


RESEARCH

Open Access



Low-kilovolt x-ray intraoperative radiotherapy for pT3 locally advanced colon cancer: a single-institution retrospective analysis

Li Ma^{1,2,3}, Junhao Qiang^{1,2}, Heliang Yin^{1,2,3}, Lin Lin^{1,2,3}, Yan Jiao³, Changying Ma^{1,2}, Xinwei Li^{1,2}, Li Dong^{1,2}, Jinglin Cui^{1,2}, Dongmei Wei^{1,2}, Ankur M. Sharma⁴, David L. Schwartz⁴, Weikuan Gu^{3,5*}  and Hong Chen^{1,2*}

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-kilovolt (kV) x-ray intraoperative radiotherapy (IORT) can achieve promising results compared with electron beam IORT (IOERT) and whether specific subgroups of patients with pT3 colon cancer may benefit from low-kV x-ray IORT.

Methods: We retrospectively reviewed 44 patients with pT3 LACC treated with low-kV x-ray IORT. Clinicopathologic characteristics were analyzed to identify patients that could potentially benefit from low-kV x-ray IORT. The Kaplan-Meier survival analysis was used to assess overall survival (OS) and progression-free survival (PFS). Correlation analysis was used to discover the association of multiple factors to the results of treatment represented by the values of OS and PFS.

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 was 82.8% and 82.1%, respectively. At median follow-up, no in-field failure within the low-kV x-ray IORT field had occurred. Locoregional and distant failure had occurred in 2 (5%) patients each. The rate of perioperative 30-day mortality was 0%, and the morbidity rate was 11%. Five patients experienced 7 complications, including 4 early complications (30 days) and three late complications (> 30 days) leading early and late morbidity rates of 9% and 7%, respectively.

Conclusion: Patients with LACC who had undergone an additional low-kV x-ray IORT can achieve encouraging locoregional control, PFS, OS, and distant control without an increase in short-term or long-term complications. Low-kV x-ray IORT can be considered as part of management in pT3 LACC.

Keywords: Low-kV x-ray, Intraoperative radiotherapy, Locally advanced colon cancer, pT3 colon cancer

* Correspondence: wgu@uthsc.edu; qszzywdm@163.com

³Department of Orthopedic Surgery and BME-Campbell Clinic, University of Tennessee Health Science Center, 956 Court Avenue, Memphis, TN 38163, USA

¹Center of Integrative Research, The First Hospital of Qiqihar, 30 Gongyuan Road, Longsha District, Qiqihar 161005, Heilongjiang, People's Republic of China

Full list of author information is available at the end of the article



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

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 was 12% and 33% in stage II and III patients, respectively [3, 4]. Multivariable analysis indicated that 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 leads 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 to an improvement of in-field and local control in selected patients [7–9]. 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 [10]. 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 [11, 12] with only a few studies describing outcomes for colorectal cancer patients using orthovoltage IORT [13–15]. At present, electronic brachytherapy is mainly recommended for breast cancer, endometrial, cervical cancer, or non-melanomatous skin cancers based on currently available data; however, electronic brachytherapy has emerged as a potential alternative for certain disease sites [16].

Currently recognized high-risk factors for recurrence of colon cancer after resection included poorly differentiated histology, lymphatic/vascular invasion, perineural invasion, or positive margins. To explore patients who would benefit from low-kV x-ray IORT 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-kV x-ray IORT among patients with pT3 LACC. We aim to evaluate whether low-kV x-ray IORT can benefit pT3 patients

not being inferior to the electron IOERT. Furthermore, we report complications associated with low-kV x-ray IORT.

Methods

The local institutional review board approved this study. We retrospectively analyzed clinical data of 44 primary colon cancer patients with T3N0-2 M0 diseases. They all received curative surgical resections and low-kV x-ray IORT 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). The operation of the INTRABEAM system was based on the use of an orthovoltage x-ray beam (photons with an energy of 50 kV). The diameters of spherical applicators ranged from 1.5 to 5.0 cm. They were used to enable accuracy and uniformities of dose distribution on the surface of the tumor bed. The dose adjustment is dependent on the proximity of surrounding risk structures (e.g., Peripheral nerve is dose-limiting for intraoperative radiotherapy, and patients receiving 15 Gy or more are at higher risk.) and the degree of adhesion of the tumor to the surrounding tissue during surgery. Higher doses (≥ 15 Gy) were delivered due to a close or positive margin. Our study was designed based on the experience of other institutes on the IORT dose administration [17–19].

The Kaplan-Meier survival analysis was used to assess overall survival (OS) and progression-free survival (PFS). Comparison was done using ANOVA analysis; *P* value less than 0.05 was considered as significant. Correlation analysis was used to discover the association of multiple factors to the results of treatment represented by the values of OS and PFS. For the *r* value equal or more than 0.7 or -0.7 , we treated it as significant correlation. For an *r* value between 0.35 and 0.69 or -0.35 and -0.69 , we regard it as existence of a correlation. When *R* values fell between 0 and 0.35 or 0 and -0.35 , we regarded these data as no correlation. Statistical analyses were performed with the 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 low-kV x-ray IORT 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 low-kV x-ray IORT is described in Table 2.

Median follow-up of patients was 20.5 months (range, 6.1–38.8 months). At the time of analysis, 38 (86%) of 44

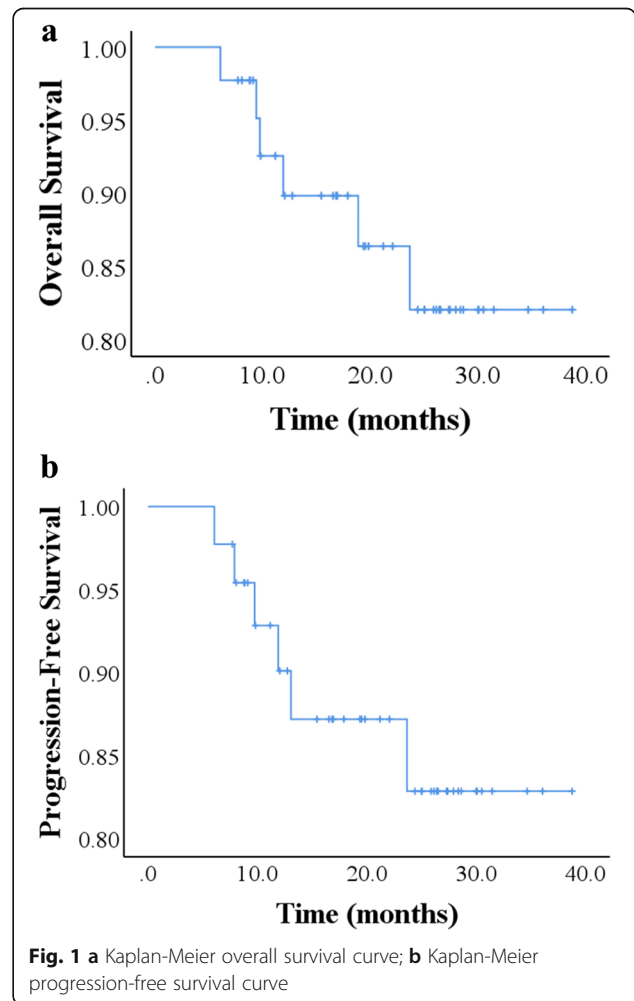
Table 1 Patient and tumor characteristics (n = 44)

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 Mean outcome and range by low-kV x-ray IORT characteristics

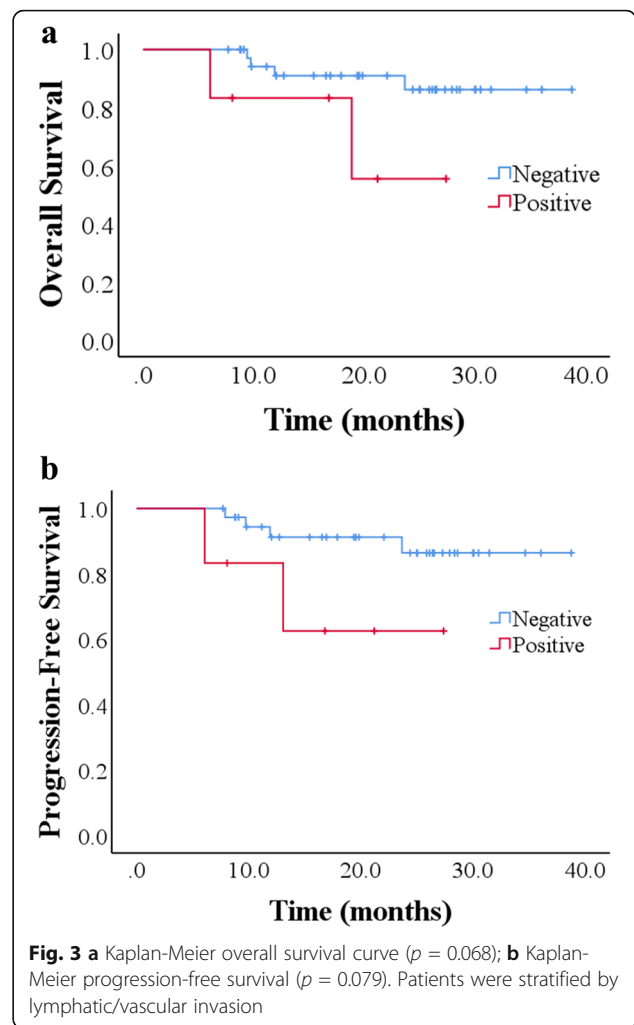
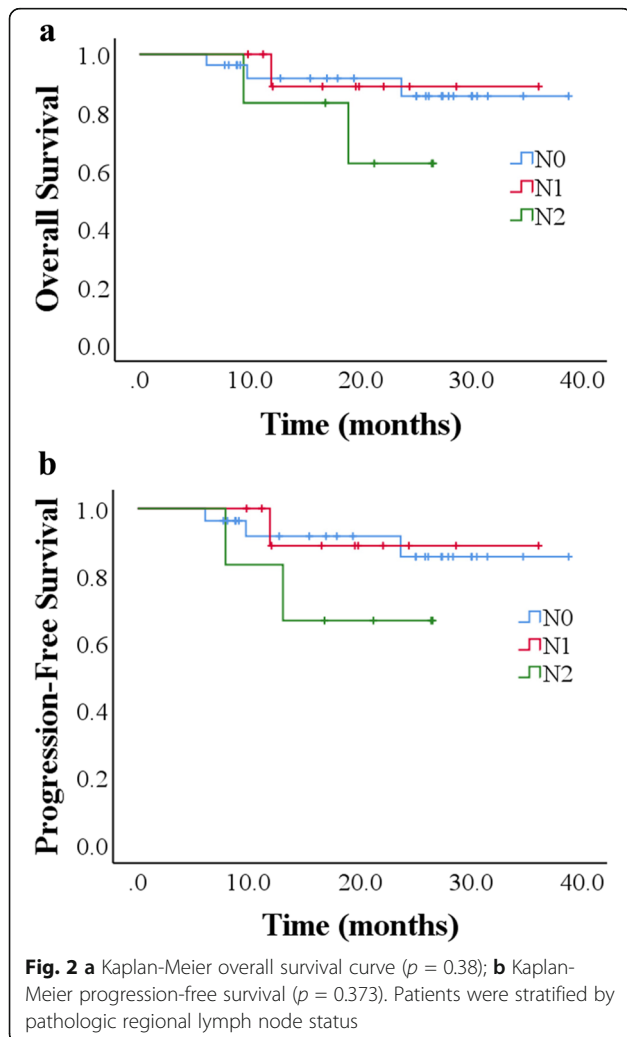
Characteristic	Number (%)
Applicator size (cm)	
Mean	3.5
Range	2.5–4.5
Dose (Gy)	
Mean	15
Range	10–18
Time (min)	
Mean	15.7
Range	9.2–26.6

patients were alive, and 6 (14%) patients were dead. The 3-year Kaplan-Meier of OS and PFS for the entire cohort was 82.1% and 82.8%, respectively (Fig. 1a, b). At median follow-up, no central failure within the low-kV x-ray IORT 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% for 2-year ($p = 0.373$) (Fig. 2a, b). 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 invasion positive (Fig. 3a, b). The margins of our patients were negative. Therefore, no additional statistical analysis was performed.

We have performed statistical analysis on the influence of several disease factors and treatment parameters to the PFS and OS. The factors include age, gender, tumor size, number of positive lymph nodes, total number of lymph nodes examined, N stage (all patients are T3M0, only N stage is different), perineural invasion, lymphatic/



vascular invasion, adjuvant chemotherapy, applicator size, IORT dose, and time of IORT (Supplemental Table 1). None of the r values are higher than 0.3 or lower than -0.3 . Our data showed that none of any of other factors has association with the OS or PFS.

Perioperative 30-day mortality was 0%, while 7 complications were occurring in 5 patients. Early complications (≤ 30 days) 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.

Discussion

Currently, there was very limited data available on IORT for colon cancer, especially for locally advanced colon cancer [20, 21]. A Russian literature showed their experience with 20 T3-4 colorectal adenocarcinoma patients

Table 3 Early and late complications after the combination therapy of surgery and IORT

Complication	Total (number)
Early (30 days)	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 day)	3
Peripheral neuropathy	0
Small bowel obstruction	3
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

using Intrabeam® PRS after curative surgery [17]. A dose of 14–17 Gy was distributed to the surface. Authors indicated the possibility of IORT to be used with curative resection with minimal early complications. For eradicating microscopic and subclinical disease after surgery, the surface dose ranged from 13 to 23 Gy according to a retrospective review of the Cleveland clinic experience for rectal cancer [18]. The study proved that Intrabeam® PRS, which provides IORT for patients with rectal cancer, seems to be a safe technique. This year, Sergey et al. reported that a single dose of 10–20 Gy for low-kV x-ray IORT was a valuable alternative for LACC patients in the absence of access to external beam radiotherapy (EBRT) [19]. Our IORT dose of 10–18 Gy was within the safe range based on the experience of other institutions. The final dose given is determined by the radiologist but requires, necessarily, a multidisciplinary collaboration with the surgeon and pathologist.

In our study, the present in-field local control was 100%. It was a very encouraging result. Additionally, based on current obtainable results, the 5-year local control was between 86 and 89% due to multimodality treatment including surgery, EBRT, and IOERT. Liska et al. found that the median time to LR was 21 months [5]. This was comparable to our median follow-up time. It was reasonable to infer that we achieved better locoregional control of 95%. Despite 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 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 the early report [21]. The 5-year distant failure was 12% according to the previous data, which is much higher than our 5% [20].

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 outcome consciousness, it is essential to assess complications associated with the combination of low-kV x-ray IORT and surgery. Our results suggest that patients treated with low-kV x-ray IORT had encouraging PFS and OS and without an increase in short-term or long-term complications in comparison to previous multimodality studies, whose acute complications were not more than 10% and long-term morbidities were between 37 and 53% [22]. 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 low-kV x-ray IORT time = 15.7 min, range 9.2–26.6 min). Our analysis indicated that the addition of low-kV x-ray IORT 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 [23, 24]. 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 suggested a potential role for low-kV x-ray IORT in the management of LACC, in particular, the setting of pT3 disease with pathologically involved lymph nodes and/or lymphovascular invasion positive patients. Our data showed that none of any of the other factors has association with the OS or PFS, confirming that OS and PFS in this study are the results from the treatment of low-kV x-ray, not from other sources. 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 the 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 [25]. Comparing with non-mucinous adenocarcinoma, mucinous adenocarcinoma was a distinct subgroup of colon cancer with a worse prognosis [26]. Thus, instead of affecting our current results, it indicated that we achieved quite good results.

Our study has several limitations which include it being a retrospective, non-randomized, single-center study with no control group. There may also be a 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 results from this study to a larger population.

Despite these limitations, our results suggest a potential role for low-kV x-ray IORT 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 low-kV x-ray IORT.

Conclusion

Patients with LACC who have undergone an additional low-kV x-ray IORT can achieve encouraging locoregional control, PFS, OS, and distant control without an increase in short-term or long-term complications. Low-kV x-ray IORT can be considered as part of management in pT3 LACC. Further long-term follow-up is still needed.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12957-020-01903-x>.

Additional file 1: Supplementary Table 1. The correlation r values of OS and PFS with disease factors.

Additional file 2. Data collection.

Abbreviations

LACC: Locally advanced colon cancer; kV: Kilovolt; 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

Acknowledgements

Not applicable.

Authors' contributions

LM: Manuscript draft and analysis data. JHQ, XLW, 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.

Funding

This work was partially supported by funding from The First Hospital of Qiqihar City (R073290127 to WG), Heilongjiang province, People's Republic of China; a Merit Award (I01 BX000671 to WG) from the US 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.

Availability of data and materials

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

Ethics approval and consent to participate

This retrospective analysis was approved by the Institutional Review Board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Center of Integrative Research, The First Hospital of Qiqihar, 30 Gongyuan Road, Longsha District, Qiqihar 161005, Heilongjiang, People's Republic of China. ²Affiliated Qiqihar Hospital, Southern Medical University, 30 Gongyuan Road, Longsha District, Qiqihar 161005, Heilongjiang, People's Republic of China. ³Department of Orthopedic Surgery and BME-Campbell Clinic, University of Tennessee Health Science Center, 956 Court Avenue, Memphis, TN 38163, USA. ⁴Department of Radiation Oncology, University of Tennessee Health Science Center, 920 Madison Avenue, Memphis, TN 38163, USA. ⁵Research Service 151, VA Medical Center, 1030 Jefferson Avenue, Memphis, TN 38104, USA.

Received: 3 March 2020 Accepted: 2 June 2020

Published online: 17 June 2020

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144:1941–53.
2. Haddock MG. Intraoperative radiation therapy for colon and rectal cancers: a clinical review. *Radiat Oncol*. 2017;12:11.
3. Willett CG, Tepper JE, Cohen AM, et al. Failure patterns following curative resection of colonic carcinoma. *Ann Surg*. 1984;200:685–90.
4. Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Dis Colon Rectum*. 2018;61:1016–25.
5. Liska D, Stocchi L, Karagkounis G, et al. Incidence, patterns, and predictors of locoregional recurrence in colon cancer. *Ann Surg Oncol*. 2017;24:1093–9.
6. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2007;69:504–11.
7. Nuyttens JJ, Kolkman-Deurloo I-KK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. *Int J Radiat Oncol Biol Phys*. 2004;58:106–12.
8. Terezakis S, Morikawa L, Wu A, et al. Long-term survival after high-dose-rate brachytherapy for locally advanced or recurrent colorectal adenocarcinoma. *Ann Surg Oncol*. 2015;22:2168–78.
9. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. *J Clin Oncol*. 2007;25:971–7.
10. Brady JT, Crawshaw BP, Murrell B, et al. Influence of intraoperative radiation therapy on locally advanced and recurrent colorectal tumors: a 16-year experience. *Am J Surg*. 2017;213:586–9.
11. Alektiar KM, Zelefsky MJ, Paty PB, et al. High-dose-rate intraoperative brachytherapy for recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys*. 2000;48:219–26.
12. Tom MC, Joshi N, Vicini F, et al. The American Brachytherapy Society consensus statement on intraoperative radiation therapy. *Brachytherapy*. 2019;18:242–57.

13. Kim HK, Jessup JM, Beard CJ, et al. Locally advanced rectal carcinoma: pelvic control and morbidity following preoperative radiation therapy, resection, and intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys.* 1997;38: 777–83.
14. Dubois JB, Gu SD, Hay MH, et al. Intra-operative radiation therapy (IORT) with 100 kV X photons. Experience on 170 patients. *Pathol Biol (Paris).* 1992; 39:884–5.
15. Daly ME, Kapp DS, Maxim PG, et al. Orthovoltage intraoperative radiotherapy for locally advanced and recurrent colorectal cancer. *Dis Colon Rectum.* 2012;55:695–702.
16. Tom MC, Hepel JT, Patel R, et al. The American Brachytherapy Society consensus statement for electronic brachytherapy. *Brachytherapy.* 2019;18: 292–8.
17. Lyadov K, SS KV, Krymskiy A. Improvement of curativity of video-assisted surgery for colorectal cancer due to intra-operative contact radiotherapy using the Intrabeam system. *Rev Cancer* 2008; 2008: 8.
18. Guo S, Reddy CA, Kolar M, et al. Intraoperative radiation therapy with the photon radiosurgery system in locally advanced and recurrent rectal cancer: retrospective review of the Cleveland clinic experience. *Radiat Oncol.* 2012; 7:110.
19. Potemin S, Kübler J, Uvarov I, et al. Intraoperative radiotherapy as an immediate adjuvant treatment of rectal cancer due to limited access to external-beam radiotherapy. *Radiat Oncol.* 2020;15:11.
20. Schild SE, Gunderson LL, Haddock MG, et al. The treatment of locally advanced colon cancer. *Int J Radiat Oncol Biol Phys.* 1997;37:51–8.
21. Mathis KL, Nelson H, Pemberton JH, et al. Unresectable colorectal cancer can be cured with multimodality therapy. *Ann Surg.* 2008;248:592–8.
22. Cantero-Munoz P, Urien MA, Ruano-Ravina A. Efficacy and safety of intraoperative radiotherapy in colorectal cancer: a systematic review. *Cancer Lett.* 2011;306:121–33.
23. Quere P, Facy O, Manfredi S, et al. Epidemiology, management, and survival of peritoneal carcinomatosis from colorectal cancer: a population-based study. *Dis Colon Rectum.* 2015;58:743–52.
24. Huh JW, Lee JH, Kim HR, et al. Prognostic significance of lymphovascular or perineural invasion in patients with locally advanced colorectal cancer. *Am J Surg.* 2013;206:758–63.
25. Saclarides TJ, Szeluga D, Staren ED. Neuroendocrine cancers of the colon and rectum. Results of a ten-year experience. *Dis Colon Rectum.* 1994;37: 635–42.
26. Reynolds IS, O'Connell E, Fichtner M, et al. Mucinous adenocarcinoma of the colon and rectum: a genomic analysis. *J Surg Oncol.* 2019;120:1427–35.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

