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Orignal Article

Adjuvant radiation therapy for T4 non-rectal colon adenocarcinoma provides a cause-specific survival advantage: A SEER database analysis

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ABSTRACT

Purpose: While there is no level 1 evidence supporting the use of adjuvant radiotherapy (RT) for non-rectal colon cancer in the modern chemotherapy era, there are studies that suggest a local control benefit. This treatment modality is not part of standard treatment recommendations, and we hypothesized that adjuvant RT provides a benefit in locally advanced disease. Due to the limited number who receive post-operative RT, a national database was searched to provide sufficient power.

Materials and methods: A retrospective analysis using the Surveillance, Epidemiology, and End Results (SEER) database was performed. Inclusion criteria were: non-rectal colon cancer, AJCC 6th or 7th edition T4 and M0, oncologic resection, and 1st cancer site. Patients were excluded for RT prior to or during surgery, or if the sequence of RT was unknown. Using a Cox proportional hazard model, the relative risk of cause-specific mortality for "RT after surgery" versus "No RT" was calculated.

Results: 21,789 patients were identified who met the inclusion criteria. Of these, only 1001 received adjuvant RT, and 64% were node-positive (53% RT vs. 65% no RT). When comparing RT vs. no RT, after adjusting for sex, age, N stage, and grade, we determined the relative risk of death from cancer was 0.8849 (95% CI: 0.8008–0.9779; p = 0.0165), suggesting that only 14 patients with T4 disease need receive adjuvant radiation to spare a cancer-related death.

Conclusions: Adjuvant RT is not routinely utilized for definitive treatment of T4 non-rectal colon cancer, but this analysis shows a significant cause-specific survival benefit.

Adenocarcinoma of the colon and rectum is a leading cause of cancer-related deaths in the United States. The estimated incidence for 2018, according to the NCI at the National Institutes of Health, is 140,250 individuals, representing 8.1% of all new cancer cases. The projected mortality from these cancers is 50,630, or 8.3% of all cancer deaths, making it the fourth most common malignancy is men and women, and third most common cause of cancer death in both sexes. The 5-year relative survival, as determined from 2008 to 2014 NCI data, is 64.5% and fortunately, the 5-year relative survival has been gradually improving since 1975, from 48.6% to 66.2%. This is primarily due to improvements in screening, as survival is closely tied to stage, with patients presenting with early stage disease having a high 5-year relative survival of 89.9%. However, patients with locally advanced disease (T3, T4 or node positive) have a much lower 5 year survival of 71.3% [1].

Radiotherapy (RT) has been investigated as adjuvant and neoadjuvant therapy for locally advanced rectal adenocarcinoma, with a confirmed local control benefit across numerous phase III trials [2–6]. Based on these trials, RT is considered standard of care in patients with T3, T4 or node positive adenocarcinoma of the rectum. Although further investigation has made neoadjuvant radiotherapy the standard of care for locally advanced rectal cancer, in patients who do not receive pre-operative RT, adjuvant RT is still recommended over observation or chemotherapy alone [7].

However, despite consensus that colon and rectal adenocarcinoma are similar and continuous pathologies [8], the available data do not show the same benefit for the addition of RT for surgically resected colon cancer [9]. Data from Massachusetts General Hospital (MGH) and the Mayo Clinic show an improvement in local control with adjuvant chemoradiotherapy for locally advanced, resected colon cancer [10,11]. More recently, a single-institution study from Duke University suggests a locoregional control and disease-free survival benefit when utilizing adjuvant RT for American Joint Committee on Cancer 7th edition (AJCC) T4 colonic adenocarcinoma [12], defined as tumor invading or adherent to other organs. Unfortunately, a phase III randomized control evaluating radiotherapy vs. chemoradiation for resected T3/4 colon cancer closed due to slow accrual. Based on the 187 (of planned 700) eli-

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gible patients, there was no difference in any of the endpoints between the two groups, however, the power to detect a difference was very low. Based on a lack of strong data, the most recent edition of the National Comprehensive Cancer Network (NCCN) Guidelines for colon cancer omit any recommendation or discussion of radiotherapy as neoadjuvant or adjuvant treatment for resectable colon cancer [13].

The natural history and patterns of failure of stage T4 colon cancer have been examined in the existing literature and compared to early stage disease. Data from MGH compared patterns of failure based on various stages of colon cancer. They evaluated stage B3 disease (the equivalent to stage T4 in the most recent AJCC staging criteria) versus earlier stage disease. In this analysis, it was shown that stage B3 colon cancer has a significantly higher local failure rate, 30% at 5 years compared to 3–11% for less advanced disease, and distant failure rate of, 27% at 5 years, versus 3–20% for less advanced disease [14]. As radiotherapy is a local treatment that can improve local control, it would be feasible to consider applying it in situations like T4 colon cancer, where local failure is high and may be the driver of ultimate disease progression and death.

Given the fact that RT improves local control in locally advanced rectal adenocarcinoma, we hypothesized that it would have a similar benefit for locally advanced colonic adenocarcinoma. As compared to the wealth of phase III data evaluating RT in resectable rectal adenocarcinoma [2–6,15–17], randomized trials for adjuvant RT in locally advanced resectable colonic adenocarcinoma are limited in number and enrollment [9]. As such, we believe that the role of RT in this patient population has been understudied. Review of our institution's records showed fewer than 100 patients treated with adjuvant RT for colon cancer in the last 10 years, which is consistent with the low rate that this modality is employed at other institutions [12], and not conducive to robust analysis. Therefore, we employed the SEER database to evaluate the benefit of adjuvant RT in the setting of locally advanced adenocarcinoma of the colon.

Methods and materials

A retrospective analysis using the NCI's SEER database was performed using data up to and including 2015. The SEER database incorporates 17 registries representing approximately 26% of the population of the United States. To identify cases of stage T4 colon cancer, the SEER database November 2015 submission was queried for all cases of colon cancer from 1973 to 2013. SEER*Stat software, version 8.3.2 was used to perform all queries. We limited our query to ICD WHO site recode of "colon excluding rectum" and cancer-directed "surgery performed." In addition, patients were only included if they were AJCC TNM 7th edition stage "all T4," but no M1. Lastly, cases were required to be categorized as "first cancer." We collected the following data for each case: sex, age, year of diagnosis, tumor grade, nodal stage, and use of RT. The SEER database specified if RT was provided before surgery, during surgery, after surgery, or timing unknown.

We consolidated the above parameters in order to perform subgroup analysis on the SEER data. Age was categorized into groups of <50, 50–59, 60–69, and ≥70 years. In addition, we subdivided patients into AJCC TNM stage N0 and N1 or greater, and sex (male or female). Tumor grade was grouped as I, II, III, or IV (undifferentiated). Across each of these subgroups, we compared patients categorized as "no radiation" to those categorized as "radiation after surgery." Patients who received RT before or during surgery, or those whose order of RT was unknown, were excluded. Of note, chemotherapy utilization data were not available and could not be incorporated in this analysis.

The primary endpoint of the analysis was cause-specific survival (CSS), which was ascertained by specifying colon cancer as the cause of death, measured from time of diagnosis of colon cancer to time of death, in months. Patients with non-colon cancer deaths or with an unknown cause of death were excluded from the survival analysis. In addition, we determined median survival time and overall survival (OS) at 5 years and 10 years.

Kaplan–Meier's curves were generated for CSS and OS with 95% confidence intervals. Cox proportional hazard models were used to estimate the hazard ratios between cases of "no RT" and those with "RT after surgery," with a hazard ratio of less than 1 indicating a better prognosis and greater than 1 indicating a worse prognosis. In the Cox model, when evaluating RT, we control for other covariates, such as age, N stage, sex, and grade; these covariates were set to be a mode or a median, specifically as {Sex = Female, N Stage = 1, Age group = 60–69, Grade = 2}. Data analysis was done using the R software (https://www.r-project.org/), with the survival package.

Results

21,789 patients were identified who met the inclusion criteria. Of these, 1001 (4.6%) received adjuvant RT and 20,683 (94.9%%) received no adjuvant RT. 46% were male (52% RT vs. 46% no RT) and 54% were female (48% RT vs. 54% no RT). 46% were age 70 or older (27% RT vs. 47% no RT), and 64% had node-positive disease (53% RT vs. 65% no RT). Other baseline characteristics are summarized in Table 1.

Analysis of the entire population yielded a 5-year cause-specific survival of 40.1% (95% CI 0.393–0.409), and 10-year CSS of 33.6% (95% CI 0.325–0.346). When grouped based on nodal status, 5-year CSS was 61.2% for node-negative disease (95% CI 0.598–0.625) and 28.5% for node-positive disease (95% CI 0.276–0.294). At 10 years, the respective CSS rates were 53.1% (95% CI 0.510–0.551) and 22.9% (0.218–0.240). There was also a difference in cause-specific survival between age groups with 5-year CSS for patients younger than 70 years 44.8% (95% CI 0.437–0.458), versus 34.3% for patients 70 or older (95% CI 0.331–0.355). At 10 years, these rates were 37.3% (95% CI 0.359–0.387) and 29.0% (95% CI 0.275–0.305), respectively, as summarized in Table 2.

Using a Cox proportional hazard model, the CSS difference at 5 and 10 years for patients who had received adjuvant RT was compared to those who had not received any RT for colon cancer (no RT). We found a statistically significant difference at both 5 and 10 years, in favor of the adjuvant RT group, as shown in Fig. 1. At 5 years, the CSS rates were 43.7% for the adjuvant RT group (95% CI 0.397–0.476), and 38.3% for the no RT group (95% CI 0.363–0.403). At 10 years, the CSS rates were 36.6% (95% CI 0.325–0.407) and 31.2% (95% CI 0.291–0.333), respectively. Furthermore, OS at 5 years was 42.8% for the adjuvant RT group (95% CI 0.390–0.465) and 35.7% for the no RT group (95% CI 0.339–0.376). At

Table 1
Patient characteristics from SEER query.

		No RT (%)	RT after surgery (%)
Age (yrs)	<50	2720 (13)	194 (19)
	50–59	3749 (18)	278 (28)
	60–69	4561 (22)	261 (26)
	≥70	9653 (47)	268 (27)
Nodal stage	N0	7309 (35)	468 (47)
	N1 or greater	13,342 (65)	533 (53)
Sex	Female	11,149 (54)	478 (48)
	Male	9534 (46)	523 (52)
Grade	I	1179 (6)	61 (6)
	II	11,295 (55)	604 (60)
	III	6506 (31)	261 (26)
	IV	867 (4)	32 (3)

Table 2
Cause-specific survival (CSS) for colon cancer.

		5-year CSS (95% CI)	10-year CSS (95% CI)	p value
Age (yrs)	<70	44.8% (0.437–0.458)	37.3% (0.359–0.387)	<0.00001
	≥70	34.3% (0.331–0.355)	29.0% (0.275–0.305)	
Nodal stage	N0	61.2% (0.598–0.625)	53.1% (0.510–0.551)	<0.00001
	N1 or greater	28.5% (0.276–0.294)	22.9% (0.218–0.240)	

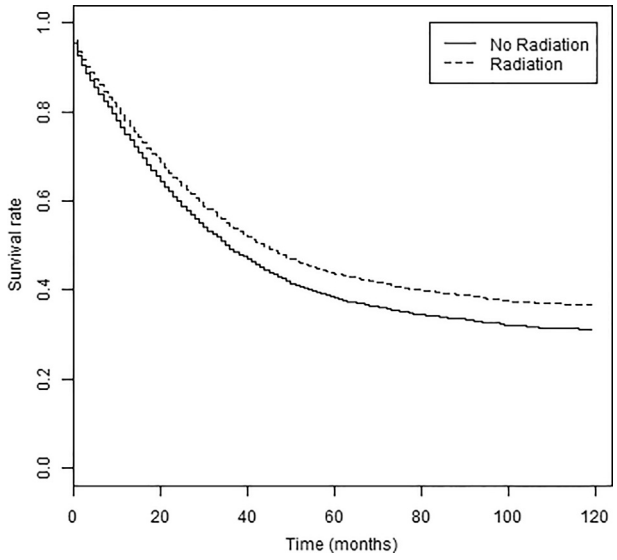

Fig. 1. Cause-specific survival at 5 years and 10 years based on use of adjuvant radiotherapy.

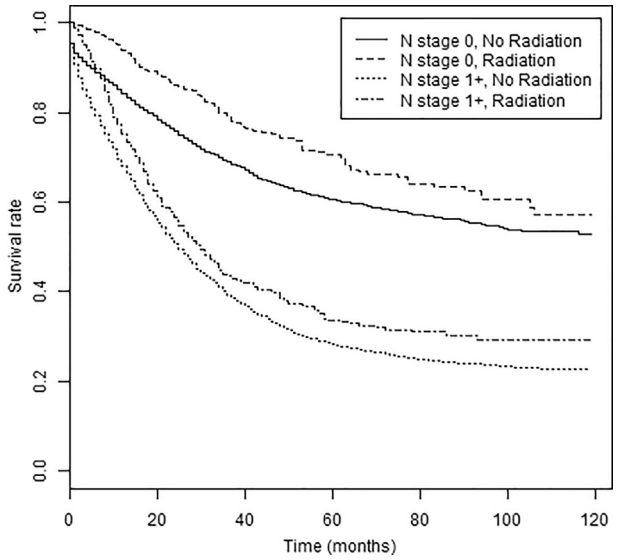

Fig. 2. Cause-specific survival at 5 years and 10 years based on use of adjuvant radiotherapy, grouped by nodal stage.

10 years, OS was 32.0% for the adjuvant RT group (95% CI 0.282–0.358) and 25.1% for the no RT group (0.232–0.270). Median overall survival was determined to be 43 months for patients who received adjuvant RT, versus 34 months for those who received no RT (Table 3).

We also explored whether there was a difference in survival been adjuvant RT and no RT groups based on nodal status. As seen in Fig. 2, there is a greater absolute survival benefit for adjuvant RT in node-negative patients at 5 years, which was 70.7% (95% CI 0.654–0.753), as compared to 60.7% for the no RT group (95% CI 0.593–0.620). For node-positive patients, 5-year CSS rates were 33.7% (95% CI 0.290–0.394) and 28.3% (95% CI 0.273–0.292), respectively.

When comparing RT vs. no RT, after adjusting for sex, age, N stage, and grade, we determined the relative risk of death from cancer was 0.8849 (95% CI 0.8008–0.9779) with a p-value of 0.0165. In other words, for patients with T4 colon cancer, adjuvant RT decreased the relative risk of death from colon cancer by 11.5% at 5 years. In other words, the number needed to treat with adjuvant RT to spare a single cancer death is 14.3 patients.

Discussion

Using a well-managed large database, this analysis is the first to show a significant improvement in CSS at 5 years for the addition of adjuvant radiation therapy in patients with T4 colon cancer. This benefit is present when adjusted for sex, age, N stage, and grade, and is most pronounced in patients with T4 node negative disease.

These data are potentially practice-changing, given the paucity of prior data and the inferior rates of survival in patients who present with locally advanced disease. The largest prospective, randomized trial to address this scenario to date, the Intergroup 0130 study evaluated chemotherapy (fluorouracil and levamisole) with or without radiotherapy in the adjuvant setting and did not show a benefit for disease-free survival, overall survival, or local recurrence with the additional of RT. However, the study was limited by poor accrual (222 of 700 planned patients enrolled), and the high proportion of patients enrolled but deemed ineligible for a treatment arm [9]. Given these limitations, the study was considered underpowered, and the results used with caution. Since the publication of the Intergroup trial in 2004, radiation therapy plan-

Table 3
Comparison of existing series evaluating adjuvant radiotherapy for non-rectal colon cancer.

Series	Patients (N)	% T4	Follow-up (mos)	Local control (yrs)	DFS (yrs)	CSS (yrs)	OS (yrs)
Shebata et al, 1987	31	45	Median 48	87 (crude)	63 (crude)		
Wong et al, 1985	48	No data	Median 43	67 (5)			68 (5)
Amos et al, 1996	78	33	Minimum 36	88 (5)		63 (5)	
Willett et al, 1999	110	100	Median 79	78 (10)	48 (10)		
Martenson et al, 2004	222	81	Median 79.2	81 (5)	51 (5)		58 (5)
SEER analysis, 2018	21,789	100	Median 20			44 (5)	43 (5)
						37 (10)	36 (10)

ning and delivery techniques have improved significantly. Additionally, the chemotherapy drugs and dosing in colon cancer have changed with FOLFOX becoming standard of care.

Various prospective, randomized trials have evaluated the role of adjuvant chemotherapy for stage III colon cancer. The MOSAIC trial, which compared fluorouracil and leucovorin versus fluorouracil and leucovorin plus oxaliplatin (FOLFOX4) for resected stage II to III colon cancer, demonstrated an overall survival benefit for FOLFOX, making this the standard of care regimen. The 10-year overall survival rates for high-risk stage II (T4N0) patients from this trial were 71.7% with 5-FU leucovorin versus 75.4% with FOLOFOX, 10-year overall survival rates for stage III patients (including T4N1-2) were 59.0% versus 67.1%, respectively. Interestingly, analysis of the 5-year data showed no added survival benefit with oxaliplatin for T4 disease, which suggests that bulkier local disease may require a local adjunct, such as radiotherapy.

Based on MOSAIC and the IDEA collaborative studies, 6 months of adjuvant chemotherapy is the standard treatment after surgery in "high risk" (T4 or N2) locally advanced colon cancer. One of the challenges of adding radiation into the treatment paradigm for colon cancer is when in the sequence of therapies it should take place. A commonly employed strategy is to treat with a "sandwich" sequence with 3 months of FOLFOX before and after chemoradiation, similar to INT 0114 in adjuvant rectal adenocarcinoma [18]. This "sandwich" type sequencing following resection could be considered as an experimental arm in future studies on locally advanced non-rectal colon adenocarcinoma, to be compared against the current standard of surgery with adjuvant chemotherapy.

Other challenges potentially limiting use of adjuvant radiation include concerns for toxicity, particularly in combination with chemotherapy. In the Intergroup 0130 study, 20% of patients experienced acute diarrhea in the chemoradiotherapy arm, as compared to 13% in the chemotherapy arm, although this difference was not statistically significant. Despite the concern that abdominal RT causes upper GI toxicity, such as nausea, only 5% of patients in the chemoradiotherapy arm of the Intergroup study reported acute nausea[9]. It should be noted, however, that concerns regarding toxicity may be misplaced, as treatment planning and delivery have significantly improved since the time of the Intergroup 0130 study; now outdated techniques and poor target delineation of organs at risk likely contributed to the reported acute toxicity. Contemporary radiotherapy technique is unlikely to produce similar rates of adverse events.

The limitations of this study, similarly to all SEER studies, include the lack of information of receipt of chemotherapy, patient performance status, or reasons for not receiving adjuvant radiotherapy as they are not included in the SEER database. In addition, SEER data do not provide details on non-cancer death, such as treatment toxicity. However, we would not expect significant mortality from post-operative RT in this setting, which is consistent with the aforementioned randomized data for both colon and rectal cancers. Based on the data discussed, it is reasonable to assume that most patients received adjuvant chemotherapy, and it is possible that the addition of RT to chemotherapy in this population further improves CSS. In fact, patients considered for adjuvant radiotherapy often have a lower performance status than those considered for chemotherapy, which could further enhance on the benefit of RT in this patient population.

To conclude, adjuvant RT is not routinely utilized for definitive treatment of T4 non-rectal colon cancer, but this analysis shows a significant benefit in cause-specific survival that warrants attention. The limitations of conducting a randomized trial and small patient numbers were mitigated with the use of this large database. However, use of chemotherapy, performance status and physician bias were unknown. These data provide impetus for the oncology community to re-evaluate the use of RT in locally advanced non-rectal colon cancer. With advances in systemic therapy long term survivorship is common and local control with adjuvant RT will play a more profound role in the definitive treatment of resectable T4 colon cancer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.026.

References

[1] National Cancer Institute. Cancer Stat Facts: Colon and Rectum Cancer. https://seer.cancer.gov/statfacts/html/colorect.html. Published 2018. [Accessed 1 May 2018].

[2] Peeters KCMJ, Marijnen CAM, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years. Ann Surg 2007;246(5):693–701. https://doi.org/10.1097/01.sla.0000257358.56863.ce.

[3] Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: national surgical adjuvant breast and bowel project protocol R-02. JNCI 2000;92(5).

[4] Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23(24):5644–50. https://doi.org/10.1200/JCO.2005.08.144.

[5] Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. JNCI 1988;80(1):21–9.

[6] Thomas P, Lindblad A. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. Radiother Oncol 1988;13(4):245–52.

[7] NCCN.org. Clinical Practice Guidelines in Oncology (NCCN Guidelines) Rectal Cancer. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Published 2018. [Accessed 30 August 2018].

[8] Taliano R, LeGolvan M, Resnick M. Immunohistochemistry of colorectal carcinoma: current practice and evolving applications. Hum Pathol 2013;44(2):151–63.

[9] Martenson Jr JA, Willett CG, Sargent DJ, et al. Phase III study of adjuvant chemotherapy and radiation therapy compared with chemotherapy alone in the surgical adjuvant treatment of colon cancer: results of intergroup protocol 0130. J Clin Oncol 2004;22(16):3277–83. https://doi.org/10.1200/JCO.2004.01.029.

[10] Schild S, Gunderson LL, Haddock MG, Wong W, Nelson H. The treatment of locally advanced colon cancer. Int J Radiat Oncol Biol Phys 1997;37(1):51–8.

[11] Willett C, Goldberg S, Shellito P, et al. Does postoperative irradiation play a role in the adjuvant therapy of stage T4 colon cancer? Cancer J Sci Am 1999;5(4):242–7.

[12] Ludmir EB, Arya R, Wu Y, Palta M, Willett CG, Czito BG. Role of adjuvant radiotherapy in locally advanced colonic carcinoma in the modern chemotherapy era. Ann Surg Oncol 2016;23(3):856–62. https://doi.org/10.1245/s10434-015-4907-3.

[13] NCCN.org. Clinical Practice Guidelines in Oncology (NCCN Guidelines) Colon Cancer. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Published 2017. [Accessed 12 August 2017].

[14] Willett CG, Tepper JE, Cohen AM, Orlow E, Welch CE. Failure patterns following curative resection of colonic carcinoma. Ann Surg 1984;200(6):685–90. https://doi.org/10.1097/00000658-198412000-00001.

[15] Park J, Yoon SM, Yu CS, Kim JH, Kim TW, Kim JC. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer 2011;117:3703–12. https://doi.org/10.1002/cncr.25943.

[16] Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017;18(3):336–46. https://doi.org/10.1016/S1470-2045(17)30086-4.

[17] Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30(16):1926–33. https://doi.org/10.1200/JCO.2011.40.1836.

[18] Shi Q, Sobrero AF, Shields AF, et al. Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemother. J Clin Oncol 2017;35(suppl):abstr LBA1.