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Treatment Volume, Dose Prescription and Delivery Techniques for Dose-intensification in Rectal Cancer: A National Survey

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on behalf of Gastrointestinal Study Group of AIRO (Italian Association of Radiation Oncology and Clinical Oncology)

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Key Words: Rectal cancer, dose intensification, intensity modulated radiotherapy, simultaneous integrated boost, gross tumor volume.

Abstract. *Background/Aim: The aim of the study was to investigate boost volume definition, doses, and delivery techniques for rectal cancer dose intensification. Patients and Methods: An online survey was made on 25 items (characteristics, simulation, imaging, volumes, doses, planning and treatment). Results: Thirty-eight radiation oncologists joined the study. Twenty-one delivered long-course radiotherapy with dose intensification. Boost volume was*

delineated on diagnostic magnetic resonance imaging (MRI) in 18 centres (85.7%), and computed tomography (CT) and/or positron emission tomography-CT in 9 (42.8%); 16 centres (76.2%) performed co-registration with CT-simulation. Boost dose was delivered on gross tumor volume in 10 centres (47.6%) and on clinical target volume in 11 (52.4%). The most common total dose was 54-55 Gy (71.4%), with moderate hypofractionation (85.7%). Intensity-modulated radiotherapy (IMRT) was used in all centres, with simultaneous integrated boost in 17 (80.8%) and image-guidance in 18 (85.7%). Conclusion: A high quality of treatment using dose escalation can be inferred by widespread multidisciplinary discussion, MRI-based treatment volume delineation, and radiation delivery relying on IMRT with accurate image-guided radiation therapy protocols.

A correlation between radiation therapy (RT) doses and tumor response has been reported in rectal cancer (1). Indeed, a dose intensification strategy has been investigated to improve oncological outcomes and pathologic complete response (pCR) rate, as favourable prognostic factor (2, 3) in locally advanced rectal cancer (LARC) patients (4, 5), especially in those less likely to respond to preoperative long-course radiotherapy (LCRT) or to select patients for organ-preserving. A high rate of pCR has been reported when the administered dose was escalated up to 50-60 Gy (30% *vs*. 12-15% in standard treatment) (6-14).

Preoperative intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) have also resulted in a high rate of pCR with a low acute toxicity profile, excellent compliance to treatment (8-10) and effectiveness in several prospective phase II studies (15-28) and in an Italian pooled analysis (29).

Although international guidelines suggest dose intensification up to 54 Gy in cases of high risk tumor (bulky disease or circumferential resection margin involvement) (30, 31), some issues regarding boost planning and delivery (*i.e.* volumes definition, best imaging for delineation, and delivery technique) are still debated. Based on these considerations, a national survey was proposed by the Italian Association of Radiation and Clinical Oncology (AIRO) gastrointestinal study group aimed at evaluating the pattern of care in the setting of dose intensification at the national level.

Patients and Methods

In May 2019, an online survey was set up within www.surveymonkey.com. Members of AIRO gastrointestinal study group were individually contacted by email to request their willingness to participate in the survey. An expertise in rectal cancer treatment was required based on the professional experience and their involvement in a multidisciplinary team for rectal cancer treatment. Dose intensification was defined as a total dose up to 54 Gy (>2 Gy fraction), or more than 54 Gy.

Table I. *Selection criteria for dose intensification.*

Options	N	%
All patients	8	38.1
cT4	11	52.4
cT3, MRF+	10	47.6
cT3, N0-N+, low rectum	8	38.1
BulkycN+ extra-mesorectum	6	28.6
cN2	6	28.6
Unfit for concurrent CHT	3	14.3

MRF+: Mesorectal fascia involvement; T: tumor; N: lymph node; +: pathologic; CHT: chemotherapy.

Questionnaire. The questionnaire comprised 3 main sections and 25 items focused on: centre characteristics (5 items), simulation (3 items), imaging (4 items), volumes and doses (5 items), planning and treatment (8 items). Most of these questions were close ended questions, including quantitative and multiple-choice answers, besides the opportunity for free text comments.

Section 1: Patient care and therapeutic approach. Centre's characteristics (public, private, university), number of LARC patients treated every year, professional members of the Interdisciplinary Group for Cancer Care, and type of diagnostic imaging were investigated.

Section 2: Simulation. Patient set-up, immobilization, and use of Iodinated contrast medium during CT simulation were explored.

Section 3: Planning and delivery. Selection criteria for dose intensification, imaging for boost delineation, boost volume definition, margins applied to generate the planning target volume (PTV), boost technique, image-guided RT (IGRT) protocols, and chemotherapy schedules were evaluated.

Statistics. The statistical analysis was provided by www.surveymonkey.com and included a description of all variables. Responses were tabulated, and the percentage values are reported.

Results

Thirty-eight centres (Public=27, Private=7, University=4) of different Italian regions (northern Italy:25, center:8, south:5) joined the survey.

Section 1: Patient care and therapeutic approach. Fourteen centres (36.8%) declared to treat >30 patients per year with dose intensification preoperative LCRT, and 11 (28.9%) between 10-20 patients. All centres reported case discussion by the Interdisciplinary Group for Cancer Care, where different specialists were involved: Radiation Oncologist= 100%, Medical Oncologist=100%, Surgeon=100%, Radiologist=86.1%, Endoscopist=75%, Pathologist=69.4%, Nuclear Medicine physician=27.8%; Psychologist=11.1%,

Table II. *Detailed areas included in the Boost volume delivered on the gross tumor volume (GTV) and clinical target volume (CTV), respectively.*

Options	N	%
Gross tumor volume (GTV)		
Macroscopic tumor	14	66.7
cN+	11	52.4
BulkycN+ extra-mesorectum	10	47.6
Clinical target volume (CTV)		
Macroscopic Tumor + margin	6	28.6
Macroscopic Tumor + mesorectum	6	28.6
cN+ intra-mesorectum	3	14.3
cN+ intra-mesorectum + margin	4	19
Bulky cN+ extra-mesorectum + margin	2	9.5
Bulky cN+ extra-mesorectum + corresponding nodal level	4	19

T: Tumor; N: lymph node; +: pathologic.

Table III. *Selection criteria for patient treated with induction or consolidation chemotherapy and treatment schedules.*

Options	N	%
Induction chemotherapy		
All patients	1	7.69
cT4	8	61.5
cT3, MRF+	1	7.7
cT3, N0-N+, low rectum	0	0
BulkycN+ extra-mesorectum	7	53.8
cN2	3	23
Consolidation chemotherapy		
All patients	0	0
cT4	4	66.7
cT3, MRF+	2	33.3
cT3, N0-N+, low rectum	1	16.7
BulkycN+ extra-mesorectum	3	50
cN2	3	50

MRF+: Mesorectal fascia involvement; T: tumor; N: lymph node; +: pathologic; CHT: chemotherapy.

Geneticist=5.6%, Anesthesiologist=2.8%, Geriatrician=2.8%, Nutritionist=2.8%. Preliminary exams requested in all centres for diagnosis and staging are reported in Figure 1.

Section 2: Simulation. Immobilization devices were used in 35 centres (92.1%), including belly board in 47.37% of cases. Irradiation in the prone or supine position were equally preferred.

Iodinated contrast medium was administered during CT simulation in one centre; Fluorodeoxyglucose-positron emission tomography (FDG-PET) simulation (with same treatment set-up position) was routinely used in 3 centres (7.9%) and for specific indication in 8 centres (21.1%); Magnetic resonance imaging (MRI) simulation (with same treatment set-up position) was routinely used in 5 centres (13.2%) and for specific indications in 3 centres (7.9%). In 26 centres (68.4%) an empty bladder filling protocol was used.

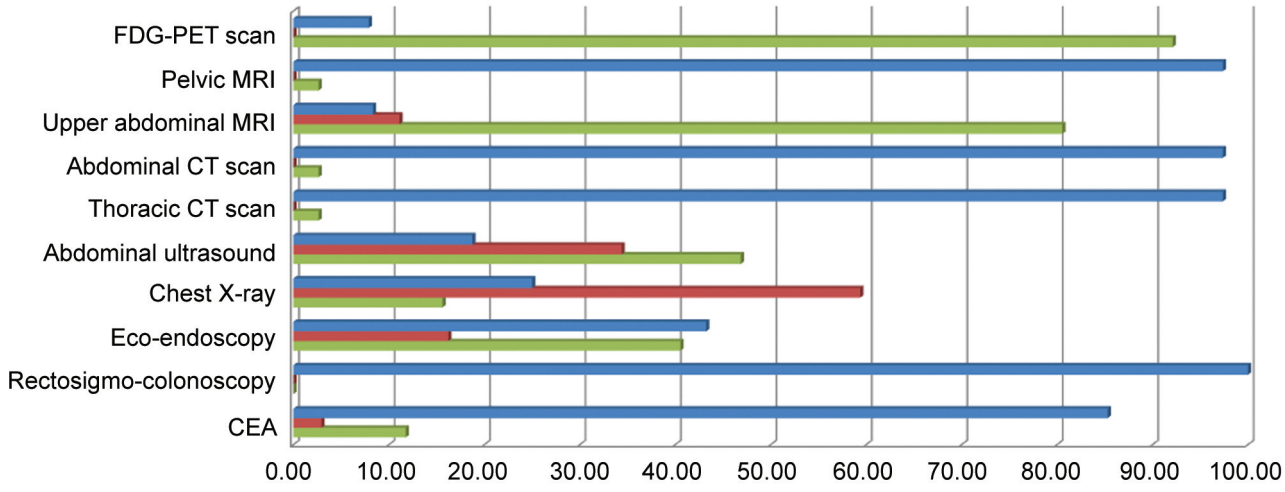
Section 3: Planning and delivery. Twenty-one centres declared to perform dose intensified preoperative LCRT. Table I shows the selection criteria for dose intensification. Volumes delineation: Boost volume was delineated on diagnostic MRI in 18 centres (85.7%), and on CT scan and/or FDG-PET-CT in 9 centres (42.8%). Co-registration with CT simulation was always performed in 16 centres (76.2%), for selected cases in 3 centres (14.3%) and never in 2 centres (9.5%). A boost dose was delivered on the gross tumor volume (GTV) in 10 centres (47.6%), and on the clinical target volume (CTV) in 11 centres (52.4%). Detailed areas included in the boost volume are shown in Table II. PTV for the boost volume was generated as an isotropic, anisotropic and adapted margin in 16 (76.1%), 3 (14.3%) and 2 (9.5%) centres, respectively.

Dose and fractionation schedule. SIB is the preferred modality for boost delivery (17 centres=80.8%). Daily sequential or concomitant boost was delivered in 4 (19%) and 3 (14.3%) of the institutions, respectively. Boost was delivered up to a total dose of 54-55 Gy in15 centres (71.4%), and >55 Gy (range=56-61.6 Gy) in 6 centres (28.6%), with moderate hypofractionation in 19 centres (90.5%).

Techniques. Intensity-modulated radiotherapy (IMRT) was used for dose intensification treatment in all the centres. Three-dimensional conformal radiotherapy (3D-CRT) is alternatively used in 1 centre. Image-guided RT (IGRT) is used in 18 centres (85.7%). Modality and protocols are shown in Figure 2.

Concurrent chemotherapy. Nineteen (90.5%) out of 21 centres offered dose intensified radiotherapy with concurrent chemotherapy: Capecitabine (17 centres=89.4%), 5-FU (1 centre=5.2%) or 5-FU plus oxaliplatin (FolOx, 2 centres= 10.5%).

Intensified treatment employing chemotherapy was also investigated. Induction chemotherapy was given in selected patients in 13 centres (42.8%). Consolidation chemotherapy (post-RT and before surgery) was administered in selected cases in 4 centres (19%). Selection criteria for patients treated with induction or consolidation chemotherapy and treatment schedules are shown in Table III. FolOx is the preferred schedule prescribed for both induction (61.5%) and consolidation (66.7%) chemotherapy.



	CEA	Rectosigmo-colonoscopy	Eco-endoscopy	Chest X-ray	Abdominal ultrasound	Thoracic CT scan	Abdominal CT scan	Upper abdominal MRI	Pelvic MRI	FDG-PET scan
Always	85.30	100.00	43.24	25.00	18.75	97.37	97.37	8.33	97.37	7.89
Never	2.94	0.00	16.22	59.38	34.38	0.00	0.00	11.11	0.00	0.00
In selected cases	11.76	0.00	40.54	15.62	46.87	2.63	2.63	80.56	2.63	92.11

Figure 1. *Preliminary exams requested in all centres for diagnosis and staging. CEA: Carcinoembryonic antigen; CT: computed tomography; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose - positron emission tomography.*

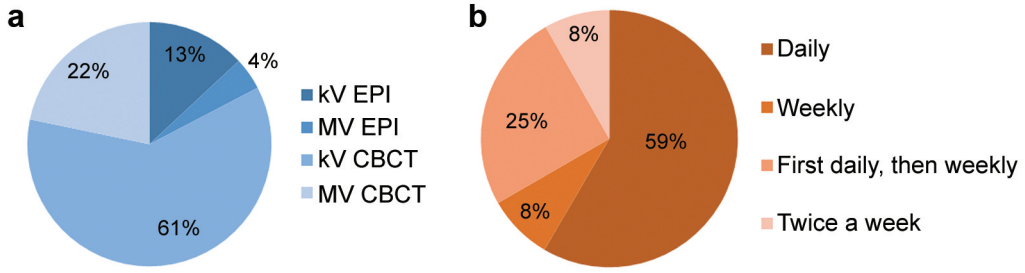


Figure 2. *Image-guided radiation therapy (IGRT) modality (a) and protocols (b). kV EPI: kV Electronic portal imaging; MV EPI: MV electronic portal imaging; kV CBCT: kV cone-beam computer tomography; MV CBCT: MV cone-beam computer tomography.*

Discussion

The clinical outcome of LARC patients is largely dependent on tumor response to chemo-radiotherapy (CRT) (1, 2). A pCR rate of 26.7%, with TRG1-2 rate of 41.8%, was shown in a dose intensification study of 322 patients with LARC. The 5- and 10-year OS, DFS and LC rates were 82.5%±2.5% and 65.5%±3.8%, 81.2%±2.4% and 79.3%±2.9%, 93.1%±1.7% and 90.5%±2.1%, respectively (32). Moreover, an exponential increase in pCR-rate after neoadjuvant radiation dose ≥60 Gy, has been shown by mathematical and clinical dose–response prediction models (pCR=50% with >92 Gy) (6). These data were confirmed by a systematic review and meta-analysis of 14 studies on 487 patients treated with ≥60 Gy, reporting high pCR-rates (20.4%; 95%CI=16.8-24.5%) with acceptable early toxicity (grade ≥3 toxicity in 10.3%; 95%CI=5.4-18.6%) (7). None of the studies included in this meta-analysis used IMRT. In the last two decades, a progressive increase in the use of IMRT in respect to 3D-CRT has been reported in a retrospective cohort study including a total of 1,773 patients receiving neoadjuvant chemoradiotherapy, especially in LARC patients with huge tumors (cT4) (33).

The effect of dose intensification delivered with modern radiation and/or planning techniques, has been tested in phase II studies reporting favourable results in terms of feasibility and toxicity when using IMRT with SIB intensification in

Table IV. *Dose prescription and boost parameters in the 18 studies, on 649 patients treated with >60 Gy, included in the systematic review by Burbach J et al. (7).*

Author, year	Study design	Ptz (n)	Pelvic dose (Gy)	Fraction numbers/ dose fraction (Gy)	Total Boost dose (Gy)	Boost fraction numbers/ dose fraction (Gy)	EQD2 dose (total)	Boost timing (Technique)	pCR %	Boost volume definition	Boost volume margin (CTV)	Imaging for Boost volume delineation
Concomitant boost												
Marks, 1993	P	52	45	31/1.8; 22x2.5	60	5/1	61-64	EBRT	NR	NR	NR	NR
Mohiuddin, 2006	RCT	16	45.6	38 1.2 BID	60	12/1.2 BID	56	EBRT	31.3	GTV-T	3-cm around (sacral hollow)	NR
Concomitant plus sequential boost												
Pfeiffer, 2005	Phase I-II	18	48.6	27/2	60	3/2	60	EBRT	7.1	GTV-T	NR	CT scan + MRI
Vestermark, 2008	Phase II	36	48.6	27/2	60	3/2	60	EBRT	8.3	GTV-T	1 cm	CT scan + MRI
Lindebjerg, 2009	P	8	54.0	27/2	65	3/2; 5	66	EBRT + BRT	12.5	GTV-T	NR	NR
Vestermark, 2012	Phase I	16	48.6	27/2	60	3/2	60	EBRT + BRT	31.3	GTV-T	1 cm	CT scan + MRI
Sequential boost												
Meade, 1995	NRCT	20	45	25/1.8	60	9/1.8	60	EBRT	0.0	GTV-T	NR	NR
Movsas, 1998	Phase I-II	27	45	25/1.8	62	14/1.2 BID	60	EBRT	NR	GTV-T + GTV-N	2 cm, all directions	NR
Mohiuddin, 2000	NRCT	33	50.0	38/1.2 BID	60	12/1.2 BID	56	EBRT	44.4	GTV-T	3 cm	NR
Rouanet, 2002	P	43	37.8	18/2.1	60	10.5/2.1	60	EBRT	16.3	NR	NR	NR
Movsas, 2006	Phase II	21	45	25/1.8	62	14/1.2 BID	60	EBRT	0.0	GTV-T + GTV-N	1.5-2 cm, all directions	NR
Ho-Pun-Cheung, 2007	P	29	45	25/1.8	60	9/1.8	60	EBRT	NR	GTV-T	1.5 cm	NR
Maluta, 2010	Phase II	76	50.0	25/2	60	5/2	60	EBRT	23.7	GTV-T	NR	Endoscopy
Engineer, 2013	RCT	44	45	25/1.8	65	11/1.8	64	EBRT	11.4	GTV-T	1 cm	CT scan + MRI
Jakobsen, 2006	P	50	54.0	27/2	65	3/2+5	66	EBRT + BRT	26	GTV-T	1 cm	CT scan + MRI
Jakobsen, 2008	P	35	54.0	27/2	65	3/2+	66	EBRT+ BRT	20.0	GTV-T	NR	CT scan
Sun Myint, 2007	P	16	45	25/1.8	75	1/10	61	BRT	43.8	GTV-T + mesorectal deposits	NR	MRI
Jakobsen, 2012	RCT	109	50.4	28/1.8	60	2/5	62	BRT	18.3	GTV-T	NR	NR

Ptz: Patients; P: prospective; RCT: randomized controlled trial; NRCT: no randomized controlled trial; BID: twice-a-day; EQD2: equivalent dose in traditional 2 Gy fractions; EBRT: external beam radiotherapy; BRT: brachytherapy; pCR: pathologic Complete Response; GTV-T: Primary tumor; GTV-N: grossly enlarged lymph nodes; NR: not reported; CT: computed tomography; MRI: magnetic resonance imaging.

combination with fluoropyrimidine-based chemotherapy (15-28). Then, outcomes within studies using modern inverse-planning techniques (IMRT, volumetric modulated arc therapy and tomotherapy) and moderate intensified schedules (54-60 Gy) have been evaluated in a recent meta-analysis (34). The estimated pooled pCR rate was 24.1% across 37 eligible studies (1,817 patients), and 25.7% when inverse-planning was delivered (17 publications, 959 patients).

Included in this metanalysis, a retrospective multicentric Italian study on 76 LARC patients was conducted, reporting a pCR rate of 27.8% for patients treated with dose ranging from 52.5 to 57.5 Gy (median 54 Gy) to the SIB boost volume. Treatment was well tolerated with grade ≥3 acute toxicity rates of 4-25% (29). The main critical issues of this study were represented by the different SIB doses employed due to the different IMRT modalities available at each

Table V. *Dose and boost volume parameters in modern prospective or randomized studies with boost dose/fraction between 2-2.5 Gy (19, on 1209 patients treated with a total accumulation of EBRT dose between 45-60 Gy). If not clearly reported, EQD2 total dose was calculated considering α/β= 10 for tumor * (7), and α/β=5.06 for rectal tumor ** (24).*

Author, year	Study design	Ptz (n)	Pelvic dose (Gy)	Fraction numbers/ dose fraction (Gy)	Total Boost dose (Gy)	Boost fraction numbers/dose fraction (Gy)	EQD2 dose (total, Gy)	Boost technique	pCR %	Boost volume definition	Boost volume margin (CTV)	
Caravatta, 2011 (11)	Phase II	25	45	25/1.8	55	25/2.2	56.7**	CB	32	GTV-T + GTV-N + M	2 cm CC	CT scan + MRI
Osti, 2014 (12)	P	65	45	25/1.8	55	25/2.2	NR (56.1*/ 56.7**)	CB	17	GTV-T + M	No margins	CT scan + MRI
Picardi, 2016 (13)	Phase II	18	45	25/1.8	55	25/2.2	56.7**	CB	27.7	GTV-T + GTV-N + M	2 cm, CC	CT scan + MRI
Valentini, 2019 (14)	RCT (INTERACT)	280	45	25/1.8	55	25/2.8 (twice weekly)	67.7	CB	24.4	GTV-T + GTV-N + M	1-2 cm CC	CT scan + MRI
Burbach, 2015 (ongoing) (15)	RCT (RECTAL BOOST study)	Estimated 120	50	25/2	65	5/3	66.3*	CRT and VMAT/ IMRT	Estimated 30	GTV-T	No margins	T2-we and DWI MRI
Ballonoff, 2008 (16)	Phase II	8	45	25/1.8	55	25/2.2	56.1*	SIB IMRT	38	GTV-T + GTV-N	NR	NR
De Ridder, 2008 (17)	Phase II	24	46	23/2	55.2	23/2.4	NR (56.9*/ 58.1**)	SIB IMRT	14	GTV-T + M	No margins	MRI
Li, 2012 (18)	Phase II	63	41.8	22/1.9	50.6	22/2.3	NR (51.6*/ 52.7**)	SIB IMRT	31	GTV-T + GTV-N + M	NR	NR
Passoni, 2013 (19)	P	25	41.4	18/2.3	45.6	12/2.3; 6	54	SIB - adaptive Tomo-therapy	30	GTV-T + GTV-N	NR	MRI
Engels, 2014 (20)	Phase II	108 (57)	46	23/2	55.2	23/2.4	NR (56.9*/ 58.1**)	SIB IMRT	8	GTV-T	NR	NR
Zhu, 2014 (21)	Phase II	78	50	25/2	55	25/2.2	NR (56.1*/ 56.7**)	SIB IMRT	24	GTV-T + M	2 cm CC	CT scan + MRI
Hernando-Requejo, CT 2014 (22)	P	71	46	23/2	57.5	23/2.5	60.4 *	SIB IMRT	31	GTV-T + GTV-N	0.5 cm	CT/PET-simulation
But-Hadzic, 2016 (23)	Phase II	51	41.8	22/1.9	46.2-48.4	22/2.1-2.2	56.1*	SIB IMRT	25.5	GTV-T + M	1 cm CC	CT scan + MRI
Picardi, 2017 (24)	Phase II	18	45	25/1.8	57.5	25/2.3	59.94**	SIB VMAT	25	GTV-T + M	1 cm CC	MRI
Alongi, 2017 (25)	P	40	54	30/1.8	60	30/2	60 (51.6*/ 52.7**)	SIB VMAT	17.5	GTV-T + GTV-N + M	NR	PET-CT (at least SUV=5)
Tey, 2017 (26)	Phase II	23	45	25/1.8	55	25/2.2	NR (56.1*/ 56.7**)	SIB IMRT	35	GTV-T + GTV-N	2 cm for GTV-T; 0.5 cm for GTV-N	CT scan + MRI
Yang, 2019 (27)	Phase II	26	50	25/2	58.75	25/2.35	NR (51.6*/ 52.7**)	SIB VMAT	32	GTV-T + GTV-N	5 mm radial, 5-10 mm CC	CT scan + MRI
Zhao, 2019 (28)	P	141	50	25/2	55	25/2.2	NR (56.1*/ 56.7**)	SIB Tomo-therapy	22.7	GTV-T + GTV-N	No margins	T2-we, DWI MRI and PET-CT

Table V. *Continued*

Table V. *Continued*

Author, year	Study design	Ptz (n)	Pelvic dose (Gy)	Fraction numbers/ dose fraction (Gy)	Total Boost dose (Gy)	Boost fraction numbers/dose fraction (Gy)	EQD2 dose (total, Gy)	Boost technique	pCR %	Boost volume definition	Boost volume margin (CTV)	
Lupattelli, 2017 (29)	Pooled analysis	76	45	25/1.8	median 54 (52.5-57.5)	25/ 2.1-2.3	median 55.22** (53.24-59.94)	SIB IMRT	27.8	GTV-T + M	1-2 cm CC	MRI

Ptz: Patients; P: prospective; RCT: randomized controlled trial; NRCT: no randomized controlled trial; BID: twice-a-day; EQD2: equivalent dose in traditional 2 Gy fractions: EBRT: external beam radiotherapy; BRT: brachytherapy; pCR: pathologic complete response; CB: concomitant boost; SIB: simultaneous irradiation boost; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; GTV-T : primary tumor; GTV-N : grossly enlarged lymph nodes; NR: not reported; CC: cranio-caudal; CT: computer tomography; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography: DWI; diffusion weighted imaging.

participating centre and by the limited sample size, probably related to the lack of significant indication, including the RT dose level. On the contrary, since the 5 participating centres had previous collaborated in the INTERACT rectal cancer trial (14), they shared the same delineation criteria for boost volume, defined as tumour and corresponding mesorectum plus an MRI-based cranio-caudal extension of 1-2 cm.

Most of evaluated patients were staged as IIIB (64.5%) and mesorectal fascia involvement (MRF+) was documented in 45% of them. Indeed, a dose intensification strategy could be particularly demanded in locally advanced high risk tumors such as T4-tumors, those with mesorectal fascia involvement, or suspicious bulky lymph nodes, aiming to improve resectability and local control.

Based on the aforementioned critical issues and the still debated considerations regarding the setting of dose intensification, this survey was proposed by the gastrointestinal study group of Italian Association of Radiation and Clinical Oncology (AIRO) to evaluate the pattern of care at the national level.

Pelvic MRI routinely performed for staging definition and risk factor identification in 97.4% of centres (Figure 1). This is in agreement with current guidelines that recognize MRI of the rectum as able to accurately predict the depth of extramural spread and the involvement of the mesorectal fascia and then recommend MRI for local staging, as well as for preoperative assessment of patients with high risk tumors, where dose intensification could be carried out (35, 36). Consequently, the selection criteria for dose intensification applied in this survey mainly included patients with high risk tumors, especially cT4 (52.4%), MRF involvement (47.6%), and/ or low rectum (38%) (Table I).

The target volume delineation represents one of the major sources of uncertainty in radiotherapy and, it may have a significant impact on the delivery dose to the tumor, especially when dose intensification is planned and highly conformal techniques, such as SIB-IMRT, are used. Then, accuracy in the choice of the appropriate image for delineating volumes, in the delineation of the volume itself and image-guidance protocols is strongly recommended (37). Although many guidelines are currently available for elective CTV delineation in rectal cancer (38-40), no consensus or guideline is currently available for the definition and delineation of the boost volume.

In order to compare our results with the available data in the literature, details about prescribed doses, definition of volumes and possible margins were investigated in the 18 studies, included in the review of Burbach et al., on 649 patients treated with >60 Gy (7) (Table IV), and in 19 modern prospective and or randomized studies with boost dose/fraction between 2-2.5 Gy (Table V). Compared to historical studies using conformational technique, SIB boost is often delineated as primary tumor with corresponding mesorectum and or macroscopically suspicious lymph node, with different margins to generate the CTV.

The ability of modulated intensity techniques to deliver high doses sparing the organs at risk (OARs) allows to consider a margin to the GTV for tumor spread. The need to add a margin to the GTV, with the possible inclusion of the mesorectum, is related to the evidence that microscopic metastatic foci were reported within the mesorectum in up to 38.7% of patients (41) and that one of the main prognostic factors in rectal cancer is the status of the circumferential resection margin (CRM). Indeed, the CRM involvement has been associated with a poor prognosis, not only for local recurrence, but also for the development of distant metastases and patient survival (42). Location and depth of tumor invasion, nodal involvement, and tumor size >2 cm, mucinous adenocarcinomas and signet ring cell carcinomas, high grade tumors, and lymphovascular and perineural invasion have been identified as features independently associated with a positive CRM (41). Bulky lymph nodes

with mesorectal fascia involvement and/or suspicious extra mesorectal nodes could then benefit of dose intensification. Finally, the inclusion of pathological lymph nodes could be individually considered based on their dimensions and the proximity of OARs and the related tolerability (*i.e.* bowels).

The improvement of diagnostic imaging allowed for a prediction of a potentially involved margin. Currently, preoperative MRI is considered highly accurate for the prediction of CRM involvement and represents the standard of care in assessing T-stage and margin status of tumor within a tolerance of 0.5 and 1 mm, respectively, resulting in more adequate treatment planning with a further decrease in cases of positive resection margins at surgery (43, 44). Moreover, Diffusion-weighted imaging (DWI) looks promising for delineation due to its ability to discriminate tumors from healthy tissue upon diffusion-restriction, resulting in smaller GTV compared to T2-weighted MRI and lower inter-observer variability (45-47). Fourteen of the evaluated studies (74%, Table V) specifically reported the use of MRI for GTV delineation, with DWI in two studies.

Our results are comparable, showing that boost volume is delineated on diagnostic MRI in 18 centres (85.7%), and on CT scan and/or PET-CT in 9 centres (42.8%). Boost dose was delivered on the macroscopic disease (GTV) in 10 centres (47.6%), and included the macroscopic tumor, cN+, or bulky cN+ extra-mesorectum in 66.7%, 52.4% and 47.6% of the cases, respectively (Table II). Boost dose was delivered on the CTV in 11 centres (52.4%), including high-risk areas (Table II). IMRT was used for dose intensification treatment in all centres and SIB was the preferred modality for boost delivery (80.8%), with moderate hypofractionation in 19 centres (90.5%), and chemotherapy was administered concurrently to dose intensification radiotherapy in 19 of 21 (90.5%) centres.

Finally, Image-guided RT protocols were used in 18 centres (85.7%). This seems particularly relevant considering that large deformation in the shape of the mesorectum have been described and that changes in rectal filling have been found to be the major cause of changes (48-50), with significant clinical impact when modulated intensity techniques are performed (51). Based on these considerations, an individualized anisotropic margin should be evaluated and an optimal IGRT strategy (imaging modality and frequency) should be identified based on the height of the tumor and site-specific set-up calculations (52).

In conclusion, locally advanced rectal cancer patients could benefit from different radiation treatment strategies including dose modulation, appropriate volume delineation, organ motion evaluation, IGRT protocols and modern delivery techniques aimed to improve oncological outcomes. Although there is currently no consensus in the literature regarding boost volume definition and relative margins, our survey is in accordance with the main prospective and randomized studies of preoperative LCRT with dose intensification. The current status in this setting in Italy showed a high quality of treatment, as highlighted by multidisciplinary discussion in all centres, volume delineation based on MRI in the majority of centres, and SIB-IMRT for delivery in all centres, with accurate IGRT protocols. Considering the growing interest in dose intensification treatment, these requirements could therefore be considered essential when moderate escalation (54-60 Gy) with modern inverse-planning techniques is delivered.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

LC, ML, GM, MAG and DG designed and coordinated the study and the analysis. All authors provided data. CL, CR and LG performed main data analysis, provided pictures and drafted the manuscript. ML, GM, MAG, DG, FP, and VD critically revised the study and the manuscript. All Authors reviewed and approved the final manuscript.

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