JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Radiation Oncology

Commentary

Challenges in Radiotherapy Treatment Planning in the High-Precision Radiotherapy Era

Rex Cheung*, MD, PhD

*Corresponding author: Dr. Rex Cheung, 275 S. Bryn Mawr Ave, K43, Bryn Mawr, PA 19010, USA, Email: cheung.r100@gmail.com

Received: 12-01-2014

Accepted: 12-29-2014

Published: 01-03-2015

Introduction

In modern era of high-precision radiotherapy including stereotactic radiotherapy (SRT), intensity modulated radiotherapy (IMRT), and image guided radiotherapy (IGRT) [1], 3-dimensional (3D) target delineation has become very important [1,2]. For example, in Japan, there are now about 50% of centers equipped for high-precision radiotherapy [1]. The precision of modern radiotherapy is very high, radiation dose are becoming very high and the safety margin needs to be very small to spare normal tissues [2]. Traditional 2D simulator we used only twenty years ago are now being replaced by 3D simulation using computed tomography (CT) and magnetic resonance imaging (MRI) [3]. Modern radiotherapy relies on 3D imaging data [4] that require contouring of the gross target volume (GTV), clinical target volume (CTV), internal target volume (ITV) and planning target volume (PTV) [2]. GTV includes the tumor imaged and detected by clinical examination [2,5]. CTV includes clinical target volume at risk of microscopic spread including the lymph nodes at risk [2,5]. PTV includes additional margin to cover the organ motion and set up errors [6]. Radiotherapy machines continue to evolve. IMRT could be performed using linear accelerator (LINAC) with segmented multileaf collimators (MLC) and with more advanced machines using dynamic MLC that can continue to move while the machine and/or the table move [7].

Emerging imaging techniques, radiotherapy technologies and new systemic treatments will continue to influence how we design our radiation treatment volumes. This paper is part of a series discussing current challenges of designing radiation treatment target volumes. This paper includes quite a bit of technical details of radiotherapy and the associated local and systemic treatments because the target volumes needed in radiation treatment are intimately related to the treatment techniques being used, and the other treatments the patients receive. This paper is a commentary, part of a series of papers [8-12], on the current difficult clinical scenarios encountered in radiotherapy. This paper attempts to make choices on the best practices in radiotherapy. Hopefully, it will be a useful fountain of knowledge for the readers.

Lung cancers

Lung cancer targeting is currently more focused on gross tumors and positive lymph nodes to allow safe dose escalation [13]. With modern photon and particle radiotherapy techniques, radiation dose could safely be escalated to 74 Gy in 2 Gy fractions even when combined with chemotherapy [13,14]. Although a randomized intergroup RTOG phase III trial showed no benefits of using 74 Gy over 60 Gy for chemo-radiotherapy of non-small cell lung cancer (NSCLC) with or without cetuximab [15]. Tyrosine kinase inhibitors (TKIs) have emerged as very effective drugs for lung cancers. For example, for lung cancer patients with leptomeningeal carcinomatosis and mutant epidermal growth factor receptor (EGFR), TKI have been found to prolong median survival to about 11 months [16]. TKIs will increasingly be used with radiotherapy and their safety and efficacy will continue to be studied.

Positron Emission Tomography (PET) has emerged as a major tool in treatment planning of lung cancer radiotherapy. PET can locate the gross tumors and involved lymph nodes better and this could potentially avoid over-contouring and hence avoid over-treating uninvolved regions. For an excellent review, see [17]. PET values of about 2.5 in absolute standardized uptake

value (SUV) and about 30–40% of maximum SUV appear to be the optimal level to use to define the target volumes of gross tumors and positive lymph nodes based on correlative studies with tumors measured on pathological slides [17].

With better systemic therapy, the target volumes in postoperative radiotherapy (PORT) for NSCLC are also evolving. For example, in a recent paper [18], the PORT target volumes included bronchial stump, ipsilateral hilum, and only involved mediastinal lymph node stations when PORT was combined with adjuvant cisplatinum-based chemotherapy [18]. In this study, number of involved mediastinal lymph nodes were also found to be an important prognostic factor for postoperative radiotherapy (PORT) for NSCLC in addition to involved lymph node stations [18].

Stomach cancers

The standard postoperative chemo-radiation of stomach cancers consisted of 45 Gy in 1.8 Gy fractions, with concurrent 400 mg/m^2 5-fluorouracil (5-FU) and 20 mg/m^2 leucovorin for 5 days, followed by radiotherapy for 5 weeks with 5-FU and leucovorin for the first 4 and last 3 days, two 5 days cycles of 5-FU and leucovorin were given 4 weeks after the completion of the chemo-radiotherapy [6]. This regimen was found to be effective for stomach cancers after D0 and D1 [19] or D2 lymph node dissection [20]. As in treating other gastrointestinal cancers, radiotherapy of stomach cancers is often limited by the radiation sensitivity of the adjacent abdominal organs. As more advanced radiation treatment machines are becoming available, studies are being performed to find the best ways to spare the sensitive abdominal organs. For example, in one study, radiotherapy with advanced technologies using volumetric modulated arc therapy (VMAT) a dosimetric advantage over more traditional treatment techniques treating stomach cancer postoperatively except the duodenum [6]. In this study for stomach cancers treatment [6], CTV was defined as the surgical bed and the peri-gastric lymph nodes [6]. PTV was defined as adding 5 – 10 mm to the CTV to account for setup errors and organ motion [6]. The lymph nodes contoured were according to SWOG/INT-0116 [6,19]. The lymph node stations contoured in this study included the para-cardial, para-aortic, celiac, para-esophageal, hepatic portal, pancreaticoduodenal and splenic hilum lymph nodes if deemed high risk [6]. As expected, since duodenum mobility is limited by the ligament of Treitz, it is more susceptible to radiation injury [21]. As demonstrated by multiple studies, duodenal sparing remains challenging even with advanced radiation treatment machines [6,21,22].

Pancreas cancers

Radiotherapy of pancreas cancers has been limited by sensitive organs at risk (OARs) including duodenum that could tolerate only about 54 Gy of external beam radiotherapy (EBRT) [22,23]. Multiple imaging modalities have been developed to stage pancreatic cancer including trans-abdominal ultrasound, computed tomography, magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography (ERCP) [24]. Endoscopic ultrasound (EUS) has about 90% accuracy in detecting pancreas cancer because it can put a high frequency transducer right next to the tumor, with recent development of contrast enhancement, EUS could be used to differentiate pancreas from chronic pancreatitis and neuroendocrine tumors, and EUS-FNA could be used for histological diagnosis [24]. Surgical resection remains the only hope of cure of pancreas cancer [24,25]. When surgery is performed for exocrine ductal pancreas cancer, tem or more lymph nodes should be obtained [25]. Preoperative chemo-radiotherapy treatments are often needed as many pancreatic cancers are not resectable at diagnosis.

Gemcitabine-based or fluorouracil-based preoperative radiotherapy treatments are often used to treat pancreatic cancers that are borderline resectable. A well accepted gemcitabine-based preoperative chemo-radiotherapy regimen for pancreas cancer was studied by M.D. Anderson Cancer Center (MDACC) [22,23]. This regimen consists of four weekly 400 mg/m^2 gemcitabine and hypofractionated 30 Gy EBRT over two weeks [22,23]. The target volume is defined as gross primary tumor and lymph nodes, and used a 3 cm cradiocaudal block margin and a 2 cm radial margin [22,23]. Radiotherapy is scheduled Monday to Friday, starts 48-72 hours after a dose of Gemcitabine on Saturday. This regimen has been found to be safe and effective.

Other treatment techniques are also being explored. In this study, accelerated EBRT to 50 Gy in 2.5 Gy fractions with concurrent 825 mg/m^2 capecitabine twice daily on days of radiation was used [24]. The investigators [24] used MDACC classification for borderline resectability was used [26]: category A, abutment < 180 degree of the superior mesenteric artery and/or celiac axis, abutment or encasement of a short segment hepatic artery and involvement of the portal vein and hepatic vein amenable to vascular reconstruction. Category B, concern for extrapancreatic metastasis because of either a indeterminate nodule detected by imaging or pathologically proven lymph node metastasis . Category C, borderline patient performance status to tolerate the pancreatic resection. Less than 20% of gastric volume was allowed to receive 45 Gy (V45 < 20%) [24]. Target volume (GTV) included the gross tumor and draining lymph nodes, without covering the porta hepatitis and para-aortic lymph nodes [24]. 4D CT was performed to assess tumor motion, but the motion in all cases was too limited to use 4D CT for planning. 0.5 – 1.5 cm was added to the GTV radially and 1– 2 cm craniocaudally to define the PTV [24]. The study was stopped early because two patients developed severe gastritis and gastric ulceration a few weeks after

completion of chemo-radiotherapy [24]. Metastatic or locally advanced (unresectable) pancreatic cancers should be treated with a palliative intent [25].

Rectal cancers

Preoperative radiotherapy is better than postoperative radiotherapy in terms of local recurrence and sphincter preservation [27]. National Surgical Adjuvant Breast and Bowel Project (NSABP) R03 showed improved disease free survival at 5 years and a trend towards improved overall survival at 5 years with pre-operative radiotherapy [28]. Total Mesorectal Excision (TME) has become the standard of care surgical technique recently. TME was developed about 30 years ago, the procedure removes the entire rectal mesentery including perirectal fat, blood supply and lymphatic drainage [29]. The recurrence rate when Dr. Heald demonstrated this technique was 0% at 2 years for 100 cases without adjuvant therapy [29]. In Danish preoperative trial, at 10 years, local recurrence was also low at 11% after TME, and even lower that 5% after preoperative radiotherapy and TME [30].

Acute grade 3 gastrointestinal (GI) toxicities (diarrhea) could occur in up to 29% of rectal cancer patients receiving adjuvant radiotherapy [27]. Treatment breaks may affect the outcome, therefore avoiding the GI toxicities is important [27]. In rectal cancer treatments, the mesorectum, internal iliac lymph nodes and presacral lymph nodes are contoured [27,31]. Classic rectal 3-field radiotherapy would include using a prone belly board, the superior border is set at L5/S1 interspace, there is a 2 cm margin from bony pelvic inlet, the inferior border is set at below ischiotuberosity or 3 cm below gross tumor, the posterior border is set at 1 cm posterior to bony sacrum, the anterior border is set at 3 cm anterior to the sacral promotory [2,27]. This traditional 2D treatment technique has been compared with 3D conformal radiotherapy (3DCRT) and IMRT, the PTV expansion for 3DCRT and IMRT was 7mm, no contrast was used and no instruction was given to the bladder filling during simulation and treatment [27]. Contrast CT closest to the date of simulation was used to help with contouring the small bowel [27]. Small bowels are contoured 2 cm superior and inferior to the PTV [27]. In this study the heterogeneity was limited to 107% [27]. In this study, 7 beams IMRT plans were used with highest optimization priority set to cover the PTV, and to avoid the small bowels [27]. Heterogeneity Index (HI) (D5% - D95%/prescription dose) and Conformality Index (CI) were calculated as volume receiving the prescription dose relative to the target volume (V45Gy/PTV) [27]. V15Gy (volume receiving 15 Gy) <150 cc of small bowel is associated with low treatment related diarrhea rate, and the majority of patient who had grade 3 or higher diarrhea had V15Gy > 300 cc [27,32]. This study found using IMRT with belly board reduced the V15Gy to V45Gy [27]. IMRT took longer time to deliver when compared with the 3DCRT doses, but this may be overcome with modern and faster radiation treatment machines [27] as discussed below.

Anal cancers

Rotation IMRT using RapidArc has been found to reduce treatment time and monitor units significantly in treating a complicated T3 anal canal cancer with inguinal lymph nodes involvement with comparable coverage compared to step-and-shoot IMRT [5]. In this study, the patients was simulated with 3D imaging in a supine position immobilized by a Vac-Loc device [5]. The target volumes were contoured according to established contouring guidelines [5,31]. GTV included the primary tumor and macroscopically involved lymph nodes. CTV 59.4 Gy was defined by adding 1 cm margin to the GTV excluding bone structures [5]. The PTV 59.4 Gy was defined by adding 0.5 cm to the CTV 59.4 Gy [5]. The CTV 49.5 Gy was defined as the high-risk area without evidence of disease [5]. This included the rectal walls, ischioanal fossa, mesorectum, anal canal, perirectal nodes, internal and external iliac lymph nodes, obturator and inguinal nodes [5]. PTV 49.5 Gy was defined by adding 1 cm to the CTV 49.5 Gy [5]. Dose higher than 107% of prescription was limited to lower than 2% [5]. The iliac wings were contoured from acetabula [5]. IMRT was found to reduce the dose to iliac wings from average of 27 Gy to a clinically significant18 Gy [5]. Studies have shown that keeping the iliac bones below about 20 Gy would lower the hematologic toxicity to an acceptable level [33,34]. Thus more effective radiotherapy has become available because of the development of more advanced radiotherapy machines [5].

Prostate cancer

The consensus atlas of pelvic lymph nodes for high-risk prostate cancer has been developed by RTOG [35]. The targeted pelvic lymph nodes include distal common iliac, presacral lymph nodes from S1-S3, external iliac, internal iliac, and obturator lymph nodes from L5/S1 to pubic symphysis [35], arteries and veins plus 7 mm around them are used as surrogate for the lymph nodes carving out the bladder, muscles, bones, small bowels [35]. A recent interesting study using modulated ARC (mARC) with optimization occurs every 10 degrees, one segment per 10 degrees, therefore a total of 36 segments, compared with step-and-shoot IMRT with 11 beams, 3 segments per beam, a total of 33 segments, the dosimetry appeared similar [36]. Since it takes time to stop and re-initiate the treatment machine, mARC reduces treatment time for a prostate cancer case from 5 minutes needed by IMRT by half [36]. Rectal radiation dose tolerance has been found to be similar in patients treated with 3DCRT and IMRT, but the treatment is now faster and potentially could decrease the impact of organ motion with modern radiotherapy machines [37].

Skin cancers

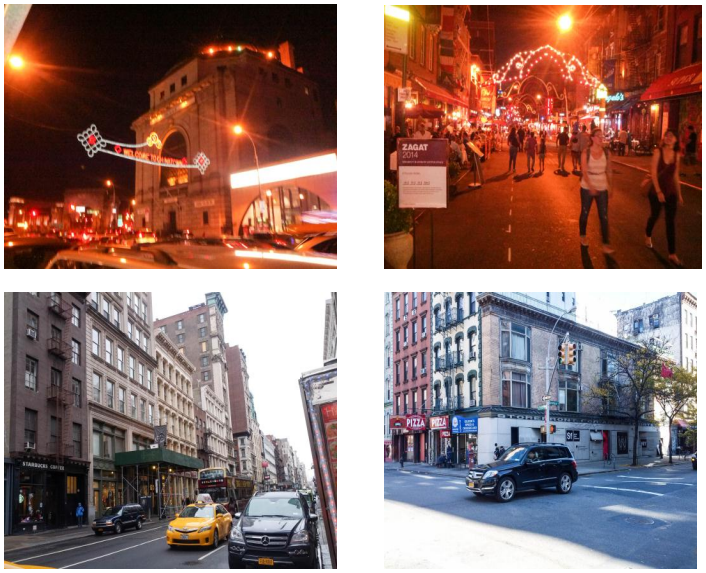
The cure rate for skin cancers with surgery is about 95% [38]. For an excellent review paper, see [38]. Topical treatments include imiquimod (5% cream 5 times a week for about 6 weeks for small BCC < 7.25 cm^2), 5-flourouracil, and photodynamic therapy are associated with about 80-90% cure rate [38]. Other local treatments include using CO_2 or Erbium:YAG lasers, and cryotherapy (liquid N_2 at -196°C) with a freezing time about 10-20 seconds [38]. Systemic hedgehod inhibitor vismodegib has been used for metastatic BCC [38]. For inoperable or after an incomplete (R1 or R2) excision, radiation therapy of basal cell carcinoma (BCC) produced about 95% cure rate [38]. The most common types of BCC are nodular, infiltrative, multicentric superficial that could be treated with horizontal or shave excision, and the rare pigmented, ulcerative BCC [2,38]. Microscopically controlled surgery (e.g. Mohr surgery) with 3D reconstruction produces a recurrence rate of about 2%, about half of conventional surgery combined with conventional histology [38]. The conventional radiotherapy margin recommended for infiltrative type BCC is 0.3 - 1 cm [38]. After R1 resection, a dose of 50-60Gy in 2 Gy fractions could be used, after R2 resection, a dose of 60-70 Gy in 2 Gy fractions could be used [38]. Radiation is contraindicated in nevus BCC syndrome and xeroderma pigmentosa [38].

Squamous cell carcinoma of skin (SCC) and BCC are generally treated similarly with radiotherapy [39]. For hypofractionated radiotherapy for BCC and SCC, 40 Gy in 10 fractions, or 50 Gy in 20 fractions have been used [40], for larger than 5 cm lesions, 54 Gy in 18 fractions or 44 Gy in 10 fractions could be used [39]. Using megavoltage photon machines may increase the risk of recurrence compared with using electron and orthovoltage photon machines, tumor larger than 2 cm, and SCC history do worse than BCC [40]. With modern radiotherapy machines, IMRT could now be used to treat challenging SCC and BCC deeply invasive and near critical organs such the eyes [2,38,40].

Conclusion

In the 3D era, the initial challenges of recognizing the intended target in 3D are being solved and consensus contouring atlases are being developed [31,35,41-43]. However, with continuous development of new oncologic treatments and imaging capacities, it is only natural that the needed targets for radiotherapy will continue to evolve.

After thoughts:



Neighborhoods: Left top, New York City China Town; right top, NYC Little Italy; left bottom, Broadway; right bottom, a museum near SoHo. Lower Manhattan has been the place where newcomers gather and grow like the leaves of grass (Walt Whitman). This has been an impossible place where people sometimes have to make impossible choices. Making the choice to do or not to do, to treat or not to treat, oftentimes is Shakespearean and also Marcel Duchamp's. One person's urinal could be another person's fountain. Sometimes I am excited and inspired by this place to think about what can make impossible possible and new again – for our patients and me.

References

1. Tomita N, Kodaira T, Teshima T, Ogawa K, Kumazaki Y et al. Japanese structure survey of high-precision radiotherapy in 2012 based on institutional questionnaire about the patterns of care. Jpn J Clin Oncol. 2014, 44(6): 579-586.

2. Cox JD, Ang KK. Radiation Oncology: Rationale, Technique, Results, 9th Edition. 2009.

3. Krishnatry R, Patel FD, Singh P, Sharma SC, Oinam AS et al. CT or MRI for image-based brachytherapy in cervical cancer. Jpn J Clin Oncol. 2012, 42(4): 309-313.

4. Qiu H, Wild AT, Wang H, Fishman EK, Hruban RH et al. Comparison of conventional and 3-dimensional computed tomography against histopathologic examination in determining pancreatic adenocarcinoma tumor size: implications for radiation therapy planning. Radiother Oncol. 2012, 104(2): 167-172.

5. Cendales R, Vasquez J, Arbelaez J, Bobadilla I, Torres F et al. IMRT, RapidArc(R) and conformal radiotherapy in the treat-

ment of tumours of the anal canal. Ecancermedicalscience. 2014, 8: 469.

6. Li Z, Zeng J, Wang Z, Zhu H, Wei Y. Dosimetric comparison of intensity modulated and volumetric arc radiation therapy for gastric cancer. Oncol Lett. 2014, 8(4): 1427-1434.

7. Koca T, Basaran H, Sezen D, Karaca S, Ors Y et al. Comparison of linear accelerator and helical tomotherapy plans for glioblastoma multiforme patients. Asian Pac J Cancer Prev. 2014, 15(18): 7811-7816.

8. Cheung MR. Target Volumes, Image Fusion and Contouring in Modern Radiotherapy Treatment Planning. J J Rad Oncol. 2014, 1(2): 1-4.

9. Cheung R, Kang J, Yeung V. Using a Robotic Stereotactic Radiation Treatment System for Re-Irradiation may be Safe and Effective. J J Rad Oncol. 2014, 1(1): 1-3.

10. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. Austin J Radiat Oncol & Cancer. 2014, 1: 2.

11. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. Austin J Cancer Clin Res. 2014, 1: 2.

12. Cheung R. Using stereotactic radiation systems to irradiate and re-irradiate head and neck cancers. J J Rad Oncol. 2014, 1(1): 1-3.

13. Wink KC, Roelofs E, Solberg T, Lin L, Simone CB et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. Front Oncol. 2014, 4: 292.

14. Ohno T, Oshiro Y, Mizumoto M, Numajiri H, Ishikawa H et al. Comparison of dose-volume histograms between proton beam and X-ray conformal radiotherapy for locally advanced non-small-cell lung cancer. J Radiat Res. 2014.

15. Bradley JD, Komaki R, Masters G. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/− cetuximab for stage IIIa/IIIb non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617. ; In: 53rd Annual Meeting of the American Society of Radiation Oncology, Miami, FL., October 2–6, 2011.

16. Umemura S, Tsubouchi K, Yoshioka H, Hotta K, Takigawa N et al. Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama Lung Cancer Study Group. Lung Cancer. 2012, 77(1): 134-139.

17. Chi A, Nguyen NP. The utility of positron emission tomography in the treatment planning of image-guided radiotherapy for non-small cell lung cancer. Front Oncol. 2014, 4: 273.

18. Takanen S, Bangrazi C, Graziano V, Parisi A, Resuli B et al. Number of Mediastinal Lymph Nodes as a Prognostic Factor in PN2 Non Small Cell Lung Cancer: A Single Centre Experience and Review of the Literature. Asian Pac J Cancer Prev. 2014, 15(18): 7559-7562.

19. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001, 345(10): 725-730.

20. Kim S, Lim DH, Lee J, Kang WK, MacDonald JS et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys. 2005, 63(5): 1279-1285.

21. Huang J, Robertson JM, Ye H, Margolis J, Nadeau L et al. Dose-volume analysis of predictors for gastrointestinal toxicity after concurrent full-dose gemcitabine and radiotherapy for locally advanced pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2012, 83(4): 1120-1125.

22. Thompson RF, Mayekar SU, Zhai H, Both S, Apisarnthanarax S et al. A dosimetric comparison of proton and photon therapy in unresectable cancers of the head of pancreas. Med Phys. 2014, 41(8): 081711.

23. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008, 26(21): 3487-3495.

24. Gonzalo-Marin J, Vila JJ, Perez-Miranda M. Role of endoscopic ultrasound in the diagnosis of pancreatic cancer. World J Gastrointest Oncol. 2014, 6(9): 360-368.

25. Seufferlein T, Porzner M, Heinemann V, Tannapfel A, Stuschke M et al. Ductal pancreatic adenocarcinoma. Dtsch Arztebl Int. 2014, 111(22): 396-402.

26. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008, 206(5): 833-846.

27. Mok H, Crane CH, Palmer MB, Briere TM, Beddar S et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses

to small bowel in rectal carcinoma. Radiat Oncol. 2011, 6: 63.

28. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009, 27(31): 5124-5130.

29. Ridgway PF, Darzi AW. The role of total mesorectal excision in the management of rectal cancer. Cancer Control. 2003, 10(3): 205-211.

30. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol , 2011, 12(6): 575-582.

31. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys. 2009, 74(3): 824-830.

32. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010, 76(3 Suppl): S10-19.

33. Mell LK, Schomas DA, Salama JK, Devisetty K, Aydogan B et al. Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2008, 70(5): 1431-1437.

34. Bazan JG, Luxton G, Mok EC, Koong AC, Chang DT. Normal tissue complication probability modeling of acute hematologic toxicity in patients treated with intensity-modulated radiation therapy for squamous cell carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2012, 84(3): 700-706.

35. Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2009, 74(2): 383-387.

36. Dzierma Y, Bell K, Palm J, Nuesken F, Licht N et al. mARC vs. IMRT radiotherapy of the prostate with flat and flattening-filter-free beam energies. Radiat Oncol. 2014, 9(1): 250.

37. Someya M, Hori M, Tateoka K, Nakata K, Takagi M et al. Results and DVH analysis of late rectal bleeding in patients treated with 3D-CRT or IMRT for localized prostate cancer. J Radiat Res. 2014.

38. Berking C, Hauschild A, Kolbl O, Mast G, Gutzmer R. Basal cell carcinoma-treatments for the commonest skin cancer. Dtsch Arztebl Int. 2014, 111(22): 389-395.

39. van Hezewijk M, Creutzberg CL, Putter H, Chin A, Schneider I et al. Efficacy of a hypofractionated schedule in electron beam radiotherapy for epithelial skin cancer: Analysis of 434 cases. Radiother Oncol. 2010, 95(2): 245-249.

40. Khan L, Breen D, Zhang L, Balogh J, Czarnota G et al. Predictors of recurrence after radiotherapy for non-melanoma skin cancer. Curr Oncol. 2014, 21(2): e326-329.

41. Fuller CD, Nijkamp J, Duppen JC, Rasch CR, Thomas CR Jr. et al. Prospective randomized double-blind pilot study of site-specific consensus atlas implementation for rectal cancer target volume delineation in the cooperative group setting. Int J Radiat Oncol Biol Phys. 2011, 79(2): 481-489.

42. Toita T, Ohno T, Kaneyasu Y, Uno T, Yoshimura R et al. A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer. Jpn J Clin Oncol. 2010, 40(5): 456-463.

43. Toita T, Ohno T, Kaneyasu Y, Kato T, Uno T et al. A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer. Jpn J Clin Oncol. 2011, 41(9): 1119-1126.