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Modern External Beam Radiotherapy Techniques for Endometrial Cancer

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1. Introduction

Endometrial cancer is one of the most common gynecological cancers in the world. The standard treatment of endometrial cancer includes hysterectomy with bilateral salpingo-oophorectomy, pelvic and/or para-aortic lymph node dissection/sampling, and/or adjuvant radiotherapy [1]. Selection of adjuvant therapy is based on an approximation of the risk of recurrence with features such as stage, tumor histology, lymphovascular space invasion, and patient age. Randomized trials indicated that whole pelvic radiation therapy (WPRT) reduced the rate of pelvic disease recurrence in patients who undergone hysterectomy for endometrial cancer with high risk of recurrence. Radiotherapy is generally administered as external irradiation alone and/or vaginal brachytherapy. The delivery technique is a critical part of the success of radiotherapy for patients with endometrial cancer. Careful consideration of the related factors involved and critical assessment of the techniques available are fundamental to good and effective practice. The purpose of this chapter is to review the modern external beam radiotherapy techniques available for endometrial cancer, including 3D-CRT (Three-dimensional Conformal Radiation Therapy), IMRT (Intensity-modulated Radiation Therapy), HT (Helical Tomotherapy) and VMAT (Volumetric Modulated Arc Therapy), in terms of their physics and technical characteristics, dosimetric advantage, planning and delivery efficiency, taking into account recent advances in this field. A novel conformal arc radiotherapy technique for postoperative WPRT of endometrial cancer will be proposed. The effect of intravenous contrast agent on dose distribution in treatment planning for postoperative WPRT of gynecologic cancer will also be discussed. In addition, the significance of selecting beam energy for the radiotherapy of endometrial cancer will also be covered. Finally, the clinical choice of different techniques will be discussed.

2. 3D-CRT

Three dimensional conformal radiation therapy (3D-CRT) is a technique where multiple beams of radiation are shaped to match the tumor's size and shape, limiting exposure to nearby tissue and organs. Whereas, radiation beams matched the height and width of the tumor in the conventional radiation therapy era, meaning that much of the healthy tissue had to be exposed to the beams. Usually, three dimensional imaging modalities (typically computerized tomography, CT) are used to define the relevant patient anatomy including tumor target(s) and normal tissues in 3D-CRT. Three dimensional dose calculation algorithms and dose analysis tools, and also three dimensional conformal treatment planning and delivery tools (blocks, multileaf collimators, beams' eye view) are used to maximize dose to the defined target and minimize dose to defined normal tissues. 3D-CRT has been shown to be more effective in killing tumors, while minimizing damage to the healthy surrounding tissue since it was implemented clinically in end of 1980s.

WPRT with 3D-CRT improves the dose distribution for the targets and also the critical structures of the endometrial cancer patients dramatically compared with the conventional four box fields. However, conventional WPRT with 3D-CRT exposes most of the contents of the true pelvis to the prescribed dose, due to the cup-shaped tissue volume produced by the pelvic floor and iliac lymph nodes [2]. In addition, a mount of small bowel tends to fall into the vacated space in the true pelvis after hysterectomy, increasing the amount of bowel treated to high dose. This in turn increases the risk of acute and late small bowel complications, limiting the dose that can be delivered to paravaginal and nodal tissues that are at risk for recurrence. Even with modest doses of radiation therapy (45-50 Gy), the risk of severe injury from postoperative radiation therapy is between 5% and 15%. Although severe chronic toxicities (proctitis, obstruction, fistulas) are uncommon, many women treated with WPRT suffer from a variety of chronic problems including intermittent diarrhea, intolerance to certain foods, and malabsorption of vitamins, lactose and bile acids [3].

3. IMRT

IMRT is an advanced mode of high-precision radiotherapy that utilizes computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor. In contradistinction to 3D-CRT, where the radiation intensity is generally uniform within the radiation portal, IMRT allows for the radiation dose to conform more precisely to the three-dimensional shape of the tumor by modulating the intensity of the radiation beam. Because the ratio of normal tissue dose to tumor dose is reduced to a minimum with IMRT, higher and more effective radiation doses can safely be delivered to tumors with fewer side effects compared with conventional radiotherapy techniques. IMRT has been shown to be a promising approach to give higher than conventional conformal dose with better sparing of bladder, rectum, and small bowel for WPRT [4-7]. The improved conformity of IMRT has been shown to significantly reduce the acute and late toxicities of organs at risk (OARs) for patients with endometrial cancer [8-9].

4. HT

HT is a new method of IMRT that delivers highly conformal dose distributions in a helical pattern. HT was first proposed by Mackie and is now commercially available from TomoTherapy (TomoTherapy Inc, Madison, WI, USA) [10]. In HT, a fan beam of radiation rotates around the patient who is translated through the bore of the tomotherapy machine as in conventional CT. The beam trajectory follows a helical path during delivery and is modulated by a binary MLC. Treatments are optimized from 51 projections and can be conceptualized as IMRT beams delivered from 51 equally spaced angles. The benefit of HT in improving dose homogeneity and a reduced dose to critical structures have been reported in prostate cancer [11], nasopharyngeal cancer [12], other head and neck cancer [13], breast cancer [14], and intracranial tumors [15].

5. VMAT

VMAT is a newer way of IMRT planning and delivery technique, in which the dose rate, MLC leaf positions, as well as the gantry rotation speed vary continuously during the treatment. It falls into the more general category of intensity-modulated arc therapy (IMAT), which was first proposed by Yu [16]. The most important characteristic of VMAT compared with the conventional IMRT is the higher delivery efficiency, with similar or better dose distribution. Cozzi et al [17] evaluated VMAT for the whole pelvic radiotherapy for cervix uteri cancer. They found Systematic and highly statistically significant reduction of bladder and rectum involvement with uncompromised target coverage compared to conventional IMRT.
A systematic study on 3D-CRT, IMRT and HT for WPRT in postoperative endometrial cancer patients has been performed and published by the Peking University Third Hospital [18]. They compared the dosimetric characteristics of 3D-CRT, IMRT and HT, and also systematically investigated the integral dose (ID) and low dose bath to organs at risk (OARs) and normal tissue (NT). They found that compared with the 3D-CRT plans, IMRT can achieve more conformal PTV coverage, lower volume of OARs and NT receiving dose higher than 20 Gy, and lower ID to OARs and NT, a little higher volume of NT receiving dose lower than 10 Gy. IMRT and HT did not increase the integral dose to NT significantly, although a larger volume of NT is irradiated to a low dose in the range of 2-10 Gy. The results were similar in HT, except that the volume of bowel and pelvic bones receiving dose of 5 Gy and 10 Gy increased, and the ID to NT increased slightly. But, the difference in ID to NT between HT and 3D-CRT is less than <5%. The mean conformity index was 0.67, 0.87 and 0.87 for 3D-CRT, IMRT and HT plans. Compared directly with IMRT, HT showed more homogeneous PTV dose and better sparing of rectum and bladder, but higher volume of bowel, pelvic bones and NT receiving dose lower than 20 Gy, and slightly higher ID to pelvic bones and NT.

6. Conformal arc

Conventional WPRT with 3D-CRT exposes most of the contents of the true pelvis to the prescribed dose. IMRT provides more conformal dose distribution and better sparing of critical structures for WPRT. However, IMRT is more complicated in planning and delivery, requiring more expensive equipments and time-consuming quality assurance, with many small, irregular, and off-center fields. Not all the institutions have the facilities and personnel for IMRT, especially in the developing countries and regions. Yang et al [19] explored and evaluated a novel conformal arc radiotherapy technique for postoperative WPRT of endometrial cancer. This technique involves two-axis conformal arc therapy (2A-CAT) each with 180 degrees rotation around two isocenters in two separate dose shaping structures, which were formed by cutting off the central 2.5 cm of PTV in the sagittal plane of the body. In order to produce concave and conformal dose distributions to protect the organs at risk, these two dose shaping structures were considered as the target volume for the dynamic MLC instead of the PTV itself. They demonstrated that the mean conformity index was 0.83, 0.61, and 0.88 for the 2A-CAT, 3DCRT and IMRT plans, respectively. The mean homogeneity index was 1.15, 1.08 and 1.10. The mean dose to small bowel and colon, rectum, bladder and pelvic bones was 1.19 Gy, 3.39 Gy, 4.65 Gy and 1.64 Gy lower with 2A-CAT than with 3DCRT ($p<0.05$)，although a little higher than with IMRT. The mean dose to normal tissue was 1.87 Gy higher with 2A-CAT than with IMRT ($p=0.00$). The difference in mean dose to normal tissue in 2A-CAT and 3DCRT was not significant statistically. 2A-CAT offers more conformal dose distribution and better sparing of bowel, rectum and urinary bladder compared with 3D-CRT, although the dose uniformity and conformity is still inferior to IMRT.

This new 2A-CAT technique was found advantageous in many aspects. First, it only requires a linear accelerator equipped with a MLC device, it is more available than IMRT, and can be implemented in most institutions, while it may not be feasible to implement IMRT techniques in much of the developing world, where many gynecologic malignancies, in particular cervical cancer, are quite common. This technique, if adopted, may significantly improve the delivery of radiation in gynecology patients in parts of the world where IMRT may not be possible to implement. Second, it needs less manpower for planning (forward planning for 2A-CAT and inverse planning for IMRT), verification, and quality assurance. Since, in endometrial cancer, the geometrical correlation of the target volume and organs at risk is consistent, it is relatively easy to prepare a treatment plan template. Third, 2A-CAT has the added advantage of shorter fractional delivery time and less MU. The mean number of MU is 240, 451 and 877 for 3D-CRT, 2A-CAT and IMRT plans in their study. Lastly, this new 2A-CAT could be considered as a treatment of selection for postoperative WPRT of endometrial cancer patients, and likely for a wide group of postoperative or even preoperative and definitive WPRT indications, including cervical cancer, prostate cancer and rectal cancer. They are further exploring this 2A-CAT technique for these tumor sites. Eventually, it is possible that this practical 2A-CAT technique would have utility as a short-cut method and would become an accepted alternative for IMRT in external beam radiotherapy (EBRT) of these indications, especially in the not well equipped institutions in facilities and personnel. It will enhance the feasibility and availability of the clinical practice of high precision conformal radiotherapy with its simplicity, extensive availability combined with further improvement and refinement.

7. Beam energy

Higher energy photons were usually used in the conventional conformal radiotherapy for the endometrial cancer due to the higher penetration ability and better dose distribution in terms of the target coverage and sparing of the critical structures [20].

The basic teaching in radiotherapy has been that higher energies (≥10 MV) are preferred for deep-seated pelvic/abdominal lesions, particularly for larger target volumes or larger size patients. Recent work in the field of IMRT has suggested that this energy dependence disappears once beam modulation is added, especially when more beams are used although some researchers suggest that there is still a value to higher energies for deep-seated targets as the volume of the target increase [21]. The value to higher energies for deep-seated targets in IMRT is still a controversial issue. Yang et al [18] found that, the use of 18 MV reduced the IDs to the OARs, NT and the whole body compared with 6 MV for conformal plans. This is consistent with the essentials of radiotherapy physics found in the classic textbooks: higher penetrative quality, more pronounced build-up, lower skin dose, steeper dose gradients at the PTV margin, better dose conformation to the PTV, and more effective dose sparing of normal tissue make high energies the superior beam quality in many clinical situations, especially for the abdominal and pelvic targets. For IMRT plans, the use of 18 MV also reduced the IDs to normal tissue and the whole body, although no significant difference was found in the PTV coverage and IDs to OARs compared with the 6 MV plans. The mean integral dose to normal tissue was 2.4% lower with 18 MV plans (P=0.00). As an ancillary finding, they determined that there is an increase in monitor units (MUs) when lower energy was used in both 3D-CRT and IMRT plans. The mean MUs are 300 and 237 for 6MV-3DCRT and 18 MV-3DCRT plans, 1115 and 926 for 6MV-IMRT and 18MV-IMRT plans. It should be noted that, however, a limitation of their study is that the neutron peripheral dose was neglected in the 18 MV plans. The peripheral dose to distant normal tissue outside the radiation therapy patient's treated volume could be increased in IMRT due to the increased x-ray leakage radiation to the patient, and also from neutron leakage radiation associated with high energy x-ray beams (>10 MV).

8. The effect of intravenous contrast agent

The intravenous contrast agent (CA) during the CT simulation is helpful in accurately delineating the tumor targets and OARs for the patients with endometrial cancer due to the complex anatomy of the pelvic region, whereas, accurate contouring of the target volumes and OARs is the prerequisite to get a high degree of dose conformity in IMRT. In the treatment planning system, Hounsfield units (HU) of CT numbers are used for the dose calculation and heterogeneity correction. Iodine containing CAs, used during CT scan, lead to an increase of HU in tissues with increased CA uptake, and the high HU acts like high density tissue for dose calculation. But, the CA is only present during the CT simulation process, not during treatment. Therefore, it causes errors of the dose to be irradiated in a patient. Yang et al [22] examined the effect of intravenous contrast agent on dose distribution for postoperative whole pelvic radiotherapy (WPRT) of gynecologic cancer. They demonstrated that the doses calculated from the enhanced CTs were lower than those from the non-enhanced CTs, but the differences of mean dose to PTV, OARs and normal tissue were less than 1.0 Gy, the differences of the maximum dose to OARs and normal tissue were less than 2.0 Gy. The differences were not statistically significant between the non-enhanced and enhanced CTs. So, when the plans created from the enhanced CT are applied to a patient, the PTVs will receive more dose than planned. However, the degree of overdose seemed to be negligible clinically, because the concentration of CA was low and the volumes of the enhanced structures were small.

9. Summary

Technical innovations in the treatment planning and delivery of radiotherapy over the last three decades have changed dramatically the practice of radiation therapy. 3D-CRT is now firmly in place as the standard of practice in clinics around the world. IMRT represents a major advance in the delivery of radiotherapy which delivers higher than conventional conformal dose with better sparing of adjacent critical structures. The benefit of improved dose homogeneity and better sparing of critical structures in helical tomotherapy (HT) compared with conventional linac-based IMRT has also been reported. IMAT becomes more and more attractive due to its significant efficiency improvements with uncompromised target coverage, and the sparing of organs at risk and healthy tissue compared with conventional IMRT.

3D-CRT, IMRT, HT and IMAT are all advanced external beam radiation therapy techniques, each having their own relative merits. They differ in terms of the trade-offs between treatment planning time, treatment delivery time, and overall plan quality. IMRT plans can be created in a much shorter period of time as compared to either VMAT or tomotherapy, and VMAT (either single or dual arcs) has the lowest estimated treatment delivery time compared to both IMRT and tomotherapy. With respect to plan quality, it appears that tomotherapy can meet most of the dose-volume objectives, and can provide the most uniform dose to the PTV. For VMAT itself, the choice of 1 or 2 arcs represents a trade-off between plan quality and treatment time whereby single arc plans are expected to be deliverable in a shorter period of time. Adding an additional arc may improve the plan quality with an increase in the treatment time. However, a single arc that is delivered in less than 2 minutes may unduly compromise the plan quality for very complex cases.

VMAT reduces significantly the treatment time (beam on time) compared with both IMRT and tomotherapy. This in turn increases patient comfort, reduces patient motion and internal organ's displacement (e.g. bladder or rectum filling changes over time) during treatment. In addition to the shorter delivery time, VMAT is advantageous in its availability and versatility compared with helical tomotherapy. It can be implemented on the standard C-arm linacs, with wider utilization as, e.g., low and high energy photon beams, non-coplanar arcs in addition to dose rate, gantry speed and possibly collimator variations during delivery to better personalize treatments and increase conformal avoidance of radiotherapy.

The clinical interest of external beam radiotherapy for the gynecological cancer include the treatment of the primary site, and also the pelvic lymph nodes at various levels depending on stage, with proximity with highly sensitive OARs. As a result, gastrointestinal and genitourinary tracts are often highly involved and could lead to acute and late toxicities. The dose-volume objectives represent a significant challenge to the radiotherapy techniques, especially for the demanding cases. The dosimetric and clinical benefits of IMRT for postoperative WPRT have been demonstrated in endometrial cancer patients [8-9]. HT can deliver a more conformal dose to the target volume with greater degree of freedom of intensity modulation due to the helical pattern of dose delivery and unique binary MLC. The improved sparing of rectum and bladder of HT is expected to further reduce the acute and late toxicities, especially for the patients requiring local boost and concurrent/ sequential chemotherapy. However, these benefits of IMRT and HT are achieved generally at the cost of a greater volume of normal tissue in the irradiated volume receiving a low dose. Greater volume of pelvic bones exposed to a dose of 2-20 Gy could increase the risk of hematologic suppression [23] and bone fracture [24]. There has also been concern about the increase of normal tissue integral dose (ID) with multiple beams radiation therapy as a potential risk factor for the development of secondary malignancies in IMRT [25]. Given the life expectancy of the older patients with endometrial cancer, the risk of secondary cancers in the larger volume of NT irradiated to low dose may be small.

The study published by D'Souza and Rosen [26] suggested that the total energy deposited in a patient is relatively independent of treatment planning parameters (such as beam orientation or relative weighting when many beams are used) for deep-seated targets, the ID to NT increases with increasing size of the anatomic region for similar tumor sizes, decreases with increasing size of targets for similar anatomic region size. HT slightly increased the ID to NT and pelvic bones in reference [18] compared with IMRT. This might be attributable to the larger and longer target volumes exposed to more radiation beams in the helical pattern of radiation delivery. This finding also suggests that one technique cannot be considered the "end-all" for everything, the advantage that HT has over IMRT is that while HT reduces the dose received by critical structures at the expense of a greater volume of normal tissue exposed to a low dose. Each approach should be evaluated in terms of the specific objectives when selecting the best option for a given patient. If the objective is to always minimize ID to normal tissue, protons are emerging as an important option [27-28].

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11. References

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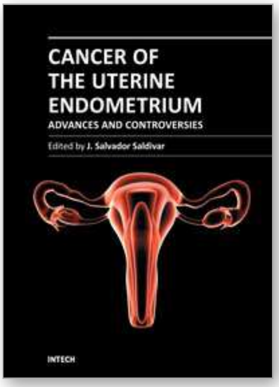

Cancer of the Uterine Endometrium - Advances and Controversies

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The book Cancer of the Uterine Endometrium - Advances and Controversies brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source of advances in the diagnosis and therapeutic strategies in this field of gynecologic cancer. Each section in the book attempts to provide the most relevant evidence-based information in the biology and genetics, modern imaging, surgery and staging, and therapies for endometrial cancer. It is hoped that future editions will bring additional authors to contribute to this endeavor. To this end, it is our patients who will benefit from this work.