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IGRT in rectal cancer

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Abstract

To date, no great interest has been shown in the clinical implementation of recent Image-guided radiation therapy (IGRT) modalities in rectal cancer since only a few studies have been published on this issue. This may be explained by the fact that with current treatment modalities locoregional recurrences are already very low (around 10%). However, there is still room for improvement in treatment of high risk patients (cT3 CRM+, cT4, N+). In these patients better results may be obtained improving radiation technique from 2D to 3D, which showed to be more reliable in terms of target coverage. Also, when higher doses are delivered, Intensity Modulated Radiation Therapy (IMRT) may be used to spare small bowel.

But before employing 3D irradiation or IMRT, a proper definition of our clinical target volume (CTV) and planning target volume (PTV) is needed. The CTV should encompass the tumour site, the mesorectum and the lateral nodes, recognized as the most likely sites of local recurrence, with different incidence according to tumour stage. Recent studies discussed the correct delineation of these target volumes in respect of tumour site and stage. From the preliminary results of a study conducted in Rome University 2D planning seemed insufficient to cover the different target volumes especially in T4 patients compared to 3D planning. Also an appropriate PTV margin is necessary in order to manage set-up errors and organ motion. Particularly in these patients, the knowledge of mesorectal movement is required to avoid target missing. Large mesorectal displacements were observed in a study carried out in Leuven University in collaboration with Rome University.

A systematic review of the literature together with the data from these first experiences led to the awareness that IGRT could help us to follow the target volume and organs at risk during the treatment, allowing adjustments to improve accuracy in dose delivery, especially when dose escalation studies are planned in the treatment of rectal cancer.

Image-guided radiation therapy (IGRT) is referred to as frequent imaging during a course of radiation therapy with decisions based on the results of this re-imaging during treatment [1–6].

Radiation therapy has always been guided by imaging as Electronic Portal Imaging Devices (EPID) were first described by Leong et al. in 1986 and even before other studies reported about initial attempts to manage radiotherapy uncertainties [7]. EPID, using skeleton anatomy to verify the treatment field edges, enables to measure daily changes in patients positioning. However, it is well known that many tumours are not attached to the skeleton and that the soft tissues anatomy can change in respect to the bones.

New IGRT modalities such as Cone Beam CT (CBCT) or CT scan (tomotherapy), providing information on internal anatomy, organ motion and change in shape and volume can increase significantly our awareness of set-up error and organ displacements during the course of the treatment. These recent IGRT developments become especially useful as novel quality assurance modalities when new radiation techniques such as IMRT or Stereotactic Body Radiation therapy (SBRT) are employed. Indeed, these techniques which adopt sharp dose gradients in order to deliver higher doses to the target volume sparing the nearby healthy tissues need improved accuracy to be safely applied.

To date, no great interest has been shown in clinical implementation of IGRT in rectal cancer since only a few studies have been published on this issue. This may partially be explained by the fact that the treatment modalities currently employed in rectal cancer use large fields with no steep dose gradients and dose levels (45–50.4 Gy) that are not

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an absolute constraint for any nearby organ at risk, reaching yet an excellent tumour local control with a very low rate of loco-regional recurrence (around 10%). However, there may be still room for improvement in treatment of high risk patients.

The Dutch Colorectal Cancer Group showed that preoperative radiotherapy improves local control even after TME [8]. From the subgroup analysis of total mesorectal excision (TME) arm in the Dutch trial the tumours most likely to recur were confirmed to be stage III tumours, those located below 10 cm from the anal ring and those with a circumferential margin inferior to 2 mm [9]. These patients might benefit from higher doses to achieve a better local control. Also in patients with low-seated tumours higher doses could improve the tumour downsizing improving the rate of sphincter preservation [10,11], even if this benefit is still controversial [12]. Better results can be simply achieved by improving our radiation treatment technique from 2- dimensional (2D) to 3-dimensional (3D). Still, even employing 3D radiation therapy, when higher dose are delivered, normal tissues complications could dangerously increase. IMRT can be employed on purpose to spare healthy nearby tissues such as small bowel and can be safely applied if there is an IGRT device that ensures about the accuracy of the treatment.

To exploit the possibilities of IGRT in rectal cancer, this review focuses on target definition, organ motion and evolution in rectal cancer radiotherapy techniques referring to literature data.

It also reports the preliminary data of two studies conducted in Rome Catholic University and Leuven University which deal with these topics.

Areas at risk of local recurrence: CTV definition

The introduction of TME has unavoidably changed the scenario of rectal cancer treatment, lowering the rate of local recurrences from 29% to 5–15% [13]. Still, in the TME era, data from the Dutch trial and MRC 07 trial [14,15] showed that radiotherapy furthermore decreases the rate of local recurrences when added to TME.

Roels et al. carefully reviewed the main sites of local recurrence mostly from surgical series of the"pre-TME era" [16]. However, looking at literature data on the patterns of recurrences after TME, there seems to be no substantial differences (Table I) [17–20]. Particularly the recurrences are mostly described in the lower two-thirds of the pelvis while lateral recurrence does not seem to be a major cause of local failure after TME [17]. Nevertheless the role of lateral pelvic lymph node dissection remains controversial especially in patients with clinical suspected lateral node disease [19]. Moreover, preoperative radiotherapy can be effective in the reduction of local failure in the lateral pelvis [20].

The CTV of rectal cancer should always include the mesorectum with its fascia, the presacral spaces, the tumour bearing site and the lateral spaces according to the stage at diagnosis. The mesorectum, defined as the lymphovascular fatty tissue lying around the rectal wall, is recognized to be the main site of rectal tumour spread because of the absence of anatomical borders. The majority of mesorectal nodes seem to lie along the sigmoid rectal artery and its branches and the patterns of spread are related to the tumour position in the rectal wall [21,22].

The presacral spaces are located behind the posterior mesorectal wall, anteriorly to the sacrum. This area, difficulty cleared by surgeons, is recognized as the most likely site for recurrence after TME and radiotherapy, even when higher dose of radiotherapy are used [17].

The lateral spaces include the pelvic nodes areas outside of the mesorectum which can be distinguished in internal iliac nodes (IIN), obturator nodes (ON) and external iliac nodes (EIN) [23]. The lateral node involvement appears to be strongly correlated to the tumour height with an increased risk for low tumours <5 cm to the dentate line

Table I. Patterns of recurrences after TME.

Author/ref	Year	N° pts	Pelvic subsite	Treatment
Syk [17]	2005	880	Anastomosis, presacral pelvic wall, pelvic floor	preoperative RT+surgery (528 pts); surgery alone (352 pts)
Roeder [18]	2006	243	retrovescical/retroprostatic, anastomosis, promontorium, ileocecal, perineum	Surgery +IOERT to the presacral space
Kim [19]	2008	366	tumor bed, anastomosis, anterior lateral spaces	Preoporative RT+surgery
Kusters [20]	2008	1079	presacral, lateral spaces, anterior, anastomosis, perineum	TME alone (376), preoperative RT+TME (379), Extended limphnode dissection (ELND)+ abdominoperineal excision and resection of anterior organs (324)

[24–26], to the diameter of the mass with an increased risk with a tumour greater than 3 cm [27] and to the tumour stage at diagnosis. In fact, from surgical series was noticed that pelvic nodes were involved in 22–30% of cases in T3 tumours and in 40–43% of cases in T4 tumours [28,29].

Internal iliac nodes, lying along the internal iliac artery, should be always encompassed in the target volumes, being involved especially in advanced stages and low seated tumours [15] while obturator nodes should be included in the target volume for tumours located below the peritoneal deflection [27] and external iliac nodes if an anterior organ invasion is documented [16].

From the above considerations it is suggested to encompass in the target volume always tumour bearing site with the surrounding mesorectum, the entire mesorectum, presacral spaces and internal iliac nodes in high (>10 cm up to the anorectal ring) and middle-low (0–10 cm up to the anorectal ring) T3 tumours. In T4 tumours or in tumours with involvement of the nodes located outside of the mesorectum, obturator nodes should also be included. Also in T4 tumours with anterior organ invasion or in tumours with obturator nodes involvement it is recommended to add to the target volume the external iliac nodes. Finally in T4 tumour with anal region massive invasion the CTV should be expanded about 2 cm into the perineal region around the elevator ani muscle insertion and the inguinal nodes should be included. The latter should also be included when the lower third of the vagina is involved [30].

Set-up error and organ motion

The PTV, as defined in ICRU 62 report, includes margins in order to manage uncertainties in patient set-up and changes in organ position, shape and size.

Set-up errors may depend on technical problems, may be patient related or immobilization related and also are influenced by the accuracy in patient positioning [31]. In a review published by Hurkmans et al. the reported set-up errors for pelvic irradiation were not particularly large varying between 1.1 and 4.9 mm (1SD). No uniform results were presented on the role of immobilization in reducing set-up errors.

Roels et al. comparing two different set-up verification and correction procedures in pelvic irradiation for rectal cancer patients suggested that patient positioning on a belly-board device using laser alignment to skin marks is reproducible within 4 mm [32]. However if rigorous verification and correction protocols can lead to decreased set-up margins, managing the internal organ motion remains a big challenge.

Indeed, rectum organ motion, occurring from day to day irradiation can be extremely large due to the hollow anatomical structure which allows many shape changes and displacements of different wall portions. In a study on bladder cancer motion, Muren et al. observed that remains unclear whether the Van Herk et al. recipe for CTV internal margin can be adapted to hollow organs tumours [33,34]. From literature analysis, rectal organ motion was described almost only in patients treated for prostate and bladder cancer. Only one work discussed rectal cancer CTV organ motion in adjuvant treatment. The greatest degree of motion was observed near the anterior structures of the inferior pelvis and was most likely due to bladder filling. In this study the motion of the colo-rectal anastomosis from surgical clips observation was also described. The main clip displacement occurred in the caudal direction [35]. The main results found on this topic are summarized in Table II [35–41].

In all the studies great variations in rectal volume as well as big wall displacements were observed during the treatment course. The main displacement occurred in the anterior wall [33,38,40]. Also the superior half of the rectum exhibited larger variations than the inferior one [40]. In many studies the rectal volume was found to decrease with time during the course of the treatment [42–44]. Actually the variations appeared to decrease when the rectum was empty, but if the emptying procedure can be easily obtained when the rectum is simply an organ at risk, it cannot be applied in patients affected by rectal cancer who usually have several bowel dysfunctions.

No one study reported about mesorectal motion. Moreover, in these patients, the knowledge of the mesorectum movement and shape variations is required to avoid target missing and to assure a better tumour control.

Evolution in radiotherapy techniques

To date the major interest in the treatment of rectal cancer has been in concurrent chemotherapy agents instead of radiation therapy technique [45] so that, many centers still employ 2D radiotherapy technique as a standard planning procedure. Two-dimensional technique refers to bony anatomy as surrogate landmarks to define the field limits. It can be realized either through anterior-posterior parallel-opposed fields or a three-field technique with a posterior and two lateral portals or a four-field technique consisting of an anterior, a posterior and two lateral portals [46]. Nevertheless, as

Table II. Summary of rectal motion studies.

Author/ ref	Year	Topic	Pts	CT scans/ pts	Comments	Rectal volume variation	Main displacement and site
Tinger [36]	1998	Prostate cancer	8	5–7	– Weekly CT + daily portal images	Mean (cc) 30 ± 5-127 ± 36 76 ± 34	
Stroom [37]	1999	Prostate cancer	15	4	– CT scans on week 2, 4, 6-laxation used in planning CT	Mean (cc) Supine: 123 Prone: 166	
Nuyttens [35]	2002	Rectal cancer	10	5–6	– Weekly CT -adjuvant treatment-clips motion		1.5 cm Caudal
Muren [33]	2003	Bladder cancer	20	7–8	– Weekly CT + daily portal images	Mean (cc) 62 ± 25-72 ± 29	30 mm Anterior and left wall
Hoogeman [38]	2004	Prostate cancer	19	8–13	– CT scans on days 1, 2 and 3, at the 1° day and last day of the 2° week, then weekly – Empty rectum	Mean (cc) 74 ± 17	8 mm Anterior side
Fokdal [39]	2004	Bladder cancer	15	5	– 3 CT scan with rectal catheter filled – 2 CT scan with no rectum filling	Mean (cc) 51(26-20)-185 (70-307)	
Stasi [40]	2006	Prostate cancer	10	11–14	– empty rectum	Mean (cc) 53 ± 11.5	9.1 mm anterior wall; rectum superior half
Lotz [41]	2006	Bladder cancer	21	8–11	– Daily CT during 1° week; then weekly	Mean (cc) 51 ± 8.4-243 ± 5.3	

already has been described in studies on gynaecological malignancies [47–49] the pelvic 2D standard irradiation may provide an inadequate coverage of the target volumes and increased normal tissue complications.

Recently Borger et al. published the results on a comparison of three different planning procedures in rectal cancer radiotherapy: three-dimensional (3D) radiotherapy, the classical 2D technique and a CT-3D based technique without target delineation but with well defined anatomic landmarks [50]. The 3D CTV included the gross target volume (GTV), the mesorectal subsite, the posterior pelvic subsite, the internal iliac and the obturator nodes. An evaluation of the target volumes coverage, the volumes of normal tissue irradiated and the time used for each modalities was made for 62 patients with non-locally advanced rectal cancer who underwent short course of radiation-therapy. The 2D technique and the CT-3D technique resulted both in inadequate target volumes coverage compared to a 3D technique for all tumours sites (high: >10 cm, medium: 7–10 cm, and low: 3–7cm). It was due to an underdosage of the upper iliac internal lymph-node regions for the first procedure while for procedure 2 no clear explanation was identified. The 3D technique also ensured a lower dose to the bladder compared to the other two procedures even if it was more time consuming. The small bowel toxicity was not taken into account in this study [50].

Surely when 3D treatment planning is performed, large small bowel irradiation is expected because of the horseshoe shape of the PTV of rectal cancer, even if devices such as the belly board or the up-down table are used to shift the small bowel of the treatment field. IMRT being able to produce concave dose distributions can be used to spare the small bowel [51,52].

Recently De Ridder et al. carried out a phase II study on the use of helical tomotherapy in the preoperative treatment of rectal cancer. Twenty-four patients with T3 and T4 rectal cancer were enrolled delivering a simultaneous integrated boost to 55.2 to those with a circumferential margin <2 mm. A decreased incidence of acute gastrointestinal and urinary toxicity was recorded even in the boost group in which the mean volume of small bowel receiving more than 15 Gy and the mean bladder dose were 141 ml and 21.5 Gy respectively.

This study, which is to our knowledge the first one which exploits IGRT in treating rectal cancer, demonstrates how delivering higher doses can be successfully combined with limited toxicities [53].

Looking for an improvement: Preliminary results of two studies conducted in Rome and Leuven Universities

3D versus 2D treatment planning in locally advanced rectal cancer

In Rome Catholic University, 2D treatment planning (2D TP) was virtually compared to 3D treatment planning (3D TP). Patients with locally advanced rectal cancer who underwent preoperative long-course radiotherapy were evaluated. A 2D TP and a 3D TP were made for each of the 30 patients enrolled. The 2D TP followed the bone anatomy according to the Gunderson guidelines [46]. The T3 PTV encompassed the entire mesorectum, the obturator nodes and the internal iliac nodes. The T4 PTV included also the external iliac nodes. According to institutional guidelines the 97% coverage of the PTV should be within the 97% isodose. In respect to the percentage of prescribed dose covering the 97% of the PTV, the treatment plans were defined "optimal" when dose was $\geq$97%, "good" when dose was between 97% and 90%, "bad" when dose was $<$90%. The main results are summarized in Table III.

From our preliminary results 2D planning showed to be less reliable than 3D irradiation in terms of pattern of dose distribution and target coverage, being insufficient to cover the volumes contoured on CT especially in T4 patients. In this analysis we did not refer to the dose absorbed by nearby healthy tissues such as bladder or small bowel.

Mesorectal motion

In an observational study, carried out in the University Hospital of Leuven together with Rome Catholic University, the motion of the mesorectum was studied. Twenty patients, all with a locally advanced rectal cancer, had 4 to 6 CT-scans during radiation treatment. On every CT-scan the mesorectum was manually delineated and all CT-scans of one patient were rigidly registered by bony anatomy matching. This resulted in a CT-image with 4 to 6 different overlapping mesorectum contours. Mesorectum motion was evaluated in 4 directions (left, right, anterior and posterior). We found the largest mesorectum motion at the anterior border of the upper mesorectum (Figure 1a,b). In the upper 2/3 of the mesorectum the motion was systematically larger to the right than to the left. Surprisingly large mesorectum motion was found at the posterior part of the lower mesorectum. We do not have a unambiguous explanation for this finding but a possible explanation can be related to the rapid cone shape decrease of the mesorectal volume at this level. This results in a relatively large difference in the mesorectal diameter from one CT slice to the next. As a consequence the slightest error in bony anatomy registration can therefore erroneously result in large internal margins.

In the patient group of Leuven a decrease of the mesorectal volume during treatment was observed in 8 of 10 patients. In our patient group, 4 of 10 patients, showed this time-trend. A possible explanation of this discrepancy is that in our patient group 4 patients had the repeated CT-scans within a time period of 1 week. Further, for both groups, a positive correlation was found between the rectal air volume and the mesorectal volume. No correlation was found between the mesorectal volume and the bladder volume

Conclusions and future directions

Most recent developments in radiotherapy have mostly been applied to other diseases sites. To date 2D treatment planning is still employed in rectal cancer patients even if it has been shown that it is insufficient to ensure an adequate target coverage. 3D treatment planning improves the patterns of dose distribution allowing more precise definition of boost target volumes and more detailed volume histograms. Radiation techniques employing intensity dose modulation such as IMRT have been proposed in order to spare nearby healthy tissues. Besides, both 3D CRT or IMRT need a proper definition of

Table III. Preliminary results from 2D TP versus 3D TP comparison.

	T3		T4	
	2D	3D	2D	3D
Median volume receiving a dose $\geq$97% (%, SD)	93.91 $\pm$ 6.94	94.36 + 4.93	89.31 $\pm$ 7.18	92.59 $\pm$ 5.4
Median volume receiving a dose $>$105% (%, SD)	1.29 $\pm$ 1.92	1.31 $\pm$ 1.66	.75 $\pm$ 1.37	1.82 $\pm$ 2.02
PTV coverage (%)				
optimal	50	46.7	16.7	13.4
good	33.3	53.3	0	83.3
bad	16.7	0	83.3	3.3

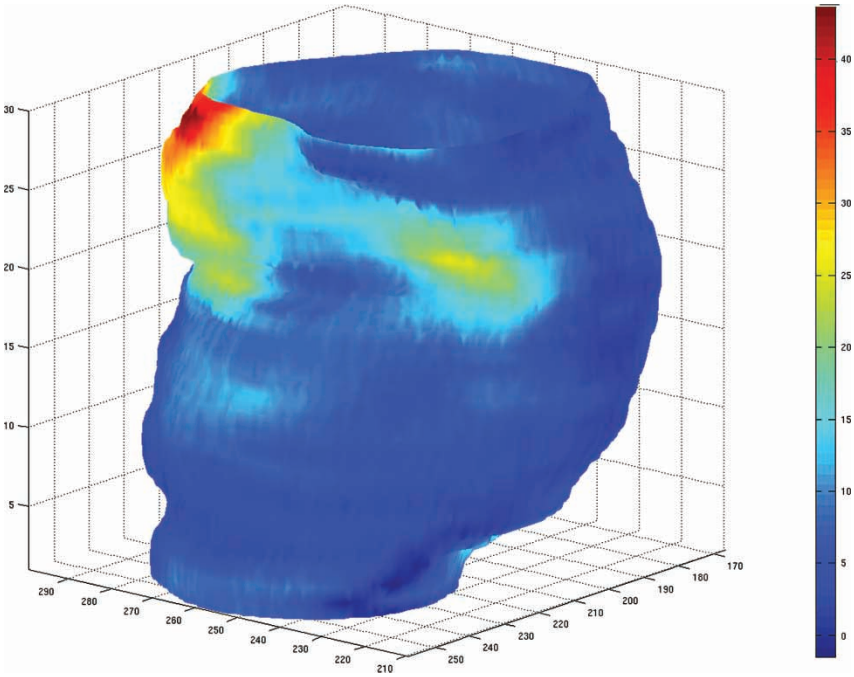

Figure 1a. Mesorectum motion observed in one patient during the course of radiotherapy: Front view.

CTV and its motion to be safely applied. IGRT, providing an exact knowledge of anatomy during the course of treatment, permits adjustments to improve accuracy in dose delivery. Also IGRT taking advantage of more reliable imaging techniques such us ultrasmall superparamagnetic iron oxide (USPIO) enhanced MRI to detect node involvement or FDG-PET to demonstrate tumour response during a radiotherapy course, can furthermore improve rectal cancer treatment.

Future developments will probably involve the use of new PET tracers in order to identify new boost areas within the CTV and the use of PET to monitor the dose deposition during treatment [54] leading to

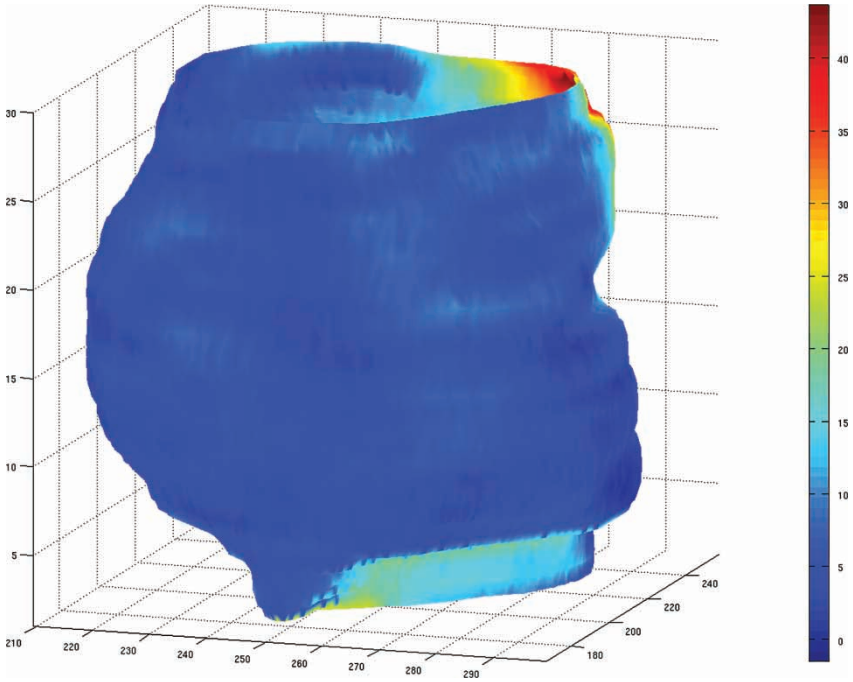

Figure 1b. Mesorectum motion observed in one patient during the course of radiotherapy: Back view.

the next radiotherapy frontier known as voxel-intensity based IMRT or dose painting by numbers.

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