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Review Article

Conformal radiotherapy in rectal cancer: a dosimetric review

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ABSTRACT

It has been a decade since preoperative chemoradiotherapy is the standard of care in the treatment of rectal cancer. Even though the main picture remains the same, there were many refinements that happened in delivery of chemotherapy, radiotherapy and, of course, surgical skills. Technical advancements in radiotherapy helped us to precisely deliver radiotherapy with minimal side effects. Nevertheless, none of these have been studied in detail to assess the effectiveness and bad effects. It has been noted that modern radiotherapy techniques even though reduces high doses to the critical organ doses, but increases the volume of normal tissues receiving low dose radiation, the adverse effects of the same need to be assessed. There hadn't been any consensus whether to treat with 3D Conformal Radiotherapy (3DCRT) or Intensity Modulated Radiotherapy (IMRT). This article reviews various dosimetric parameters of various techniques of radiotherapy presently being used in our department which includes conventional, 3DCRT and IMRT.

Keywords: 3DCRT, Chemoradiotherapy, Dosimetric review, IMRT, Rectal cancer

INTRODUCTION

From the early 90s, radical surgery and fluoropirimidine-based chemoradiotherapy (CHRT) have been regarded as the gold standard for the management of locally advanced rectal cancer. Studies carried out by the North Central Cancer Treatment Group and the Gastrointestinal Tumor Study Group concluded that postoperative chemo-therapy coupled with radiotherapy resulted in achieving local tumor control as well as increased survival in stage II and III carcinoma of the rectum, compared with surgery alone.[1,2]

Even though the big picture of this treatment currently remains steadfast, a few of its elements have transformed. The major milestone in this growth was the adoption of total mesorectal excision (TME), which became the preferred surgical procedure, offering a considerable boost in local control. In fact, at one point it was thought that TME could make radiotherapy redundant. However, a randomized study soon demonstrated the maintained benefit of radiotherapy despite an excellent surgery, at least in terms of local control; the advantage showed an even greater improvement with longer follow-up.[3]

The second milestone was to shift the CHRT segment prior to the surgery. It was determined that preoperative radiotherapy enhanced the overall survival as compared to surgery alone.[4] In the previous decade, the leading tendency in the management of rectal cancer, both in North America and Europe, was the utilization of preoperative radiotherapy with conventional protracted fractionation (total dose of 45-50 Gy with daily fractions of 1.8-2 Gy for a duration of five to six weeks) with concurrent chemotherapy followed by surgery, 6 weeks later. Considerable experience with preoperative CHRT demonstrated potential positive results concerning sphincter preservation, disease control and down staging, as well as survival parameters, with an adequate toxicity profile. The chemotherapy agent most often used in this clinical circumstance is 5-fluorouracil (5-FU, given as intravenous infusion). Recently, the only phase III study which focused on the comparison between pre and post-operative CHRT also demonstrated improved tolerance, sphincter-preserving surgical procedures and local control with preoperative CHRT.[5]

Preoperative-radiotherapy alone (in the absence of chemotherapy) followed by surgery, 6 weeks later, reported down staging rates of 18%.[6] However, the use of neoadjuvant chemoradiation achieves down staging figures of about 65%.[7] In addition, the commencement of tumor down staging improves the chance of a total resection as well as the potential for sphincter-preserving surgery. Complete pathologic response rates (PCR) range from 8% to 27% by means of neoadjuvant chemoradiation. It also demonstrated reduced acute small bowel toxicities of grade 3 and 4 severity.

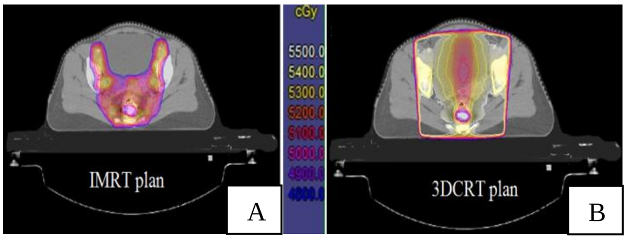

Figure 1A and B: Dose distribution in axial CT slices of same patient being planned for IMRT and 3DCRT respectively.

EVOLUTION OF CONFORMAL RADIOTHERAPY TECHNIQUES

Typical four-field conventional orthogonal planning is regarded to be a satisfactory method for preoperative CRT and chief trials which assessed long-course chemoradiation for rectal cancer have authorized the utilisation of conventional planning within their protocols.

Researchers appraised the effect of three-dimensional conformal planning versus the conventional planning of preoperative chemoradiotherapy for locally advanced rectal cancer on the bladder and small bowel and in optimizing target volume coverage.[8] Conventional and conformal plans were generated for 50 successive patients. The conformal plan defined a gross tumor volume (GTV), a clinical target volume (CTV) 1 to cover possible spread of subclinical disease, a CTV2 to delineate the lymph nodal areas and mesorectum, and a planning target volume (PTV) to take in to consideration, the set-up errors and organ movements. The conventional plan was generated with the help of digitally reconstructed radiographs (DRRs). A dose of 45 Gy was administered in 25 fractions to patients along with concomitant chemotherapy over five weeks. Dose-volume histograms (DVHs) were computed and evaluated for PTV, GTV, bladder and small bowel.

The conventional plan covered GTV in all patients. Considerable differences were demonstrated for median coverage of PTV with conformal planning as compared to conventional planning: 99.2% versus 94.2% (with a range from 95.9 to 100% versus 75.5 to 100%); $p<0.05$. The median volume of small bowel which was irradiated showed considerable reduction for CT plans at all DVH levels. Significant variation was not noted for median bladder doses. The researchers concluded that 3D conformal CT planning is better than conventional planning with regard to tumour volume coverage. It considerably decreased the volume of small bowel irradiated without any decrease in the rate of R0 resection matched up to published data, and it should currently be regarded as the standard of care for the treatment of rectal cancer.

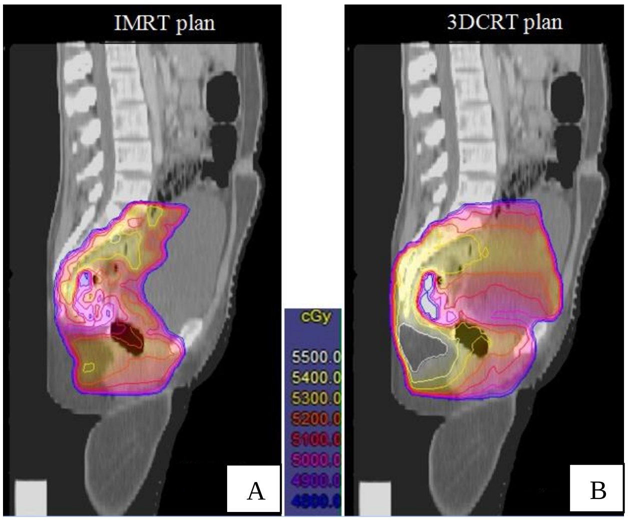

Figure 2A and B: Dose distribution in sagittal CT slices of same patient being planned for IMRT and 3DCRT respectively.

One of the models for the loco-regional management of cancer is anatomic accuracy. The goals of 3DCRT are to attain conformity of the high dose region to the target volume and thus to decrease the dose to the nearby normal tissues. This should decrease both acute and chronic morbidity.[9-13]

If the adverse outcomes of treatment can be diminished in this manner, the dose to the target volume can be enhanced with the anticipation of a more effective cancer cell killing. Technological progresses in radiation oncology, such as intensity-modulated radiation therapy (IMRT), permit greater management accuracy and dose escalation. IMRT is equipped to generate plans that are highly conformal and inhomogeneous, hence reducing the dose to nearby normal organs.

IMRT has shown dosimetric dominance over 3D-conformal radiation therapy (3D-CRT) in a vast majority of tumours. Various examples of anatomical areas in which IMRT offers a dosimetric advantage are:

- Cancer of head and neck, where the targets are positioned lateral and anterior to the spinal cord and surround externally by the major salivary glands.[14,15]
- Carcinoma prostate, where the prostate target volume is invaginated into by the rectum.[16]
- Lung cancer, where a targeted mediastinal lymph node may be placed lateral to and in front of the esophagus.
- Esophageal cancer where the aim is to spare the lungs from higher doses.[17]
- Gynaecological cancers, where the lymph node targets are positioned posterior and lateral to the small bowel.[18,19]
- Breast cancer of the left-side, where the target is concave anterior to the heart and lung.[20]

CONFORMAL TECHNIQUES IN THE TREATMENT OF RECTAL CANCER

Dosimetric results

Biological treatments and new drugs may improve global radiotherapy outcomes, thus, enhancing therapeutic effects; however, acute consequences may also be augmented. Furthermore, a dose-volume relationship has been recognized between the severity of toxicity caused by diarrhea and the irradiated small bowel volume at all dose levels in patients preoperatively treated with chemoradiation for rectal cancer.[21] The irradiated small bowel volume thresholds to envisage severe gastrointestinal toxicity is unidentified, even though a strong association subsists between the level of acute small bowel toxicity and the small bowel volume getting 15 Gy (V15).[22] The advent of innovative and sophisticated irradiation methods, such as intensity modulated radiation therapy (IMRT), signifies a stunning progress in the planning and delivery of external beam radiation. The intensity modulated radiation therapy (IMRT) produces a highly irregular and conformal shaped dose delivery while decreasing dose to nearby normal tissue structures. Moreover, IMRT has shown a dosimetric advantage over 3D-conformal radiation therapy (3D-CRT) in the many of the tumor locations throughout the body, which include pelvic tumors where the bowel irradiation can be considerably decreased.[23]

In a study carried out in the Royal Marsden NHS Trust, UK investigators examined the possibility of performing intensity-modulated radiotherapy (IMRT) sparing the small bowel, in rectal tumors.[24] The target volumes (rectal and pelvic nodal volumes), bladder and bowel were delineated in five patients. All patients were planned for conventional, 3DCRT and forward-planned multisegment three-field IMRT arrangements and compared with inverse-planned simultaneous integrated boost nine-field uniformly spaced IMRT arrangements. Uniformly spaced seven-field and five-field segmented IMRT arrangements were also assessed. 95% of the prescribed dose covered no less than ninety-five percent of both planning target volumes via all arrangements, except the conventional plan (mean rectal and pelvic nodal PTV receiving ninety five percent of the prescribed dose was 32.8±13.7 Gy and 23.7±4.87 Gy, respectively), demonstrated a considerable lack of coverage. The volume of bowel irradiated to 45Gy and 50Gy was reduced in the 3-field forward-planned IMRT plans relative to the three-dimensional conformal RT (26%±16% and 42%±27% respectively). A further decrease of 69±51 cm^3 to 45 Gy and 20±21 cm^3 to 50 Gy were attained with the nine-field uniformly spaced IMRT arrangements 64%±11% and 64%±20% decrease corresponding to the three-dimensional conformal RT. Decreasing the number of beams and optimizing the angles for the five-field uniformly spaced IMRT arrangement did not considerably decrease bowel sparing. The researchers concluded that the irradiation of bowel volume to 45 Gy and 50 Gy was considerably decreased with IMRT, which could markedly bring about less bowel toxicity. Decreasing the number of beams did not diminish bowel sparing and the five-field optimized segmented IMRT arrangement is a rational method to be evaluated in clinical trials.

Similar study performed by Leire et al evaluated target dose delivery, normal tissue avoidance, comformality, and irradiated body volume (IBV) in 3-DCRT by means of classic anatomical landmarks (c3DCRT), 3-DCRT fitting the PTV (f3DCRT), and intensity-modulated radiation therapy (IMRT) in patients having locally advanced rectal carcinoma. 15 patients with locally advanced rectal carcinoma were subjected for IMRT, c3DCRT, and f3DCRT planning. Target delineation was in accordance with the guidelines of the ICRU reports No. 62 and 50. Organs at risk (small bowel and bladder) constraints were D5 ≤50 Gy and Dmax <55 Gy. Dose was prescribed to the PTV as PTV95 ≥45 Gy and PTVmin ≥35 Gy. The coverage of target volume was evaluated with dosimetric parameters like D95, Dmin and Dmax. Comformality and target dose distribution was examined with the Conformity Index (CI) and Homogeneity Index (HI). They evaluated the normal tissue avoidance with the V40 and D5 dosimetric parameters. Additionally, they calculated IBV at 10 Gy (V10), 5 Gy (V5), and 20 Gy (V20). Results showed that the mean doses of GTV95, CTV95and PTV95 were notably lower for IMRT plans. Target dose distribution was more inhomogeneous following IMRT planning while appreciably lower conformality index was noted for 3DCRTplans. The D5 and V40 values for OAR were radically decreased in the IMRT plans. It was also found that V5 was higher for IMRT as compared to f3DCRT planning ($p<0.05$) while V20 was lesser for IMRT plans ($p<0.05$). They concluded that IMRT planning was superior for target conformality and reduced irradiation of the organs at risks at the cost of increased target heterogeneity. The IBV was higher by IMRT planning at 5 Gy or less, while lesser at 20 Gy or more.

In rectal cancer, dosimetric parameters with IMRT are optimistic. Clinical studies to evaluate acute and chronic toxicity, tumor response, tumor control, and survival are to be further conducted. The underlying principle for the utilization of chemo-IMRT in locally advanced rectal cancer is derived from the potential reduction of gastrointestinal toxicity while maintaining the tumouricidal dose to the primary tumor, draining lymph node stations the presacral region. This ability to alter the profile of gastrointestinal toxicity may also enable to decrease the number of fractions by enhancing size per fraction, which eventually may make the rate of pCR better and more cost-effective.

IMPACT OF NUMBER BEAMS ON IMRT PLANNING

Considering the complexity of IMRT and the influence it may impart on a hectic RT department, the necessity of optimizing the number of intensity-modulated beams is important. Guerrero et al have demonstrated that decreasing the number of beams from 9 to 5 did not influence the target coverage or affect bladder and bowel sparing.[24] The very small decline of the pelvic dosimetric parameters is almost certainly a consequence of preserving bowel sparing and is doubtful to have any clinical implications. The decrease in the number of beams is linked to shorter time of delivery and improved pre-treatment quality assurance, for this set of patients, 5 fields were more optimal. Nevertheless, the arrangement of five uniformly spaced fields allows admission of the anterior oblique beams via the couch bars of treatment, at which point a certain amount of dose absorption will take place, which will modify the dosimetry of the provided plan. In order to evade this, researchers formed plans with customized beam angles. These were consequently segmented for step-and-shoot method of treatment delivery. Plan degradation may occur to a certain extent, chiefly regarding target dose homogeneity, which is, in their experience with prostate, pelvis and head-and-neck treatment, commonly observed with the process of segmentation. The irradiation of bowel volume to 50 Gy was smallest with 5 fields (14 cm3); a decrease in irradiation of bladder volume to 50 Gy was also noted. This might have been the consequence of different planning constraints that were given and customized beam angles. The minute differences noted suggested that the coverage of the pelvic target was, to some extent, compromised to keep bladder and bowel sparing with the segmented plans. This method is a reasonable negotiation appropriate for clinical testing and delivery.

CONFORMAL TECHNIQUES

Clinical results

Dosimetric studies, by means of conformal methods in rectal cancer, clinical results with the same, have not been well recognized in the literature.

In a paper, published in 2012, a multicentric study scrutinized the acute adverse effects of IMRT and 3DCRT in the management of rectal cancer. Eighty-six patients with rectal cancer treated preoperatively with 3DCRT (n = 56) and IMRT (n = 30) were retrospectively analyzed. Acute adverse effect rates between 3DCRT and IMRT were compared for dehydration, anorexia, pain, diarrhea, vomiting, nausea, radiation dermatitis, weight loss, urinary frequency, fatigue, and blood counts. There were considerably less hospitalizations and visits to the emergency department in the patients treated with IMRT relative to 3DCRT (p = 0. 0 0 5) and no interruptions in treatment with IMRT compared to 20% with 3DCRT (p = 0.0002). Patients who were treated with IMRT had a significant decrease in three or more grades of toxicities (p=0.016). The occurrence of grade ≥3 diarrhea was 9% among 3DCRT patients as compared to 3% of patients receiving IMRT (p=0.31). The investigators thus concluded that IMRT for rectal cancer can decrease treatment breaks, hospitalizations, visits to the emergency department for toxicities of grades greater than or equal to 3, when matched up to 3DCRT.

As of now it is understood that IMRT is feasible in carcinoma of rectum with lesser acute side effects delivering better results. Long-term effects of low dose radiation to the normal tissue with IMRT technique could not be predicted. Further studies are required in order to considerably prove the benefits of IMRT over other techniques of radiation.

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