being considered here in North America and which groups would be appropriate to consider for such a trial based on your work?

In examining the NCDB database, you identify that less than 50% of patients with or without residual nodal disease after surgery went on to adjuvant treatment. This phenomenon in other gastrointestinal cancers such as pancreatic cancer has been related to the high morbidity of surgery and precludes their ability to receive additional chemotherapy. Might this be a compelling reason to identify those patients who truly benefit from surgery and those who should move directly on to other chemotherapeutic regimens or new targeted therapies to consolidate their treatment?

I want to thank you for this important work, which helps us serve the needs of our patients and ensures that we thoughtfully provide the care that they need to treat their conditions. Congratulations on a well-done study that will provide a foundation for future work on behalf of these patients.

**Dr Arman Erkan:** Thank you for your insightful contributions and questions. Regarding the first question, we actually performed a subgroup analysis using initial clinical stages, and this did not show a significant survival difference among patients with different initial clinical stages. However, this should be interpreted carefully. This does not mean that patients with different clinical stages demonstrate similar overall survival. These are the groups that developed a complete tumor response. I think this emphasizes the importance of the biology of the disease. So in a clinically significant group of 9%, even though the tumor regresses completely, there is still nodal involvement. This is about, we believe, the biology of the disease itself.

In terms of clinical trials, I was able to identify 12 clinical trials registered in the clinical trial registry. Most of these are from Europe and Asia. In North America, I believe there's 1 study that's being planned right now.

Regarding the third question, the morbidity after total mesorectal excision is significant and can reach up to 30% to 40%. Overall, the utilization of the adjuvant chemotherapy for colorectal cancer patients for whom adjuvant chemotherapy is recommended is about 60% to 70%. This is not only due to postoperative morbidity. Age, medical comorbidities, and other factors may also play a role. However, 10% is totally due to the nature of TME.

**Dr Sarkis Meterissian** (Montreal, QC): Thank you for your presentation. I wanted to ask you—and I could have misread that table. The table that you had with the number of lymph nodes for the N0 was 12.2 with a standard deviation of 9? That could mean that in some patients you could have had only 3 harvested nodes!

So my question is, when you had less than the appropriate number of lymph nodes, did that alter the decision making? Did that influence chemotherapy decisions in the patients with N0 disease? Because based on what I know, the lymph node harvest for rectal cancer should be 14, but have we ever looked at what is the appropriate lymph node harvest post-neoadjuvant chemoradiation? Because traditionally the number of lymph nodes we get after radiation was always lower.

Thank you.

**Dr Arman Erkan:** Thank you for your question. We didn't perform a subgroup analysis of patients with low lymph node yield. However, this would be an important point to look in future studies. Additionally, after neoadjuvant chemoradiotherapy, the lymph node yield may be lower, and there's debate going on about this subject, whether the treatment itself makes the lymph nodes completely disappear. So the lower lymph node yield may not actually mean suboptimal surgical quality. I think this will also need further investigation.