

## Neoadjuvant radiotherapy dose escalation for locally advanced rectal cancers in the new era of radiotherapy: A review of literature

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### Abstract

#### BACKGROUND

The standard treatment of locally advanced rectal cancers (LARC) consists on neoadjuvant chemoradiotherapy followed by total mesorectal excision. Different data in literature showed a benefit on tumor downstaging and pathological complete response (pCR) rate using radiotherapy dose escalation, however there is shortage of studies regarding dose escalation using the innovative techniques for LARC (T3-4 or N1-2).

#### AIM

To analyze the role of neoadjuvant radiotherapy dose escalation for LARC using innovative radiotherapy techniques.

#### METHODS

revised version of manuscript.

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In December 2020, we conducted a comprehensive literature search of the following electronic databases: PubMed, Web of Science, Scopus and Cochrane library. The limit period of research included articles published from January 2009 to December 2020. Screening by title and abstract was carried out to identify only studies using radiation doses equivalent dose 2 Gy fraction (EQD2)  $\geq$  54 Gy and Volumetric Modulated Arc Therapy (VMAT), intensity-modulated radiotherapy or image-guided radiotherapy (IGRT) techniques. The authors' searches generated a total of 2287 results and, according to PRISMA Group (2009) screening process, 21 publications fulfil selection criteria and were included for the review.

## RESULTS

The main radiotherapy technique used consisted in VMAT and IGRT modality. The mainly dose prescription was 55 Gy to high risk volume and 45 Gy as prophylactic volume in 25 fractions given with simultaneous integrated boosts technique (42.85%). The mean pCR was 28.2% with no correlation between dose prescribed and response rates ( $P$  value  $\geq$  0.5). The R0 margins and sphincter preservation rates were 98.88% and 76.03%, respectively. After a mean follow-up of 35 months local control was 92.29%. G3 or higher toxicity was 11.06% with no correlation between dose prescription and toxicities. Patients receiving EQD2 dose  $>$  58.9 Gy and BED  $>$  70.7 Gy had higher surgical complications rates compared to other group ( $P$  value = 0.047).

## CONCLUSION

Dose escalation neoadjuvant radiotherapy using innovative techniques is safe for LARC achieving higher rates of pCR. EQD2 doses  $>$  58.9 Gy is associated with higher rate of surgical complications.

**Key Words:** Rectal cancer; Radiotherapy; Volumetric Modulated Arc Therapy; Image-guided radiotherapy; Intensity-modulated radiotherapy; Neoadjuvant radiotherapy

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**Core Tip:** We analyzed the role of neoadjuvant radiotherapy dose escalation for locally advanced rectal cancers (LARC) using innovative radiotherapy techniques. A comprehensive literature search was performed on electronic database with a period limit from January 2009 to December 2020. According to PRISMA Group (2009) screening process only studies using equivalent dose 2 Gy fraction (EQD2)  $\geq$  54 Gy and Volumetric Modulated Arc Therapy, image-guided radiotherapy or image-guided radiotherapy techniques were included for the review. Neoadjuvant radiotherapy dose escalation using innovative techniques is safe for LARC with acceptable acute toxicity, achieving higher pathological complete response compared to standard treatment. EQD2 doses  $>$  58.9 Gy with a BED  $>$  70.7 Gy was associated with higher rate of surgical complications.

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## INTRODUCTION

The incidence of colorectal cancer (CRC) from 2020 declined rapidly among screening-aged individuals, but increased in adults aged younger than 55 years old. CRC represent the third most common cancer and often is diagnosed in an advanced stage. Despite an improve of survival rate in patients with CRC in last years, CRC remain the second case of death in the United States[1].

The standard treatment of locally advanced rectal cancers (LARC) consists on neoadjuvant chemoradiationtherapy (CRT) followed by total mesorectal excision[2-3].

Neoadjuvant radiotherapy improve local control of LARC (T3-4 or N1-2 disease) and subsequently can influence survival rate improving overall survival (OS). The advantages of neoadjuvant radiotherapy were recognized from 1997 by the Swedish Rectal Cancer Study Group, which found a significant reduction in local recurrence rates in 1168 patients analyzed[4].

These findings were confirmed afterwards by other randomized studies, consolidating the important role of neoadjuvant radiotherapy treatment in locally advanced rectal cancer[5-18].

The standard neoadjuvant radiotherapy treatment in rectal cancer consist in a total dose of 45-50.4 Gy delivered in 25-28 daily fractions[2,3].

Typically, up to the 2010s the main radiotherapy technique used for the treatment of rectal cancer was three-dimensional CRT (3DCRT)[5-9].

The clinical outcome after 3DCRT is largely dependent on tumor response and it is estimate that overall 15% of patients experience a pathological complete response (pCR) at the standard radiation dose[4-10].

It is also known that a higher dose to tumor consists in a better tumor rate response, but this could often lead to a higher dose in surrounding tissue and a risk of increased side effects and surgical complications[11-18].

In the last few decades there was a technological improvements in radiotherapy treatment with the introduction of new innovative techniques such as intensity-modulated radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and image-guided radiotherapy (IGRT)[19-21].

Using this innovative radiotherapy inverse planning techniques is possible to deliver a higher dose to the target avoiding surrounding tissue improving tumor response rate and disease control with the reduction of acute and late toxicity[22-26].

For these reasons in last years 3DCRT has been abandoned and replaced by new innovative techniques for the treatment of rectal cancer[22-57].

Different data in literature showed a benefit in terms of tumor downstaging and complete response rate of radiotherapy dose escalation, however there are not a lot of studies regarding the dose escalation using the innovative techniques such as IMRT, VMAT and IGRT for the treatment of LARC.

The aim of our review was to analyze the role of neoadjuvant radiotherapy dose escalation for the treatment of locally advanced rectal cancer, using innovative radiotherapy techniques.

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## MATERIALS AND METHODS

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### Search strategy

In December 2020 we conducted a comprehensive literature search of the following electronic databases: PubMed, Web of Science, Scopus and Cochrane library. The databases research was made with a combination of following keywords: "neoadjuvant" AND "radiotherapy" AND "rectal" AND "cancer" in title and abstract fields of each databases research. The limit period of research included the articles published from January 2009 to December 2020.

### Study selection

We included in this review randomized trials, non-randomized trials, prospective studies, retrospective studies and case series in patients affected by rectal cancer underwent neoadjuvant radiotherapy treatment (with or without chemotherapy), using a radiotherapy dose escalation and innovative technique. Single case reports and small case series with less than 10 cases were excluded. Moreover, we excluded studies reporting on patients with diagnoses different from rectal cancer, palliative treatment, if radiotherapy ( $\pm$  chemotherapy) was given with adjuvant intent or exclusive intent.

In case of duplicated datasets (*e.g.*, multiple articles from the same study group or institution, related to the same treatment on the same cohort of patient), only the work with the longest follow-up and the greatest number of patients were included.

Screening by title and abstract was carried out to identify only studies using a total radiation equivalent dose 2 Gy fraction (EQD2)  $\geq$  54 Gy in patients affected by LARC underwent neoadjuvant radiotherapy.

For each study following exclusion criteria were applied: (1) Studies using 3DCRT radiotherapy delivering technique, brachytherapy or proton beam radiotherapy were excluded; (2) Studies of previously irradiated patients, or recurrent disease patients; (3)

Studies that did not routinely schedule definitive surgery (*i.e.*, palliative-intent or watch-and-wait strategies); (4) Studies using short-course regimen neoadjuvant radiotherapy; (5) Total dose of pelvic irradiation lower than standard EBRT dose (< 45 Gy); (6) Studies using brachytherapy boost; (7) Case report; (8) Case series with a number of patients < 10; (9) Review or letter to editor; and (10) Age of study population < 18 years old.

The inclusion criteria for each study were: (1) Clinical investigations using innovative radiotherapy technique such as IMRT, VMAT or IGRT; (2) Clinical investigations using long-course radiotherapy and a total dose of pelvic irradiation  $\geq$  45 Gy; (3) Clinical investigations with age of study population  $\geq$  18 years old; (4) Clinical investigations with radiotherapy dose escalation of EQD2  $\geq$  54 (using SIB, concomitant or sequential RTE boost); and (5) Studies which radiotherapy treatment was given with neoadjuvant intent and routinely scheduled definitive surgery.

### Data extraction and analysis

Data extraction was performed by one reviewer and checked by a second reviewer. Subsequently all papers obtained after database research were selected by two reviewers. All Screening process was performed according to PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses. In detail, the first screening was performed by title reading of each reviewer independently. The second screening was performed after abstract reading of each article by each reviewer. Finally, after the first and second selection by title and abstract reading, full text of all retrieved papers was reviewed suitable articles were selected for this review according to selection criteria established research process. After carefully selection of articles suitable for the review, we obtained the following information from each report: author identification, year of publication, medical center, study design characteristics, study population, number of patients, age, sex, histological diagnoses, radiotherapy treatment, total dose, dose for fraction, delivered dose, chemotherapy treatment, sphincter preservation rate, R0 resection rate, local control, post-surgical complications, anastomotic leakage, toxicity, grading scale of toxicity used for each study, and follow-up time. In [Figure 1](#) is showed the flow chart of systematic literature search process according to PRISMA group guidelines. Late Radiation Morbidity Scoring Schema of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC)[30] and NCI Common Terminology Criteria for Adverse Events (CTCAE) scale version 4 and 5 were used for description of late and acute toxicities[31,32].

### Statistical analysis

All the data extracted from the selected review were processed in excel software (Microsoft office 2010 professional of © Microsoft company). At first, an exploratory phase of data was carried out; the categorical data were described by frequency and percentage, whereas continuous data by mean, median and range. If necessary, after data exploration, analysis and calculation of frequencies, median and range was performed due to description of end-points of the review.

All analyses were performed using excel software and the Statistical Package for Social Science (SPSS) version 22 technology.

## RESULTS

The authors' searches generated a total of 2287 results. Through a process of screening 21 publications fulfil selection criteria and were selected for the review. [Figure 1](#) shows in detail the flowchart of the review literature search process.

### Radiotherapy treatment

Regarding the device used for radiotherapy treatment, in majority of studies (85.7%) the radiotherapy treatment was performed by a standard LINAC device and only in 3 studies (14.3%) radiotherapy treatment was performed with Tomotherapy machine.

The main radiotherapy technique used for the treatment of LARC consisted in VMAT technique (47.6%), followed by IMRT technique (38.1%) and in three studies were used both VMAT and IMRT techniques (14.3%).

Due to avoid target missing, organ motion and set-up errors, an IGRT modality for radiotherapy dose delivery was used in 74.12% of studies by a CBCT/MVCT (87.3%) or EPID (13.3%) image guided modalities. In remaining 25.88% studies set-up verify was performed weekly or twice a week according to protocol centre.

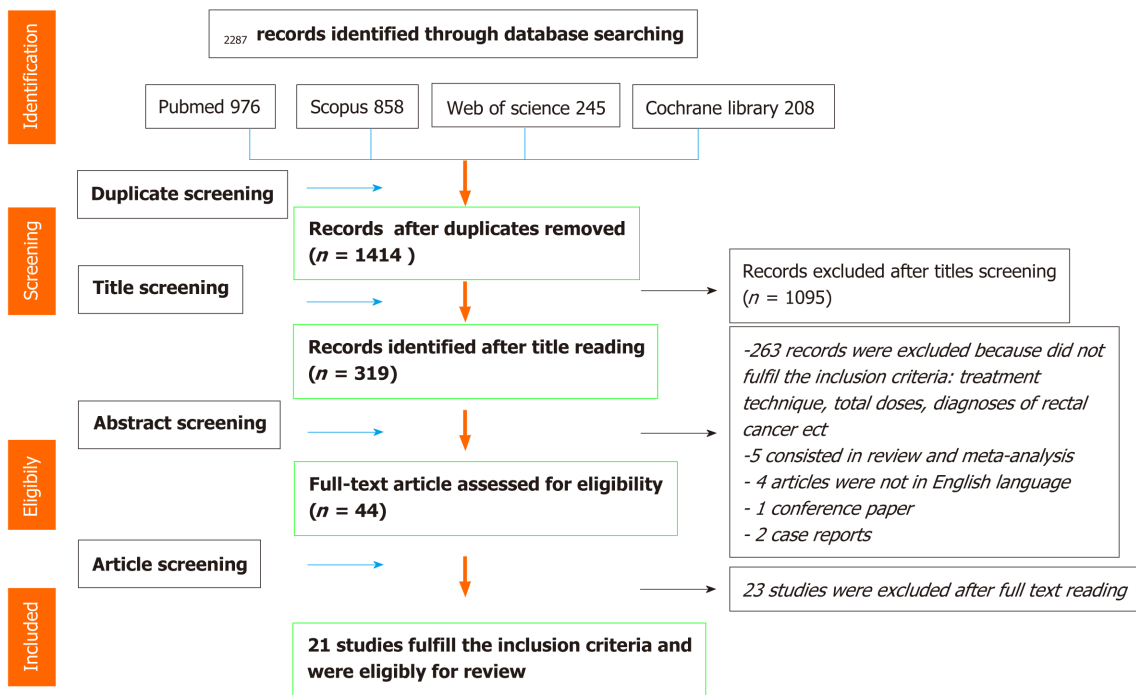


Figure 1 Flow chart of systematic literature search process according to PRISMA group guidelines.

We found a heterogeneity regarding total dose and dose for fraction dose used between the studies analyzed for this review for treatment of LARG for both prophylactic to the pelvis and as a boost dose escalation.

The main dose for fraction used for the treatment of LARC was 55 Gy to high risk volume and 45 Gy as prophylactic volume in 25 fractions (42.85% of studies) delivered with SIB technique (Table 1).

In detail, the radiotherapy EQD2 dose delivered as prophylactic doses to the pelvis varied in a range from 45-55.8 Gy (mean 48 and median 46 Gy) with a fractionation range from 1.8 to 3 Gy for fraction. High risk volume (T or N +) was treated with a total EQD2 dose (alfa/beta 10) from 54 Gy to 66.3 Gy (mean 56.4; median 55.9 Gy) and a calculated BED (alfa/beta 10) with a range wide from 63.7 Gy to 76.2 Gy (mean 70 Gy; median 67.1 Gy).

Table one shows treatment characteristics with respective outcomes for each study included in the review.

### CR, down staging, R0 and sphincter preservation

The complete response rate was reported in twenty studies selected (95.24%) and the mean pCR was 28.2%, with a range wide from 17% to 59%. In a regression analysis there was not any correlation between dose prescribed and pCR ( $P$  value = 0.234).

Regarding T down staging rate it was reported in seventeen of twenty-one studies analyzed (80.95%) with a mean of 66.96% (range 55%-97.7%). Lymph node down staging rate was described by ten authors and the mean of N down staging resulted 66.67%, with a range wide from 10.7% to 94%.

In all 16 studies which reported R0 margins rate was observed an excellent negative margins rate with a mean of 98.88% (range 95%-100%).

Finally, sixteen of twenty-one analyzed studies described sphincter preservation and the mean rate was 76.03% with a range wide from 36.8% to 100%. There was not any correlation between down staging, R0, sphincter preservation and total EQD2 dose prescribed to both prophylactic pelvis and as a boost dose escalation to high risk volumes in regression analyses ( $P$  value > 0.05).

### Survival outcomes

Unfortunately survival rates often were not endpoints of studies and for this reasons were analyzed only by few authors. Local control was reported by thirteen authors (61.9%) and resulted 92.29% (range 68.6%-100%) after a mean follow-up of 35 mo. As expected we found lower rates of PFS (mean 74.16%; range 57-100) and was described by 13 authors.



**Table 1 Characteristics and outcomes of studies included in the review**

Ref.	Nr of pts	Mean age (range)	Prescription dose / number of fraction		CR rate (%)	Local control (%)	R0 rate (%)	Sphincter preservation rate (%)	Toxicity (%)		Surgery complications (% any grade)
			Boost dose	Prophylactic dose					G2	G3 OR >	
Alongi <i>et al</i> [37], 2016	40	69 (47-83)	60/30	54/30	17.5	100	100.0	92.5	GI 15, GU 12.5	0	10.0
Couwenberg <i>et al</i> [38], 2020	51	64.5 (55-69)	50/25, + 15/5	50/25	35.9	-	-	56.3	GI 20, GU 7.8, Sk 9.4	GI 9.3, GU 1.6	26.4
Bertocchi <i>et al</i> [39], 2020	31	68.7 (47-81)	60/30	50.4/30	22.6	-	100.0	93.5	GI 16.1, GU 19.3	0	41.9
Engels <i>et al</i> [40], 2014	57	69 (32-85)	55.2/23	46/23	-	97	-	-	GI 12.2, GU 12.2, Sk 36.8	14	--
Hernando-Requejo <i>et al</i> [41], 2014	74	61.7 (33-80)	57.6/23	46/23	30.6	100	97.2	77.7	GI 28.4, GU 9.5, Sk 21.6	GI 9.5, GU 5.4, Sk 2.7	25.7
Zhu <i>et al</i> [42], 2014	78	54 (30-76)	55/25	50/25	23.7	85.4	100.0	36.8	GI 14.1, Sk 20.5	GI 10.3, Sk 17.9	17.1
Wang <i>et al</i> [43], 2019	60	56 (22-75)	55/25	50/25	28.1	90.6	100.0	38.6	/	25	24.6
Lima <i>et al</i> [44], 2019	11	45.9 (28-59)	54/30		28.5	-	-	-	40	20	-
Jankarashvili <i>et al</i> [45], 2019	22	59 (36-84)	57.5/23	46/23	59.1	-	100.0	-	GI 40.9, GU 22.7, Sk 45.5	GI 0GU 13.6, Sk 9.1	-
Parikh <i>et al</i> [46], 2019	44	67 (47-84)	55.8/31		40.9	93.2	-	100.0	6.8	0	43.0
Passoni <i>et al</i> [47], 2013	25	59 (37-77)	27.6/12 + 18/6	41.4/18	30.0	100	96.0	87.0	-	GI 12	26.0
Picardi <i>et al</i> [48], 2016	18	62 (39-79)	57.5/25	45/25	25.0	100 (1y), 68.6 (3y), 68.6 (5y)	100.0	62.5	-	44.4	-
Spatola <i>et al</i> [49], 2019	62	61.5 (36-84)	45/25 + 9/6	45/25	19.0	96.5	100.0	85.0	-	GI 10, GU 0, Sk 3	5.0
Liu <i>et al</i> [50], 2020	85	80 (75-85)	55/25	45-50/25	21.4	83.9		78.6	-	GI 5.2, GU 1.8	12.5
Yamashita <i>et al</i> [51], 2017	60	66 (44-88)	55/25	45/25	17.0	90	100.0	88.0	GU 49	0	3.0
Yang <i>et al</i> [52], 2019	26	55 (18-75)	58.75/25	50/25	32.0		100.0	60.0	GI 30.8, Sk 7.7	Sk 7.7	8.0
Alsuhaibani <i>et al</i> [53], 2018	79	59.7 (28-102)	55/25	45	20.0	-	100.0	72?	-	0	-
Chiloiro <i>et al</i> [54], 2019	22	64 (41-86)	55/25	45	27.3	-	100.0	89.5	GU 0, GI 40	GI 22.7	-
Lupattelli <i>et al</i> [55], 2016	60	64 (29-84)	57-55-54/25	45	27.8	-	96.0	85.7	-	10.5	18.1
Tey <i>et al</i> [56], 2017	20	-	55/25	45	35.0	100	95.0	85.0	0	5	0.0
Zhao <i>et al</i> [57], 2017	141	59 (50-67)	55/25	45-30	22.7	95.5	97.9	80.0	-	GI 7.8	10.6

Unfortunately, OS was reported by only 7 authors (33%) and three years median OS

There was not any correlation between calculated EQD2 dose prescription and survival outcomes (LC, PFS OS, and CSS) in regression analyses ( $P$  value  $> 0,05$ ).

### **Late and acute toxicity**

All studies reported the rates of acute toxicity which consisted in GU, GI or skin toxicity. According to RTOG/CTCAE scale the mean  $\geq$  G3 toxicity was 11.06% (range 0-44%). The mean G2 toxicity resulted 27.08% with a range wide from 6.8% to 49%. There was not any correlation between dose prescription and toxicities.

### **Surgical complications and anastomotic leakage**

Overall the surgical complications and anastomotic leakage were described by fifteen authors. The mean surgical complications rate was 15.51% with a range wide from 0% to 41.9%. In patients receiving a EQD2 doses  $< 58.9$  Gy with a BED  $< 70.7$  Gy the surgical complications rate were lower (mean 12.01%) compared to patients receiving a EQD2 dose  $> 58.9$  Gy with a BED  $> 70.7$  (mean 22.4%). This differences resulted statistically significant in a linear regression analyses ( $P$  value = 0.047) (Figure 2).

Finally, the mean of anastomotic leakage or fistula was 4.26 % with a range wide from 0% to 29%. There was not any correlation between dose prescription and anastomotic leakage at the regression analysis ( $P$  value = 0.354).

## **DISCUSSION**

To our knowledge this is the first review that systematically examine outcomes of LARC underwent neoadjuvant radiotherapy dose escalation with inverse-planning modality and innovative radiotherapy technique in new era of radiotherapy.

The benefit of achievement a pathological complete response in both disease-free and OS has been demonstrated[21-23].

The results of our review showed a high rates of pCR (28.2%), tumor down staging (66.96%) and R0 margins rate using a dose escalation EQD2 (alfa/beta 10 Gy)  $\geq 54$  Gy with innovative radiotherapy techniques and inverse planning modality.

It is known that in previously controlled trial the pCR rate of standard neoadjuvant RT-CT for the treatment of LARC is approximating 15%[2-11].

This outcomes are higher even compared to previously reviews and meta-analysis in patients with LARC underwent neoadjuvant and dose escalation radiotherapy with 3DCRT techniques.

In fact, in a previous systematic review and meta-analysis in 2014 Burbach *et al*[24] reported a pCR of 20.4% in studies using 3DCRT technique and escalating dose to  $\geq 60$  Gy. Unfortunately, authors did not report the R0 resection rate and sphincter preservation. Resectability rate and pooled acute grade 3 toxicity were 89.5% and 10.3%, respectively.

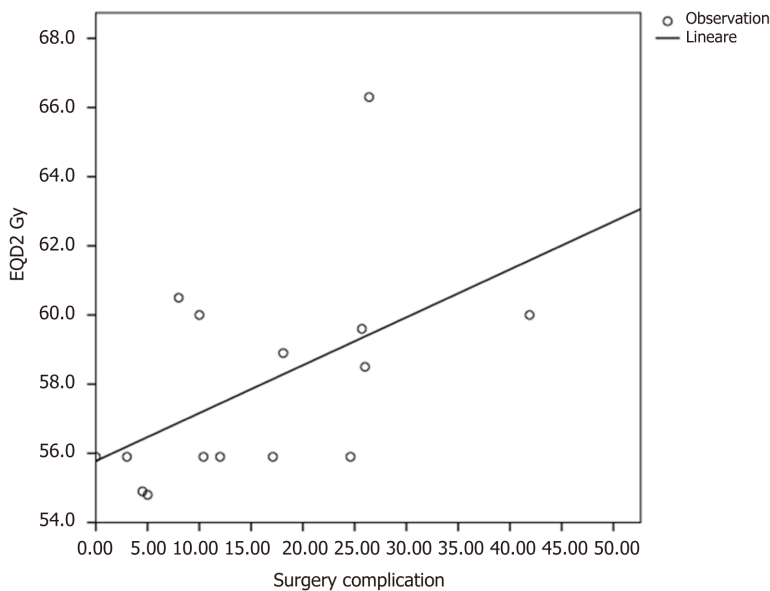
An interesting systematic review and meta-analysis was performed recently by Hearn *et al*[25] which analyzed dose escalation for the treatment of neoadjuvant LARC, screening studies for radiotherapy prescription dose  $> 54$  Gy. In this meta-analysis authors reported a pool estimated of pCR of 24.1% in all studies and 25.7% in inverse planning studies without a statistically differences between techniques. Moreover, as reported in results of our review, authors did not found any factor significantly related with pCR rates in regression analysis.

Nevertheless, pCR rates using dose escalation in our review and results of above reviews are significantly higher compared to standard neoadjuvant RT-CT doses for the treatment of LARC[2-11].

Different authors analyzed factors improving pCR in patients with LARC underwent neoadjuvant RT-CT.

Appelt *et al*[36] described, in a predictive model study, a highly significant dose-response relationship for pCR after neoadjuvant external-beam radiation therapy and brachytherapy in locally advanced rectal cancer for tumor dose levels in the range of 50.4-70 Gy. A correlation between increasing rates of pCR with escalating radiotherapy doses was confirmed in a recent meta-analysis by Teo *et al*[26] in a phase 2 neoadjuvant treatment intensification trials.

Furthermore, some authors reported a correlation between pCR and extension of surgical interval. The evidence for longer surgical intervals evolved in last years and often is recommended a minimal surgical interval of 8 wk after neoadjuvant RT-CT treatment[27,28,29]. However, in GRECCAR-6 randomized multicenter trial 265 patients were treated with standard nCRT and underwent surgical treatment. There was not a benefit regarding pCR rate and surgical interval between to arms (7 wk vs 11



**Figure 2** Linear regression analyses between equivalent dose 2 Gy fraction and surgical complications. EQD2: Equivalent dose 2 Gy fraction.

wk)[29].

The data in literature regarding a correlation between chemotherapy escalation and pCR are controversial due to some authors described a benefit improved pCR rates with the addition of concurrent oxaliplatin and/or bevacizumab compared with fluoropyrimidine treatments alone[33,34] and other studies did not show any benefit in terms of pCR, even reporting higher incidences of acute toxicity[33].

According to RTOG/CTCAE scale in our review the mean  $\geq$  G3 toxicity was 11.06% and, differently of Hearn *et al*[25] review, we did not find any correlation between EQD2 (alpha/beta 10 Gy) dose prescription and  $\geq$  G3 toxicities.

These data in literature support that the use of innovative techniques and inverse-planning techniques lead to delivery an higher dose to tumour avoiding the dose to surrounding tissue with the reduction of acute and late toxicity. For these reasons in last years a moderately dose-escalated treatment with inverse-planning techniques is often used and reported by different authors with higher pCR and acceptable acute and late toxicities[48-56].

Additionally, a real benefit of radiotherapy dose escalation with innovative technique achieving pCR can be considered in patients with low, very-low rectal cancer candidate to organ preservation with watch and wait strategy due to avoid definitive stoma. This benefit can be extended to cases of low rectal distal T2N0 disease, where minimally invasive surgical techniques may be viable to reduce procedural complications and improve sphincter preservation as reported by INTERACT protocol[35].

In our review R0 rates were higher (98.88%) in confront of Hearn *et al*[25] results (90.7%). This finding can be explain because we included only studies which used inverse-planning technique, in fact, in Hearn *et al*[25] meta-analyses was reported a significantly positively correlation between the use of inverse planning techniques and R0 rate in univariate regression analysis.

Moreover, we found a surgical complications rate comparable with other tails in literature which used standard doses of RT treatment (mean 15.51%) with a range wide from 0% to 41.9%. Some authors described an increase surgical complications with radiotherapy boost[39,43,46]. However, the data were heterogeneous due to radiotherapy techniques used, total dose prescription, dose for fractions and kind of concomitant chemotherapy used. In a regression analyses we found an higher rate surgical complications in patients receiving a EQD2 doses  $>$  58.9 Gy with a BED  $>$  70.7 (median 22.4%) compared to patients receiving a EQD2 doses  $<$  58.9 Gy with a BED  $<$  70.7 Gy (mean 12.01%).

Nevertheless, more data with randomized trials are needed in order to clarify and identify the optimal EQD2 dose escalation and surgical complication in LARC. In fact, the data reported in literature are often confounding due to retrospective analysis, complications are described as anastomotic leak, often are second end points of the studies and are not described by authors at all.



Finally, the mean of anastomotic leakage or fistula was 4.26%, as reported in previously in different data in literature. There was not any correlation between dose prescription and anastomotic leakage at the regression analysis ( $P$  value = 0.354).

Unfortunately, with the limitation of a mean follow-up of 35 mo, survival rates often were not described by authors and we did not found any correlation between survival rates, dose prescription and pCR ( $P$  value > 0.05).

Additionally, a lot of other authors have questioned the importance of achieving pCR in the context of survival and other treatment outcomes[17,23].

Gunther *et al*[14] analyzed 76 patients receiving modestly escalated treatment (52.5 Gy *vs* 45 Gy), and reported higher 10-year PFS rates (71.9% *vs* 57.6%,  $P$  value < 0.01) and OS rates (71.6% *vs* 62.4%,  $P$  value < 0.01) despite similar pCR rates between groups.

Otherwise, Hearn *et al*[25] in a systematic review and meta-analyses did not identified a survival benefit with radiotherapy dose escalation.

We encourage authors to describe and analyze and survival rates in patient affected by LARC treated with neoadjuvant dose escalation radiotherapy.

The limitation of our review consist on low number of patients analyzed for each study, the majority of eligible trials included in our review consisted in retrospective studies, shorter follow-up, heterogeneity between studies regarding modality and imaging used for definition of gross tumor volumes, different schedules of concomitant chemotherapy used and surgical intervals used in different studies.

Based on results of our review, with above mentioned limitations, we believe that neoadjuvant radiotherapy dose escalation using innovative techniques with inverse planning modality will be the standard for the treatment pf LARC in a prospective future, especially in low-very low rectal cancer patients candidate of sphincter preservation and/or “watch and wait strategy”.

## CONCLUSION

Based on our systematic review results, neoadjuvant radiotherapy dose escalation using innovative techniques with inverse planning modality is safe with acceptable acute toxicity achieving higher pCR compared to standard treatment of locally advanced rectal cancer. EQD2 doses > 58.9 Gy with a BED > 70.7 given with SIB technique seems to be associated with higher rate of surgical complications.

Finally, a real benefit in achieving higher pCR rates can be essential in patients with LARC candidate to organ preservation with “watch and wait” strategy, patients with low rectal cancer reaching R0 margins and patients with low-very low rectal cancer candidate to definitive stoma or sphincter preservation.

## ARTICLE HIGHLIGHTS

### Research background

Preoperative radiochemotherapy had an important role in locally advanced rectal cancers (LARC) improving local and disease control. A benefit on tumor downstaging and pathological complete response (pCR) rate was reported by authors using radiotherapy dose escalation.

### Research motivation

Considering the progress of radiation therapy in last decades we decided to analyzed the role of neoadjuvant radiotherapy dose escalation for LARC using innovative radiotherapy techniques such as VMAT, intensity-modulated radiotherapy (IMRT) or image-guided radiotherapy (IGRT).

### Research objectives

To evaluate clinical outcomes and toxicity for neoadjuvant radiotherapy dose escalation using innovative radiotherapy techniques.

### Research methods

In December 2020 we conducted a comprehensive literature search of the following electronic databases: PubMed, Web of Science, Scopus and Cochrane library. According to PRISMA Group (2009) screening process only studies using radiation

doses EQD2  $\geq$  54 Gy and VMAT, IMRT or IGRT techniques were analyzed included for the review.

### Research results

At the analyses we found high pCR rates (28.2%), local control (92.29%), R0 margins (98.88%) and sphincter preservation rates (76.03%).

### Research conclusions

Patients receiving EQD2 dose > 58.9 Gy and BED > 70.7 Gy had higher surgical complications rates compared to other group ( $P$  value = 0.047). G3 or higher toxicity was 11.06 % with no correlation between dose prescription and toxicities.

### Research perspectives

We believe that dose escalation neoadjuvant radiotherapy using innovative techniques is safe for LARC and can be considered the standard radiotherapy treatment in a future perspective.

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