Available online at www.sciencedirect.com
ScienceDirect
Nuclear Science and Techniques, Vol.18, No.2 (2007) 65–72
NUCLEAR SCIENCE AND TECHNIQUES

Current status of radiation therapy for prostate cancer

FU Shen* SUN Yi LU Yaohong

(Section of Molecular Radiobiology, RadioDepartment of Radiation Oncology, the Sixth People's Hospital of Shanghai Jiaotong University, Shanghai 200233, China)

Abstract Radiotherapy for the treatment of prostate cancer has been extensively explored in the past. Along with the comprehensive understanding of the biology of prostate cancer and rapid advances in terms of technology, the outcome of treatment for the patients with prostate cancer has improved. The authors review radiotherapy as the primary treatment for the disease, with particular emphasis on the technological advances from both the radiobiological and radiophysics aspects. Nonconventional fractionated irradiation like hyper- or hypo-fractionation has been implemented in the clinic, the final results still need to be confirmed in the future. Technological advances like IMRT, IGRT, in the last two decades have significantly improved the delivery of external radiotherapy to the prostate. This has resulted in an overall increase in the total dose that can be safely delivered to the prostate, which has led to modest improvements in the biochemical outcome. However, establishing the standard therapy for prostate cancer remains controversial. It is hoped that the next decades will bring continued advances in the development of biologicals that will further improve current clinical outcomes.

Keywords Prostate cancer, Fractionation, IMRT, IGRT, Brachytherapy

CLC numbers R737.25, R815.6

1 Introduction

Prostate cancer is the most common cancer in western countries. The mortality in China has increased and is ranked as seventh in all cancers. An estimate of 189,000 men were diagnosed as having prostate cancer in 2002 in China, this represents roughly 30% of all cancers[1].

The multiple treatment therapy for prostate cancer includes radical prostatectomy, radiation therapy, hormone therapy, chemotherapy, and so on. Nowadays, radiotherapy has become a standard treatment option for the variable clinical stage of patients with prostate cancer. Data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program show that radiation treatment is commonly included in primary oncologic decisions and radiotherapy has been used for more than five decades, to treat prostate cancer with curative intent. For the treatment of prostate cancer, every patient's disease must be staged before definitive treatment. It is important to present all available data regarding the natural history of the disease, prognostic significance of the diagnosis like PSA, Gleason's score, potential therapeutic benefit of the various modalities, and immediate as well as late sequelae. During the last decade, major technical improvements and advanced understanding of radiobiology have allowed an increase in the therapeutic ratio, thus improving the outcome, while reducing the radiation-induced normal tissue side effects. But several questions including how to select the optimal treatment and the best radiation approach for each individual patient, are still not solved[2, 3]. This review will cover the upstate status of radiation treatment for prostate cancer from the views of radiobiological and radiophysical updates.

Supported by the grant from Shanghai Municipal Health Bureau (044017)

* Corresponding author. E-mail: shen_fu@hotmail.com

Received date: 2007-01-23

2 Biological aspect

Radiation therapy for prostate cancer is usually delivered in 1.8 to 2.0 Gy fractions over seven to eight weeks. The development of any radiotherapy treatment plan takes into account the balance of local tumor control and normal tissue side effects. The normal tissues that are of most concern in radiation therapy for prostate cancer are the rectum, bladder, urethra, and bulb of the penis. Much attention is given to the amount of radiation received by these organs in an attempt not to exceed their tolerance. To enhance tumor control without compromising the surrounding normal tissue tolerance, the change of fractionated irradiation has been explored for the treatment of prostate cancer.

2.1 Hyperfractionation

Hyperfractionation refers to radiotherapy schedules that use multiple daily fractions with reduced fraction sizes and an increased number of fractions. The underlying aim is to maximally exploit the differential effects observed between tumors and normal tissues after irradiation with small doses. The dose-response curves for tumor and late reacting tissues indicate that higher doses can be achieved without an increase in morbidity, by using fractional doses < 1.8 to 2.0 Gy[4, 5], in other words, the lower the dose per fraction, the lower the radiation-induced damage to late normal tissue. Because most of the sublethal damage repair occurs within six hours, hyperfractionated schedules typically consist of twice-daily fractions separated by at least six hours. Since late-responding normal tissues are relatively sensitive to fraction size, the reduced fraction sizes like hyperfractionation allow for an increase in total dose, while maintaining similar or reduced complication probabilities. Improved tumor control probabilities would be expected with the higher total doses. Reported in Dr. Forman's phase I study of hyperfractionated irradiation for prostate cancer[6], two dose levels were used as either 78 Gy/six weeks, 1.3 Gy/Fx or 2.8 Gy/seven weeks, 1.15Gy/Fx, the interval between fractions in both groups was more than six hours. The three-year actuarial probability of Grade 2 gastrointestinal, urology toxicities was 17 % and 16%, there was no Grade 3 or 4 to be noted. At one year, 84% of the patients had a prostate specific antigen < 4; and 53%; < 1 ng/mL. 71% of patients had post radiation biopsies that were either negative (55%) or showed a marked therapeutic effect (16%). The primary results suggested that the use of hyperfractionated conformal radiotherapy facilitated dose escalation with no increase in chronic toxicity compared to standard doses. The initial tumor response, based on prostate specific antigen measurements and postradiation biopsies is highly encouraging. Dr. Forman also conducted a trial of a hyperfractionated conformal photon with conformal mixed neutron/photon irradiation (15 Ngy + 18 PhGy) in locally advanced prostate cancer[7], the one year results were no different from 82.8 Gy/seven weeks with conformal photon.

There are few articles that report about hyperfractionated radiotherapy for prostate cancer. One of the reasons is that prostate tumors often are so slow growing, their response to fraction size may be more similar to late-responding normal tissues (i.e., having a low α/β ratio < 5) than that of rapidly proliferating tumors (i.e., having a high α/β ratio > 10). If this is so, the smaller doses of radiation per fraction, which spare normal tissues in most other types of tumors, may not provide such an advantage in prostate cancer.

2.2 Hypofractionated radiotherapy

Hypofractionated irradiation refers to radiotherapy schedules that use daily fraction size > 2 Gy and the same or less total dose as conventional irradiation is delivered within the shorter period. Recent radiobiological analysis of the radiotherapy results for prostate cancer revealed that prostate carcinoma behaves as a late responding tissue, sharing an α/β ratio lower than 2 Gy. These findings suggest that hypofractionation may be more effective. Reduction of the overall treatment time could further increase response by abrogating the effect of rapid tumor repopulation. Hypofractionation would theoretically offer increased therapeutic benefit with improved tumor control, without increasing late toxicity because of the presumed low α/β ratio of prostate tumors compared with the surrounding normal tissue. The advantages of a hypofractionated radiation treatment regimen also include convenience for patients, increased treatment capacity, and decreased cost.

Even though hypofractionated irradiation for prostate cancer is still under investigation and most of the clinical trials were phase I/II studies, as shown in the literature, the patients with prostate cancer could well tolerate the schedule with early and late morbidity being within acceptable limits[8 - 10]. Two randomized trials further confirmed that hypofractionated irradiation would not cause more severe side effects than those caused by conventional irradiation. The primary results were encouraging so far[11, 12]. The hypofractionated regimens appear to have little potential risk as long as they have excessively short overall times (< 5 weeks) and very small fraction numbers (< 5) are avoided. Appropriately designed hypofractionation schemes would be expected to maintain current levels of tumor control and late sequelae, but with reduced acute morbidity, together with the logistic and financial advantages of fewer numbers of fractions, compared to conventional irradiation.

3 Physical aspects

External radiotherapy is a very effective treatment modality for treatment of prostate cancer, and major technical advances have been observed during the last few years. However, there are still a lot of questions concerning selection of the best treatment for each patient: the more commonly adapted radiation treatment modality is not only based on the different prognostic factors, but also on the patient's request and needs. Over the last years, radiation technology has made major improvements in the different steps of the treatment: the imaging, the treatment planning, and the treatment delivery. It has been moving from the two-dimensional (2-D) approach to the conventional 3-D approach, to the conformal 3-D approach (3-DCRT), to intensity modulated radiotherapy (IMRT) and finally to the 4-D approach (IGRT). This technical evolution allows moving from a dose of 70 Gy or less to a dose in excess of 70 Gy, with the ultimate goal of increasing the local control and decreasing the risk of acute and late complications.

3.1 Conventional (two-dimensional) external-beam radiotherapy

Radiation treatment for prostate cancer is historically back to the 1970s. Before the introduction of modern cross-sectional imaging, the anatomic boundaries of the prostate and the design of treatment fields were determined by the information obtained from conventional plain-film radiographic simulator techniques, using the location of the pubic bone, a Foley catheter balloon, bladder and rectal contrast media, and the DRE as landmarks. Large safety margins were typically required to address uncertainties of tumor target definition. Treatment was typically administered using relatively small 6 cm × 6 cm to 8 cm×8 cm fields applied with rotational arc techniques[13, 14]. Beginning in approximately 1970, treatment volumes were expanded to include the pelvic lymph node drainage of the prostate[13].

The conventional treatment techniques currently being used are based on CT (computer tomography)-assisted planning. Initially, radiation is given to the whole pelvis using a four-field approach, designed to include the prostate, seminal vesicles, and the regional lymph nodes.[14] The cross section of each beam is shaped using individualized Cerrobend blocks to shield the posterior wall of the rectum, the anal canal and sphincter, the small bowel, and the uninvolved bladder and urethra. Treatment is delivered in daily dose fractions of 1.8 to 2.0 Gy, given in five sessions per week, to a total of 45 to 50 Gy. An additional primary target "boost," delivered with either a four-field approach[14] or a bilateral 120-degree arc rotational technique is then administered to increase the dose to the prostate and seminal vesicles (surrounded by a 1- to 2-cm "safety margin" of normal tissue). A major drawback of rotational techniques is that shaped blocking cannot be used to shield normal tissues. Thus, a large volume of the bladder and the rectum receives the same dose as the prostatic tumor target. However, even with the four-field boost approach, effective customized shielding is difficult with conventional treatment planning methods. The standard boost dose is 20 Gy, delivered with the same fractionation schedule that is used in treating the large pelvic fields, with a total dose to the prostate of 65 to 70 Gy. For T1 and small T2 tumors with a low Gleason score, treatment is limited to the prostate target volume (carried to 65 to 70 Gy), because of the small likelihood of seminal vesicle involvement and metastatic spread to the pelvic lymph

nodes.[15]

In terms of efficacy, using conventional irradiation for local control became increasingly poor as the stage or Gleason score increased. In the historical experience of Bagshaw et al.[16], the 10- and 15-year survival rates were 58% and 36%, respectively, for stage B (intracapsular tumor), and 36% and 22%, respectively, for stage C lesions (extracapsular extension) in a series of 841 patients treated before the PSA (prostate serum antigen) and CT era. In a more recent series, Hanks et al.[17] reported that for 120 patients treated with 70 Gy and followed for 12 years, the biochemical control rate was only 58% for T3 disease, compared to 72% for T1 lesions.

There is a direct relation between the dose and the probability of local control. Several series have suggested a higher control rate with an increasing radiation dose. A major concern is certainly the risk of late toxicity, which may have a detrimental effect on the patient's quality of life. The risk of radiation-induced late effects is not only related to the dose and volume, but also to the technique used, hence the three-dimension conformal radiotherapy has been come into place.

3.2 Three-dimensional conformal radiotherapy (3-D-CRT)

The introduction of CT, modern 3-D treatment planning, and the conformal approach shaping the beams by blocks or through a multileaf collimator allow an increase in the dose to the tumor, while reducing the dose to the bladder and the rectum: 3-D treatment planning systems vary in details, but are based on common principles. CT images are used to segment the prostate and normal organs and to produce high-resolution 3-D reconstructions. Modern, dedicated, CT simulators incorporate traditional radiographic simulation procedures, such as establishment of the treatment isocenter and the placement of fiduciary skin marks, and CT imaging into one session. The CT data are also used in the calculation of dose distribution, because modern dose calculation formalisms are based on electron density ratios of the anatomic structures included in the treatment fields.[18] Treatment is planned and delivered to the patient in the supine or prone position, using individually fabricated immobilization devices to assure daily reproducibility of positioning on the treatment couch. Because prostatic displacement during a course of radiotherapy is affected by rectal and bladder volumes, some recommend that the patient empty his bladder and rectum before simulation and each treatment session. The prostatic target volume and the critical normal structures are segmented on every CT slice on which they appear. The planning target volume (PTV) extends from 1 cm caudal of the apex of the prostate to 1 cm cephalad of the superior tips of the seminal vesicles and encompasses the prostate with a 1-cm margin, except posteriorly at the interface of the rectum, where some investigators have suggested the use of a 0.6-cm margin to reduce the risk of rectal toxicity. The most commonly used beam arrangement consists of six coplanar fields (two laterally opposed fields and two pairs of oblique fields) shaped to conform the PTV. Dose calculations are then performed, and the adequacy of target coverage by the prescription dose is evaluated on displays of isodose or color-wash distributions and by dose-volume histograms. Some suggest restricting the rectal wall dose to no more than 30% of the prescription dose, the bladder wall dose to 50%, and the bowel dose (when the bowel happens to be included in the PTV) to 65%, to decrease the risk of toxicity.[19, 20] Beam apertures are automatically shaped by the treatment-planning computer, applying a continuously varying aperture with a margin of 0.5 cm around the outline of the tumor target, to account for beam penumbra. The planned treatment fields are then shaped with Cerrobend blocks or multileaf collimators. To assure that treatment is delivered as planned, treatment verification is performed with traditional portal films or electronic portal images, produced at least once per week.

3.3 Intensity-modulated radiation therapy (IMRT)

Intensity-modulated radiotherapy is an advanced form of 3D-CRT that uses highly specialized treatment planning and delivery systems to produce dose distributions that conform to the tumor target with significantly enhanced precision[21]. Use of IMRT in the clinic can be traced back to 1950, and two features that distinguish IMRT from 3D-CRT are inverse algorithms and treatment fields with varying intensities over the

cross section of the beam. Inverse planning uses a mathematical approach to convert a predefined desired dose distribution into a clinically applicable treatment plan, in contrast to the trial-and-error forward planning used in 3D-CRT. A computer-aided optimization algorithm iteratively adjusts the intensity profile of each radiation beam until the planned dose distribution comes as close as possible to the predefined dose specifications for the tumor and normal tissue structures. The outcome is a set of radiation beams with changing intensities across the treatment field. Multiple intensity-modulated beams with different profiles are used to achieve a composite homogeneous dose distribution within the PTV. The inverse algorithm at MSKCC (Memorial Sloan-Kettering Cancer Center) uses a least-squares objective function and conjugate gradient minimization to find an optimum solution, consistent with the predefined constraints. These include maximum and minimum dose constraints for the tumor target and both dose and dose-volume constraints for normal tissue. These constraints can be violated with a cost or penalty, weighted according to the relative importance of the constraint in meeting the goals of the plan.[22] The most distinctive feature of IMRT is the combination of multiple intensity-modulated fields that produce custom-tailored dose distributions around the target volume, with steep dose gradients at the transition to normal tissue. Delivery of such beams require multileaf collimation in either the dynamic or multisegment static (step-and-shoot) modes or tomotherapy using beams directed over a full 360-degree range, modulated by a slit, bimodal multileaf collimation in which the leaf shutters are driven in and out of the beam path. At MSKCC, a coplanar five-field IMRT technique is used to treat patients to dose levels of 81 Gy or higher.[23] The dose limit within the PTV is 110%. Compared to the 3D-CRT plan the high-dose volume in the IMRT conforms better to the shape of the PTV and sculpts around rather than transects the adjacent rectum.

There is now good clinical evidence to confirm that IMRT can reduce acute and late occurring toxicities, and thereby serve as a tool for dose escalation[24, 25]. Zelefsky[24] followed a series of 772 patients who were treated with a dose of either 81 Gy or more, for a median of 24 months. This resulted in > grade 2 toxicity of just 4% in three years. The three-year actuarial PSA relapse-free survival rates among patients with low-,medium- and high-risk for biochemical relapse treated with 81 Gy were 93%, 84%, and 81%, respectively. Within this study, the authors planned 20 patients with both 3D-CRT and IMRT for comparative analysis. Histogram analysis revealed that IMRT planning resulted in a larger volume of targeted malignant tissue receiving the prescribed dose, relative to 3D-CRT[24].

3.4 Image guide radiotherapy (IGRT)

IMRT has greatly enhanced the ability to deliver highly conformal dose distributions with rapid dose falloff. The steep dose gradient of IMRT invites the use of tight margins for dose escalation, but also increases the risk of geometric misses and normal tissue injury, especially when the prostate is moving during intra- and inter-fraction day treatment. The variability of the prostate position has been assessed using periodic CT scans during the treatment.[26] The standard deviations typically encountered are 0.1 cm in the left–right axis, 0.4 cm in the AP axis, and 0.4 cm in the cranial–caudal axis. Although these standard deviations are not significant and also do not fully represent the substantially greater range of differences in the daily prostate positions, OAR is within the hotspot during IMRT when a higher dose is required for a higher control of prostate cancer. This could be translated into severe radiation induced normal tissue damage. IMRT with reduced margins has been achieved in the treatment of tumors in the prostate cancer, albeit sometimes with invasive immobilization techniques that also refer to IGRT. IGRT was developed in the late 90s. The main advantage of IGRT is, it allows delivery of a maximally tolerable tumor dose for each prostate cancer patient. IGRT can be used to measure and correct positional errors for target and critical structures immediately prior to or during treatment delivery. Some of the most recent available methods applied for target localization are: transabdominal ultrasound, implanted markers with in-room MV or kV X-rays, optical surface tracking systems, implantable electromagnetic markers, in-room CT such as kVCT on rail, kilovoltage or megavoltage cone-beam CT (CBCT), and helical

megavoltage CT. The verification of the accurate treatment position, in conjunction with detailed anatomical information before every fraction, is essential for the outcome of the treatment. Generally speaking, when intrafraction organ motions are not significant, online image guidance methods can be used to localize the target volume, prior to treatment, thus allowing margin reduction. Likewise, off-line adaptive strategies can be effective in reducing the PTV when interfraction treatment variation during the course of treatment can be modeled. Furthermore, how much of the margin is given to CTV also depends on the methods that are used to gauge the prostate movement. In Scarbrough's paper,[27] ultrasound and fiducial seed marker kV X-ray methods suggest different shifts of the prostate. Ultrasound data reveal greater systematic/random error versus seed marker data. The ultrasound data suggest larger PTV expansion margins (approximately 9 mm) are necessary for ultrasound IGRT versus seed marker IGRT (approximately 3 mm). In terms of clinical benefit to the patients, long-term results are still to be judged, but IGRT could therapeutically improve the therapeutical index (TCP/NTCP), and especially reduce the morbility of radiation induced late normal tissue damage as the literatures report.[27, 28]

3.5 Brachytherapy

Brachytherapy is derived from the Greek root brachys, which means close or short distance. It refers to the delivery of radiation from sealed radioactive sources that are positioned in close proximity to the tumor sites. This exploits the physical distribution of radiation surrounding radioactive sources, whereby radiation exposure decreases exponentially with increasing distances from a source. Thus brachytherapy can be used to deliver high radiation doses to nearby tumor tissue, while sparing normal tissues located at more distant locations. The application of brachytherapy to treat prostate cancer dates back to the beginning of the twentieth century, until the 1970s, when the radioactive seeds became available and an open implant technique was developed by Whitmore and Hilaris at the Memorial Hospital, and this approach could be applied routinely[29].

Brachytherapy is increasingly being used in the treatment of localized prostate cancer. The results from the few comparative studies showed no difference in clinical effectiveness for prostate brachytherapy, radical prostatectomy, or external beam radiation therapy, for stage T1c, T2a, in patients with low, intermediate risk, or five-year survival could be 96%, 89%[30] that were similar to Stokes's[31]. There has been a perception that brachytherapy is associated with decreased morbidity. This view may have come up from case-series, in which both the population and the hospital/surgeon may be highly selected, and is not supported by evidence from comparative studies as shown here. While awaiting results from randomized controlled trials the increased use of prostate brachytherapy should facilitate prospective registration of outcomes, to establish comparable data on the clinical outcomes, for patients treated with brachytherapy, radical prostatectomy, and external beam radiation therapy.

External brachytherapy is frequently performed using temporary intracavitary applicators. These devices are surgically positioned into a body cavity and thereafter loaded with radioactive materials. This is not used very often for treatment of prostate cancer.

Interstitial brachytherapy with radioactive seed implantation using ^{125}I or ^{103}Pd is another promising treatment option for patients with localized prostate cancer. Improvements in technology allow for better planning of the irradiation dose distribution than was possible previously. CT or TRUS (transrectal ultrasonography) are used to design a treatment plan that provides adequate irradiation to the entire target volume. Using spinal anesthesia, seeds are inserted through the perineum under radiographic guidance. Wallner et al.[32] reported a four-year PSA-determined relapse-free survival of 63%, but longer follow-up is required. Acute toxicity of treatment was minimal and included urinary retention, dysuria, and urgency. Late toxicities included rectal ulceration, which was noted in five of 92 patients, and persistent urinary obstructive symptoms. Preservation of sexual function was clearly related to status before treatment. Among patients with potency prior to treatment, only 14% developed impotence at three years. Although more data and longer follow-up are needed, interstitial irradiation may lead to better preservation of sexual function.

4 Current practice for the treatment of prostate cancer in China

The incidence of prostate cancer ranks seventh in the malignant tumor of males in Shanghai. Because of the development of the standard of living and the prolonged average life in recent years, the number of diagnosis of the disease is increasing. In China, the major treatment for prostate cancer is the combination of surgery plus endocrine therapy, but on the urologist's further understanding of the disease, radiotherapy has been accepted as one of the radical therapies for it. In the mid 90s, three-dimensional conformal radiotherapy had been widely used in the treatment of prostate cancer, total five-year survival rate was about 70%,[33] which was the same as what had been reported abroad. At the same time, the brachytherapy for prostate cancer was applied in clinical practice, Shanghai 6th People's Hospital was one of the earliest medical centers that introduced this method in China. By the guidance of transrectal ultrasonography (TRUS), a tube array according to a template is inserted into the prostate gland, the radioactive source (often ^{192}Ir) is put into the gland through the tubes under the control of the computer, and then the tumor is irradiated. Combined with external radiotherapy, and taking PSA as an index, the five-year disease free survival rate is above 82.5%[34] and the complication is lower than pure external radiotherapy, similar to the results (83%-95%) obtained by studies from China.[35] At the end of the 90s, the intensity-modulated radiation therapy (IMRT) began to be used in the treatment of prostate cancer.

The preliminary result achieved by the Cancer Hospital of Chinese Academy of Medical Sciences is: Five-year cancer related survival rate is 91%,[36, 37] with good effect and low toxicity. Today, IMRT is the standard radical therapeutic method for prostate cancer in this hospital, and the effect is promising with a short period follow up. In recent years, as the doctors pay more attention to radiotherapy for prostate cancer, IGRT and DGRT (dose guide radiotherapy) are now adopted in this field to ensure the accuracy of the radiotherapy more efficiently.

Future directions in prostate radiation therapy will be for the use of even higher radiation doses, alternative fractionation patterns, new advanced technologies, intraprostatic targets (e.g., prostate tumor seen on magnetic resonance image (MRI)), multiple treatment modality, and improved patient selection. Patients will benefit the most from these advanced techniques.

References

1 Cancer statistical group: Tumor, 2003, **23**: 532.

2 Zietman A L, DeSilvio M L, Slater J D, *et al*. JAMA, 2005, **294**: 1233.

3 Tsuji H, Yanagi T, Ishikawa H, *et al*. Int J Radiat Oncol Biol Phys, 2005, **63**: 1153.

4 Fowler J F, Ritter M. Int J Radiat Oncol Biol Phys, 1995, **32**: 521.

5 Thames H D, Withers H R, Peters L J, *et al*. Int J Radiat Oncol Biol Phys, 1982, **8**: 219.

6 Jeffrey D, Forman M D, Marie D, *et al*. Int J Radiation Oncology Biol Phys, 1996, **34**: 655.

7 Forman J D, Shamsa F, Maughan R L, *et al*. Bull Cancer Radiother, 1996, **83** (Suppl): 101s.

8 Hong T S, Tome W A, Jaradat H. Acta Oncol, 2006, **45**: 717.

9 Soete G, Arcangeli S, De Meerleer G, *et al*. Radiother Oncol, 2006, **80**: 643.

10 Kupelian P A, Thakkar V V, Khuntia D, *et al*. Int J Radiat Oncol Biol Phys, 2005, **63**: 1463.

11 Pollack A, Hanlon A L, Horwitz E M, *et al*. Int J Radiat Oncol Biol Phys, 2005, **64**: 518.

12 Lukka H, Hayter C, Julian J A, *et al*. J Clin Oncol, 2005, **23**: 6132.

13 Bagshaw M A, Kaplan H S, Sagerman R H. Radiology, 1965, **85**: 121.

14 Bagshaw M A. Definitive megavoltage radiation therapy in carcinoma of the prostate. In: Fletcher GH, ed. Textbook of radiotherapy, 2nd ed. Philadelphia: Lea & Febiger, 1973: 752.

15 Epstein B E, Hanks G E. Semin Radiat Oncol, 1993, **3**: 179.

16 Bagshaw M A, Ray G R, Cox R S. Urology, 1985, **25**: 17.

17 Hanks G E, Hanlon A L, Hudes G, *et al*. J Clin Oncol, 1996, **14**: 1093.

18 Fuks Z, Leibel S A, Kutcher G J, *et al*. Three-dimensional conformal treatment: a new frontier in radiation therapy. In: DeVita Jr. VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: J.B. Lippincott, 1991: 151.

19 Leibel S A, Zelefsky M J, Kutcher G J, *et al*. J Urol, 1994, **152**: 1792.

20 Zelefsky M J, Leibel S A, Burman C M, *et al*. Int J Radiat Oncol Biol Phys, 1994, **29**: 755.

21 Sanghani M, Mignano J. Technol Cancer Res Treat, 2006, **5**: 447.

22 Liu Y M, Shiau C Y, Lee M L, *et al*. Int J Radiat Oncol Biol Phys, 2006, **66**: 1477.

23 Leibel S A, Fuks Z, Zelefsky M J, *et al*. Semin Oncol, 2003, **30**: 596.

24 Zelefsky MJ, Fuks Z, Hunt M, et al. Int J Radiat Oncol BiolPhys 2002, **53**: 1111.

25 Mangar SA, Huddart RA,Parker CC, et al. Euro J Cancer, 2005, **41**:908

26 Lattanzi J, McNeeley S, Hanlon A, *et al*. Int J Radiat Oncol Biol Phys, 1998, **41**: 1079.

27 Scarbrough T J, Golden N M, Ting J Y, *et al*. Int J Radiat Oncol Biol Phys, 2006, **65**: 378.

28 Song WY, Schaly B, Bauman G, et al. Int J Radiat Oncol Biol Phys, 2006, **64**:289

29 Whitmore W, Hilaris B, Grabstald H. J Urol, 1972, **108**:918.

30 Khaksar SJ; Langley SEM, Lovellz D, et al. Clin Oncol, 2006, **18**: 513.

31 Stokes SH. Int J Radiat Oncol Biol Phys, 2000, **47**:129.

32 Wallner K, Roy J, Harrison L. J Clin Oncol, 1996, **14**: 449.

33 Wang Wenling, Wen Xiaoping, Yang Xiaofeng, *et al*. Chin J Radiat Oncol (in Chinese), 2006, **15**(3): 201.

34 Zhang Qing, Xu Jun, Peng Lihua, *et al*. Tumor Nov (in Chinese), 2004, **24**: 603.

35 Jin Yenin, Wang Yajie, Sun Yinghao. Shanghai Medicine (in Chinese), 2002, **25**: 253.

36 Fang Hui, Li Yixiong, Yu Zihao, *et al*. Chin J Radiat Oncol, 2006, **15**: 197.

37 Deng Xiaoqin, Han Bo, Li Ying, *et al*. China Oncology (in Chinese), 2002, **12**: 255.