Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Technical note

Pre-operative radiotherapy to improve local control and survival in rectal cancer optimal time intervals between radiation and surgery

Antonio Cassio Assis Pellizzon

Department of Radiation Oncology, AC Camargo Cancer Center, Rua Prof Antonio Prudente, 211, 01509-200 Sao Paulo, Brazil

ARTICLE INFO

Article history:
Received 23 January 2018
Accepted 13 September 2018
Available online 10 October 2018

Dear Editor,

The addition of radiotherapy to surgery in patients with operable rectal cancers has been studied in trials using pre- or post-operative intent.[1,2] When associated to total mesorectal excision, preoperative radiotherapy (pre-RT) can reduce the risk of local recurrence after surgery by 60%.[3] Conventionally fractionated pre-RT is usually given in 25–28 daily fractions of 1.8–2.0 Gy and it is not expected to cause an important tumor regression, as it does not became maximal until several months.[4] Most often pre-RT is used in combination with chemotherapy (pre-CRT).

An alternative for operable tumors is a short-course of pre-RT schedule consisting of 5 daily fractions of 5 Gy (pre-sRT) given without chemotherapy. However, the optimal fractionation and timing of surgery in relation to pre-RT is still controversial.[5] The primary intent of pre-sRT is to reduce local failure (LF), and since there is no need for tumor regression, surgery can be performed immediately after or within 3–5 weeks from the last radiation fraction.[6]

The division of rectal cancers into three pre-treatment groups, so called "good–bad–ugly concept", to help in the decision of the initial therapy, was suggested by Blomqvist and Glimelius.[7] The good (early) tumors have a low risk of local failure and they should not be considered for pre-RT. For the bad (intermediate) tumors, including the locally advanced tumors, mostly cT3 without threatened or involved mesorectal fascia, and ugly (advanced) groups, including here cT3 with mesorectal fascia involvement and most cT4, the risk of LF after surgery alone is above 8–10% and more than 25%, respectively. These risks can be reduced by 50–70% with pre-RT or pre-CRT. It is also suggested that the ugly group is the only one in which tumor regression shall be required to achieve a lower probability of LF after surgery.[8]

Retrospective analyses of randomized trials have not detected any differences in tumor control when there was a weekend-break during the pre-sRT course.[9] Subgroup analyses of the Dutch,[9] Stockholm I and II[10] and the total mesorectal excision studies[11] endorsed that surgery after pre-sRT should be performed within no more than 11 days from the start of radiation, or otherwise delayed for several weeks in order to minimize surgical morbidity and mortality. It is important to note that down-staging can also be seen when the interval between pre-sRT and surgery is longer than 10 days, in special

E-mail address: acapellizzon@accamargo.org.br
https://doi.org/10.1016/j.rpor.2018.09.008

4–5 weeks.[12,13] Other studies have published similar conclusions, but pointing that increased morbidity is seen when surgery is performed between 10 and 20 days after the first pre-sRT fraction.[14–16]

The findings of the Stockholm III, a multicentre, randomized trial, with the primary endpoint time to LF and mostly with intermediate-risk patients were recently published. A total of 385 patients entered a three arm randomization between October 1998 and January 2013. From the total, 129 patients were assigned to pre-sRT and surgery after 1–7 days, 128 patients to pre-sRT delaying surgery to after 4–8 weeks, and 128 other patients to conventional RT with 50 Gy given in 25 fractions and delay of 4–8 weeks to surgery. The additional 455 patients entered a two arm randomization, with 228 randomly assigned to pre-sRT and surgery 1 to 7 days after that, and 227 to pre-sRT with delay to surgery. No significant difference between the three different pre-sRT regimens was observed; however, the interval between pre-sRT and delayed surgery group was not longer than 8 weeks in 75% of patients, thus, the conclusions must not be generalized for patients treated at longer intervals. On the other hand, surgery after 4–8 weeks of the end of pre-sRT showed a significant lower frequency of postoperative complications (HR: 0.61 [95% CI: 0.45–0.83], $p = 0.001$).[17] An interim analysis of this trial also showed that a higher number of patients (11.8% versus 1.7%, $p = 0.001$) achieved a pathological complete response after pre-sRT with delayed surgery, denoting that the watch and wait policy must be in the scope of further investigations.[18]

The question if a delay after the end of pre-sRT to surgery changes the oncologic outcome and complication rates is still open, but we can conclude that for selected patients conventional or short course pre-operative RT have similar local control and complication rates, with the difference that conventional course prolongs the treatment time substantially. Delaying surgery not more than 8 weeks from the end of radiation seems to be safe, if an interval between 10 and 20 days from RT is given.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;**336**(14):980–7.
2. Krook JE, Moertel CG, Gunderso LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991;**324**(11):709–15.
3. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;**373**(9666):811–20.
4. Dhadda AS, Zaitoun AM, Bessell EM. Regression of rectal cancer with radiotherapy with or without concurrent capecitabine – optimising the timing of surgical resection. *Clin Oncol* 2009;**21**(1):23–31.
5. Glimelius B. Optimal time intervals between pre-operative radiotherapy or chemoradiotherapy and surgery in rectal cancer? *Front Oncol* 2014;**4**:50.
6. Glimelius B, Graffman S, Påhlman L, Rimsten Å, Wilander E. Preoperative irradiation with high-dose fractionation in adenocarcinoma of the rectum and rectosigmoid. *Acta Radiol Oncol* 1982;**21**:373.
7. Blomqvist L, Glimelius B. The 'good', the 'bad', and the 'ugly' rectal cancers. *Acta Oncol* 2008;**47**(1):5–8.
8. Ludmir EB, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: an emerging option. *Cancer* 2017, http://dx.doi.org/10.1002/cncr.30600 [Epub ahead of print].
9. van den Broek CB, Vermeer TA, Bastiaannet E, Rutten HJ, van de Velde CJ, Marijnen CA. Impact of the interval between short-course radiotherapy and surgery on outcomes of rectal cancer patients. *Eur J Cancer* 2013;**49**(15):3131–9.
10. Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. *Radiother Oncol* 2009;**93**(2):293–7.
11. Marijnen CAM, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002;**3**: 817–25.
12. Graf W, Dahlberg M, Mazloum-Osman M, Holmberg L, Påhlman L, Glimelius B. Short-term preoperative radiotherapy results in down staging of rectal cancer: a study of 1316 patients. *Radiother Oncol* 1997;**43**:133–7.
13. Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer – treatment results at 5-year follow-up. *Langenbecks Arch Surg* 2012;**397**(5):801–7.
14. Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. *Radiother Oncol* 2009;**93**(2):293–7, http://dx.doi.org/10.1016/j.radonc.2009.08.034.
15. Hartley A, Giridharan S, Gray L, Billingham L, Ismail T, Geh JI. Retrospective study of acute toxicity following short-course preoperative radiotherapy. *Br J Surg* 2002;**89**(7):889–95, http://dx.doi.org/10.1046/j.1365-2168.2002.02136.x.
16. Hartley A, Giridharan S, Srihari N, McConkey C, Geh JI. Impaired postoperative neutrophil leucocytosis and acute complications following short course preoperative radiotherapy for operable rectal cancer. *Eur J Surg Oncol* 2003;**29**(2):155–7, http://dx.doi.org/10.1053/ejso.2002.1364.
17. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3 non-inferiority trial. *Lancet Oncol* 2017;**18**(3):336–46, http://dx.doi.org/10.1016/S1470-2045(17)30086-4.
18. Pettersson D, Lörinc E, Holm T, et al. Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. *Br J Surg* 2015;**102**(8):972–8, http://dx.doi.org/10.1002/bjs.9811, discussion 978.