

Low-energy electronic intraoperative radiotherapy for pT3 locally advanced colon cancer: a single-institution retrospective analysis

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Keywords: Low-energy electronic intraoperative radiotherapy, locally advanced colon cancer, pT3 colon cancer

Posted Date: February 17th, 2020

DOI: <https://doi.org/10.21203/rs.2.23487/v1>

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Abstract

Background

Patients with locally advanced colon cancer (LACC) treated with surgery had a high risk of local recurrence. The outcomes can vary significantly among patients with pT3 disease. This study was undertaken to assess whether low-energy electronic intraoperative radiotherapy (eIORT) can achieve promising results comparing with electron beam IORT (IOERT) and whether specific subgroups of patients with pT3 colon cancer may benefit from eIORT.

Methods

We retrospectively reviewed 44 patients with pT3 LACC treated with eIORT. Clinicopathologic characteristics were analyzed to identify patients that could potentially benefit from eIORT. Kaplan-Meier survival analysis was used to assess overall survival (OS) and progression free survival (PFS). The log-rank test was used for the subgroup comparison.

Results

The median follow-up of patients was 20.5 months (range, 6.1–38.8 months). At the time of analysis, 38 (86%) were alive and 6 (14%) had died of their disease. The 3-year Kaplan-Meier of PFS and OS for the entire cohort were 82.8% and 82.1%, respectively. At median follow-up, no in-field failure within the eIORT field had occurred. Locoregional and distant failure had occurred in 2 (5%) patients each. The rate of perioperative 30-day mortality was 0% and morbidity rate was 11%. Five patients experienced 7 complications, including 4 early complications (30-d) and three late complications (>30 days) leading early and late morbidity rates of 9% and 7%, respectively.

Conclusion

Low-energy eIORT can be considered as part of management in pT3 LACC.

Background

Colon cancer was the fourth most common malignancy and the fifth most deadly cancer worldwide according to the GLOBOCAN estimation in 2018 [1]. Completeness of surgical resection was the most important prognostic factor in almost all the studies [2]. Most colon cancer patients were sufficiently treated surgically with or without adjuvant systemic therapy. Although 70% to 90% of all patients who had colorectal cancer undergo surgical resection with curative intent, the 5-year recurrence rate were 12% and 33% in stage II and III patients, respectively [3, 4]. Multivariable analysis indicated the disease stage II and III were independent predictors of locoregional recurrence (LR). The median survival after diagnosis of LR was only 9 months [5]. Consequently, the recurrence or metastasis lead to a clinical and therapeutic challenge associated with a poor prognosis. It is therefore worth exploring how local control could be improved beyond standard care of colon cancer.

At present there is no established role for the routine use of intraoperative radiotherapy (IORT) as adjuvant therapy in primary colon cancer except for in pT4 disease. However, IORT allows for sterilization of microscopic disease in situ. Shifting healthy tissues out of the radiation field and selective shielding of surrounding structures during IORT, therefore the high, single radiation doses can be delivered while minimizing the side effects in adjacent tissues [6]. Studies have indicated that modification of IORT for colorectal cancers may lead an improvement of in-field and local control in selected patients. Brady et al. have reported that IORT may be utilized as a tool to improve local control in patients with locally advanced primary or recurrent colorectal cancer [7]. However, there were limited previous studies of IORT for primary colon cancer and most of the patients in these researches received either IOERT or high-dose-rate intraoperative brachytherapy [8, 9] with only a few studies describing outcomes for colorectal cancer patients using orthovoltage IORT [10–12]. At present, electronic brachytherapy is mainly recommended for breast cancer, endometrial, cervical cancer or nonmelanomatous skin cancers based on currently available data, however, electronic brachytherapy has emerged as a potential alternative for certain disease sites [13].

Currently recognized high-risk factors for recurrence of colon cancer after resection included poorly differentiated histology, lymphatic/vascular invasion, perineural invasion or positive margins. In order to explore patients who would benefit from eIORT in pT3 patients, we analyzed the data based on the clinicopathological characteristics of the patients. This study is the first time to investigate potential benefit from low-energy eIORT among patients with pT3 LACC. We aim to evaluate whether eIORT can benefit pT3 patients not being inferior to the electron IOERT. Furthermore, we report complications associated with eIORT.

Methods

The local institutional review board approved this study. We retrospectively analyzed clinical data of 44 primary colon cancer patients with T3N0–2M0 diseases. They all received curative surgical resections and eIORT at our hospital between August 2016 and February 2019. A tumor within 15 cm from the anal verge at the caudal margin defined as rectal cancer was excluded. We also excluded distant metastasis, recurrent colon cancer and synchronous malignancy.

Standardized curative intent surgeries were applied in all patients. We restaged the final pathologic features according to the tumor node metastasis (TNM) staging system of the seventh edition of the American Joint Committee on Cancer during data review.

Lower energy photons were performed to the tumor bed, while dose-limiting structures were separated from the irradiation field. It was applied using a dedicated INTRABEAM® PRS 500 (Carl Zeiss Meditec AG, Germany). Operation of the INTRABEAM system was based on the use of an orthovoltage X-ray beam (photons with an energy of 50 keV). The diameters of spherical applicators ranged from 1.5 cm to 5.0 cm. They were used to enable accuracy and uniformities of dose distribution on the surface of the tumor

bed. The irradiation time varied based on the dose of radiation and the diameter of the applicator for patients.

Kaplan-Meier analysis was used to create OS and PFS curves; groups were compared using the log-rank test. A value of $P \leq 0.05$ was considered statistically significant. All analyses were performed with SPSS 26.0 statistical software (IBM SPSS Statistics 26).

Results

Twenty-eight men (64%) and sixteen women (36%) were included in this study. Median age at the time of surgery and eORT was 64.5 years (range 39– 83). One patient had small intestinal neuroendocrine carcinoma; three had mucinous adenocarcinoma and all others had adenocarcinoma. Postoperative chemotherapy was administered to nineteen patients according to postoperative pathology. Except for two patients who used capecitabine for 3–8 cycles, the remaining 17 patients received regimen CAPEOX for 3–6 cycles. Additional information on patient and tumor characteristics is described in *Table 1*. The information on eORT is described in *Table 2*.

Table 1. Patient and Tumor Characteristics (n=44)	
Characteristic	Number (%)
Sex	
Male	28(64%)
Female	16(36%)
Age(years)	
Median	64.5
Range	39-83
Preoperative RT	0
Neoadjuvant chemotherapy	0
Postoperative RT	0
Adjuvant chemotherapy	19
Histology	
Adenocarcinoma	40(91%)
Mucinous adenocarcinoma	3(7%)
Small intestinal neuroendocrine carcinoma	1(2%)
Pathologic T stage	
T3	44(100%)
Pathologic N stage	
N0	27
N1	11
N2	6
Pathologic M stage	
M0	44
M1	0
Number lymph nodes examined	
Median	19
Range	7-33
Number lymph nodes positive	

Mean	2
Range	0-15
Follow-up time (months)	
Median	20.5
Range	6.1-38.8

Table 2. characteristics of eIORT	
Characteristic	Number (%)
Applicator size (cm)	
Mean	3.5
Range	2.5-4.5
Dose (Gy)	
Mean	15
Range	10-18
Time (min)	
Mean	15.7
Range	9.2-26.6

Median follow-up of patients was 20.5 months (range, 6.1–38.8 months). At the time of analysis, 38 (86%) of 44 patients were alive and 6 (14%) patients were died. The 3-year Kaplan-Meier of PFS and OS for the entire cohort were 82.8 % and 82.1%, respectively (*Fig. 1*).. At median follow-up, no central failure within the eIORT boost field had occurred and locoregional and distant failure had occurred in 2 (5%) patients each.

On univariate analysis, pathologic regional lymph node status was not predictive of OS ($p = 0.38$). The 3-year estimations of OS were 85.6% and 88.9% for N0 and N1, respectively. The 2-year OS of 62.5% was estimated for the N2. The PFS estimations for the above were 91.7% and 88.9% for 3-year and 66.7% 2-year ($p = 0.373$) respectively (*Fig. 2*).. Lymphatic/vascular invasion also did not predict for OS ($p = 0.068$) or PFS ($p = 0.079$) in our study. The 3-year estimation of OS and PFS were 86.2% and 86.4% for lymphatic/vascular invasion negative. The 55.6% and 62.5% of 2-year OS and PFS were respectively estimated for the lymphatic/vascular positive (*Fig. 3*).. The margins of our patients were negative and only two cases had perineural invasion. Therefore, no separate statistics were performed.

Perioperative 30-day mortality was 0%, while there were 7 complications occurring in 5 patients. Short-term complications occurred in 9% (n = 4) of patients, including: wound infection 5% (n = 2), anastomotic fistula 2% (n = 1) and healing delay 2% (n = 1). Three late complications (≥30 days) occurred in 3 patients, giving a long-term morbidity rate of 7%. All 3 were related to small bowel obstruction. There was no severe toxicity (CTCAE grades 3 or 4) related to the multimodality therapy. Information on complications is described in *Table 3*.

Table 3. Complications	
Complication	Total (number)
Early(30-d)	4
Mortality	0
Anastomotic leak/abscess/fistula	1
Small bowel obstruction	0
Wound infection or breakdown	2
Dehiscence	0
Ureteral injury	0
others	1
Late(≥30 d)	3
Peripheral neuropathy	1
Small bowel obstruction	2
Ureteral obstruction	0
Wound infection/breakdown	0
Fistula with abscess	0
Bladder dysfunction	0
Sexual dysfunction	0
Enteritis/proctitis	0
Pelvic or abdominal abscess	0
There was no severe toxicity (CTCAE grades 3 or 4) related to the multimodality therapy.	

Discussion

This is the first to report the use of low-energy eIORT in LACC. Currently, there was very limited data available on IORT for colon cancer, especially for locally advanced colon cancer[14, 15]. The present in-

field local control in our study was 100%. It was a very encouraging result. Additionally, based on current obtainable results, the 5-year LC was between 86% and 89% of multimodality treatment including surgery, external beam radiotherapy (EBRT) and IOERT. Liska, D. and colleagues found that median time to LR was 21 months [5]. This was comparable to our median follow-up time. It was reasonable to infer we achieved better locoregional failure of 5%. In spite of 19 of our patients received adjuvant chemotherapy according to standards, it was notable that adjuvant chemotherapy was not involved in reducing LR of patients with either Stage II or Stage III tumors [5]. The estimated 5-year OS was between 61% and 76%. We found that 3-year OS was 82.1%. Notably, at least two of the six patients who did not die directly from colon cancer in our study. Therefore, the actual survival rate should be better than what we reported here in this study. Meanwhile, our 3-year PFS was 82.8%, better than the 43% in early report [15]. The 5-year DM was 12% according to the previous data, which is much higher than our 5% [14].

In particular, extensive surgical resection is required for patients with LACC and this comes with a major risk of complications. Therefore, in the present era of increasing medical costs and outcomes consciousness, it is essential to assess complications associated to the combination of eIORT and surgery. Our results suggest that patients treated with lower energy photons had promising PFS and OS and without an increase in short-term or long-term complications in comparing to previous multimodality studies, whose acute complications were not more than 10% and long-term morbidities were between 37% and 53% [16]. In our study, early complications occurred in 9% of patients and 7% of patients had late complications; and surgery time was not extended significantly (mean eIORT time = 15.7min, range 9.2–26.6min). Our analysis indicated that addition of low-energy eIORT to standard treatment led to better results with no increased toxicity.

As has been previously shown, postoperative regional lymph node status and lymphovascular invasion directly affected tumor stage and prognosis [17, 18]. The prognosis was very different from T3N0 to T3N2 patients. However, in our study, regional lymph node status and lymphovascular invasion had no significant impact on PFS or OS in patients with pT3 colon cancer. Although our analysis showed a trend, results did not get statistically significant differences. Our results suggest a potential role for low-energy eIORT in the management of LACC, in particular, the setting of pT3 disease with pathologically involved lymph nodes and/or lymphovascular invasion positive patients. However, we cannot exclude the effect of limited follow-up time and the small patient number at present.

It was also notable that variations in histology of our study included small intestinal neuroendocrine carcinoma, mucinous adenocarcinoma and adenocarcinoma. Nevertheless, neuroendocrine tumors had a poor prognosis with 3-year survival was 15%, and five-year survival was 6%. Overall survival was poor especially for small-cell neuroendocrine carcinomas [19]. Comparing with non-mucinous adenocarcinoma, mucinous adenocarcinoma was a distinct subgroup of colon cancer with a worse prognosis [20]. Thus, instead of affecting our current results, it indicated that we achieved quite good results.

Our study has a number of limitations which include it being a retrospective, non-randomized, single center study with no control group. There may also be significant selection bias. The follow-up time is relatively insufficient. Because of current rare data on IORT for colon cancer, available results are relatively inadequate. This could limit the generalizability of result from this study to a larger population.

Despite these limitations, our results suggest a potential role for low-energy eIORT in the management of LACC, and achieve the effect of not being inferior to the electron IOERT without increasing toxicity. Larger prospective comparative analyses are needed to better evaluate outcomes for patients with LACC receiving eIORT.

Conclusion

Low-energy eIORT can be considered as part of management in pT3 LACC.

Abbreviations

LACC: Locally advanced colon cancer; eIORT: Electronic intraoperative radiotherapy; IOERT: Electron beam intraoperative radiotherapy; OS: Overall survival; PFS: Progression free survival; LR: Locoregional recurrence; IORT: Intraoperative radiotherapy; TNM: Tumor node metastasis; EBRT: External beam radiotherapy

Declarations

Ethics approval and consent to participate

This retrospective analysis was approved by the Institutional Review Board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was partially supported by funding from The First Hospital of Qiqihar City (R073290127), Heilongjiang province, PR China; a Merit Award (I01 BX000671 to WG) from the U.S. Department of Veterans Affairs; and the Veterans Administration Medical Center in Memphis, TN. The funding organization had no role in the design or conduct of this research.

Authors' contributions

LM: Manuscript draft and analysis data. JHQ, XWL and YJ: Review of the literature. HLY, LL: Participating in study design. CYM: Conceiving of the study. LD, JLC and DMW: Carrying out the clinical review required in the study. AMS, DS: Participating in the review of the drafted manuscript. WKG and HC: Manuscript revision. WKG and HC contributed equally to this article. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

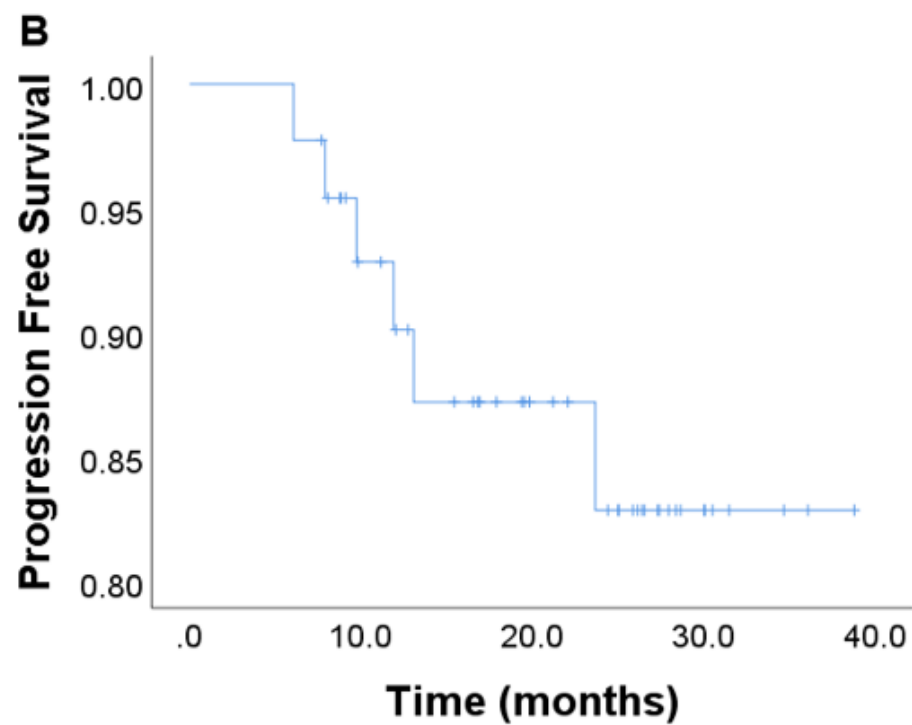
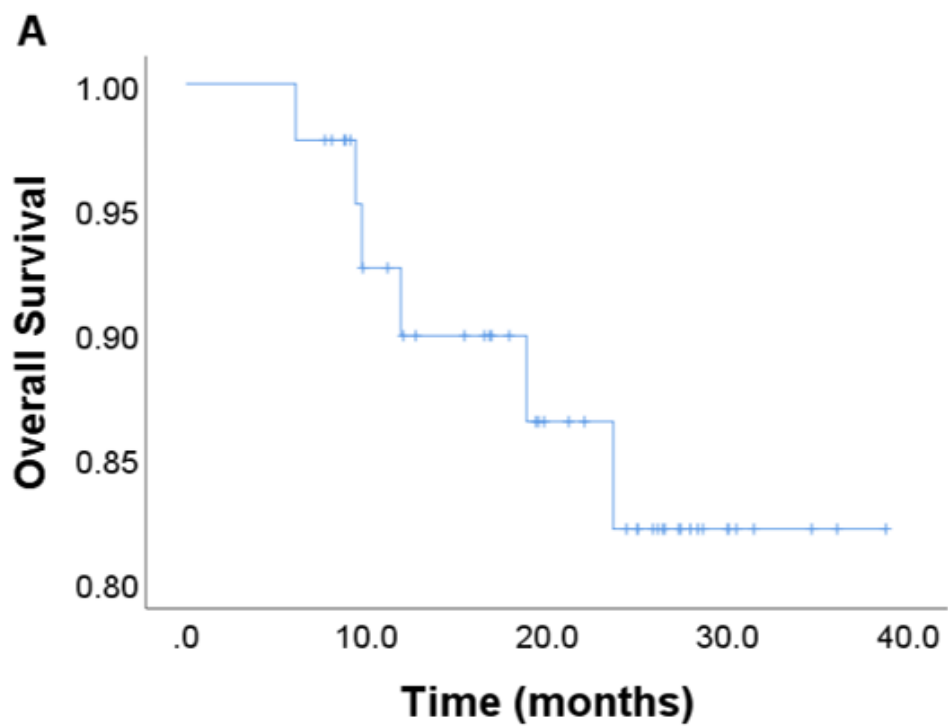


Figure 1

A. Kaplan-Meier overall survival curve; B. Kaplan-Meier progression free survival curve.

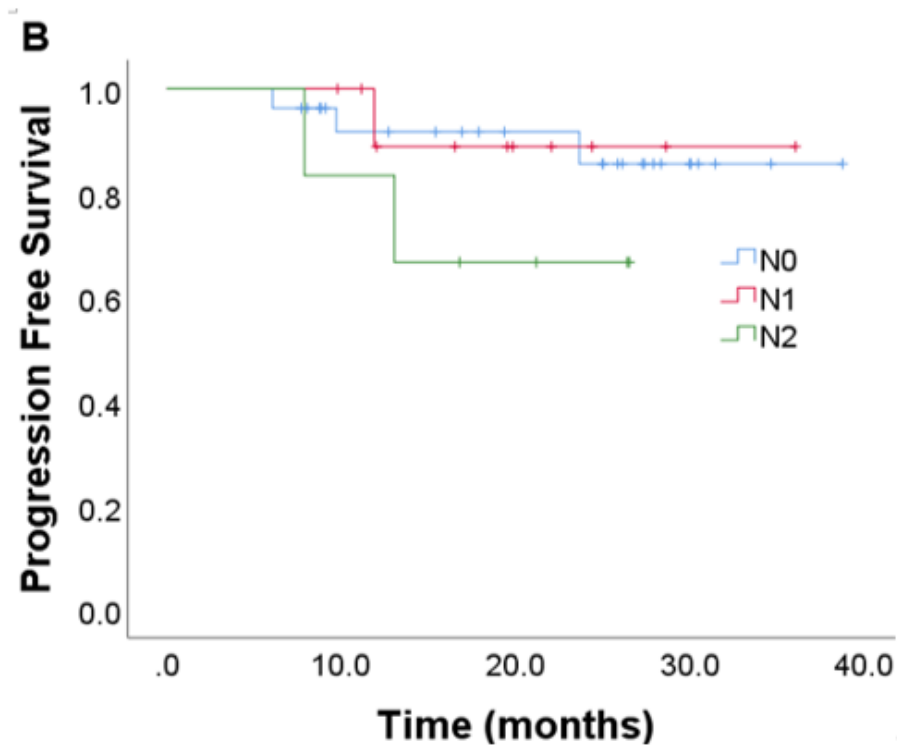
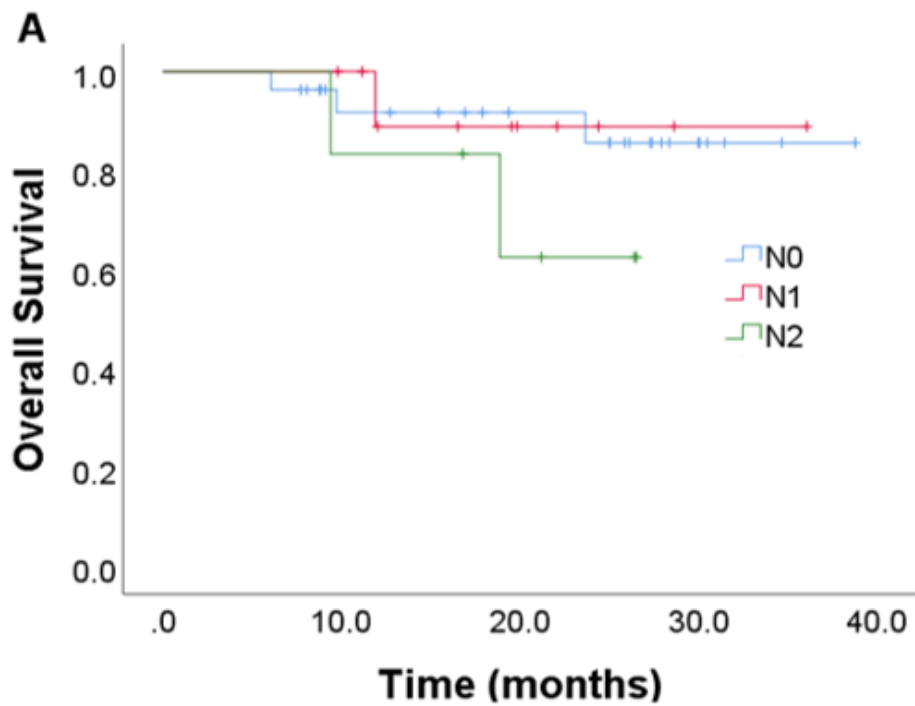


Figure 2

A. Kaplan-Meier overall survival curve ($p = 0.38$); B. Kaplan-Meier progression free survival ($p = 0.373$). Patients were stratified by pathologic regional lymph node status.

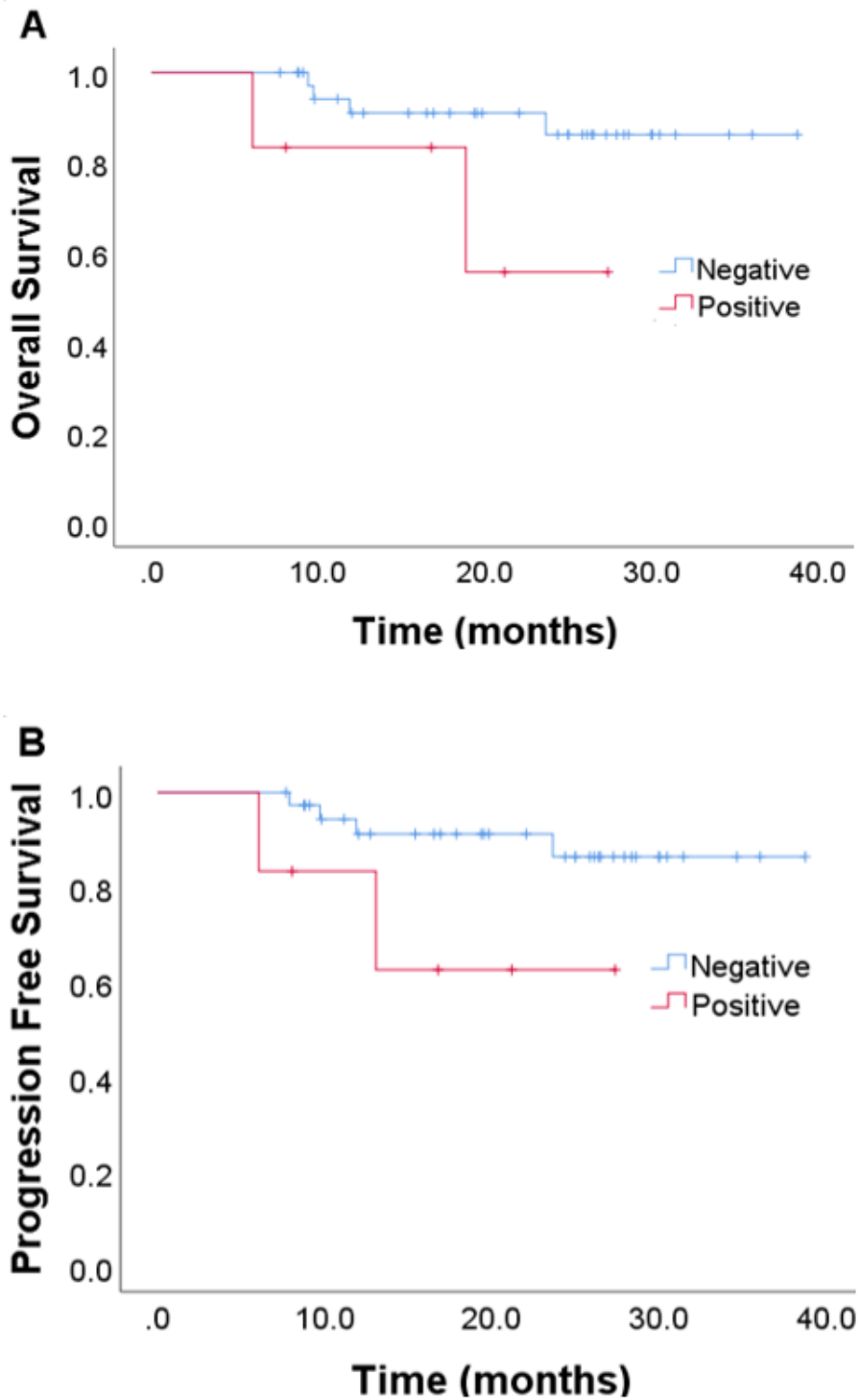


Figure 3

A. Kaplan-Meier overall survival curve ($p = 0.068$); B. Kaplan-Meier progression free survival ($p = 0.079$). Patients were stratified by lymphatic/vascular invasion.