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REVIEW ARTICLE

Stereotactic Body Radiotherapy: A Review of its Application in Prostate Cancer

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Abstract. In the recent years, remarkable progress in the field of radiotherapy has been made, especially in treatment delivery techniques. Close attention has been paid to prostate cancer, in particular because of its high incidence and the potential curability. During the last decades, strategies of radiotherapy of prostate cancer have improved with regard to dose escalation, hypo-fractionation, high-dose-rate brachytherapy, and the introduction of modern techniques such as Intensity Modulated Radiation Therapy and Stereotactic Body Radiation Therapy. Stereotactic radiotherapy for prostate cancer is used to deliver a higher dose to the prostate with better sparing for bladder and rectum, due to a high level of precision and smaller required planning target volume, in reduced number of fractions, either exclusively for early localized disease or as a boost after External Beam Radiation Therapy for more advanced localized disease. Recent clinical data showed that Stereotactic Body Radiation Therapy provides acceptable toxicities and encouraging results of biological control. More trials with long-term follow-up are required to evaluate the late toxicities and its efficacy for the consideration of Stereotactic Body Radiation Therapy as a treatment option for patients with localized prostate cancer.

Keywords: Prostate cancer, Stereotactic Body Radiation Therapy, Dose-escalation, CyberKnife, prostate boost, Hypo-fractionation.

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Rationale for Stereotactic Radiotherapy in Prostate Cancer

Biological tumor control has been improved with dose escalation[1–3], but at the expense of rectal and bladder toxicity[2,3], which has led physicians to seek more sophisticated techniques such as Intensity Modulated Radiation Therapy (IMRT) that may allow increasing the dose to the prostate while sparing the surrounding normal tissue. Even with these techniques, a relatively large margin around the prostate is needed to account for prostatic motion; consequently, this large margin defining the Planning Target Volume (PTV) will increase the radiation exposure to the normal tissue.

An interesting issue that has also been evaluated is the sensitivity of prostate cancer to the dose-per-fraction, *i.e.,* the alpha-beta ratio (α/β). The α/β ratio is the dose, when the number of cells killed by the linear component α (death due to non-repairable lethal DNA damage) is equal to the cell kill from the quadratic component β (death due to accumulation of sub-lethal DNA damages). The α/β ratio is typically high in rapidly proliferating tissue like most of the tumors and the acute responding normal tissues (*e.g.,* gastrointestinal mucosa and bone marrow) which will produce the acute toxicities. The α/β ratio is low in some tumors and in late responding normal tissue (*e.g.,* neurons, muscles, and connective tissue cells) which will result in the late toxicities. Tumors with low α/β ratio are more sensitive to high dose-per-fraction. Several studies suggest that the α/β of prostate cancer is as low as late responding tissue, unlike the usually high α/β ratio of other tumor cells[4–7]. In some reports, the α/β of prostate cancer was estimated to be as low as 1.5 Gy[4,5], which is even lower than the α/β of the surrounding late responding normal tissues. This means that prostate cancer cells are more sensitive to higher dose-per-fraction than the surrounding normal tissues. Therefore, hypofractionated treatment may increase tumor-cell-killing effect for a lower or similar risk of late toxicity.

Stereotactic Body Radiation Therapy (SBRT) of prostate cancer is used to ensure the accuracy of this hypofractionated treatment to a

localized volume, with limited necessary margins, by using highly precise stereotactic localization systems.

Feasibility and Accuracy of SBRT

Most of the SBRT studies of prostate cancer are relatively recent, attempting to integrate the radiobiological features of prostate cancer with the most developed treatment techniques and technologies to achieve the best therapeutic outcome. Their early results are encouraging.

There are many trials that showed the feasibility and accuracy of SBRT for prostate cancer[8–14]. Most of them were applied to low/intermediate risk, with the dose-per-fraction range of 6-10 Gy and five fractions being delivered in about ten days. Fiducial markers are implanted in the prostate and used for localization and positioning during treatment planning and delivery. These trials demonstrated the high accuracy of SBRT that allowed using small PTV margins with the purpose to maximize the protection of the bladder and rectum (Fig. 1). The dosimetric analysis and comparison showed the superiority of CyberKnife for sparing the bladder and rectum, target coverage, and the same dose heterogeneity when

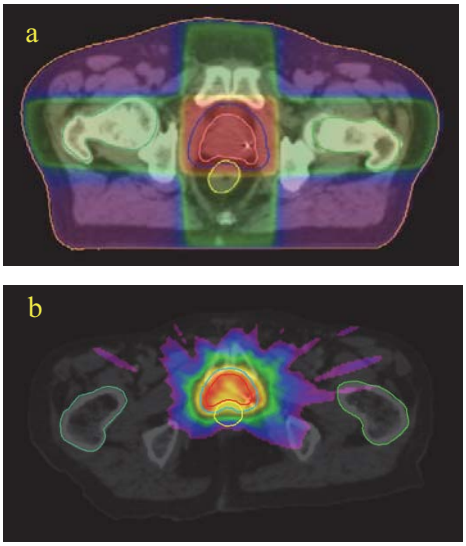

Fig. 1. Isodose-line distribution of two patients treated in Centre Oscar Lamret, Lille, France; (a) 3D-conformal radiotherapy, (b) SBRT by CyberKnife.

compared to IMRT planning[15,16]. SBRT by CyberKnife was also compared to a simulated treatment plan for high-dose-rate (HDR) brachytherapy and proved to be able to mimic the dosimetry of HDR brachytherapy while delivering the treatment noninvasively[17]. In addition, CyberKnife can precisely localize the target in real-time during the treatment by organ motion tracking, with the ability to automatically correct for displacement.

Toxicity of SBRT for Prostate Cancer

In the case of prostate cancer, expected complications of radiotherapy are genitourinary (GU) toxicity, gastrointestinal (GI) toxicity, and erectile dysfunction (ED). Radiation-induced toxicities are classified as acute or late, according to their distinct features and pathophysiological mechanisms.

The estimated α/β value for the grade ≥ 2 late rectal toxicity, as defined by Radiation Therapy Oncology Group (RTOG), is 5.4 ± 1.5 Gy[18]. Therefore, after SBRT treatment, though late toxicities are expected, the equivalent biological dose delivered to the prostate would be higher. This fact, along with the small margins used in such highly precise treatments, keeps the late toxicities within their acceptable range. The significant GU and GI toxicities in SBRT trials for prostate cancer were reported as infrequent, with comparable rates for grade ≤ 2 to other External Beam Radiation Therapy (EBRT) modalities with escalated dose. There was no reported grade 4 toxicity, and grade 3 toxicities were rare[8–14].

Unlike acute toxicity, late toxicity requires long-term follow-up to correctly confirm the safety of any treatment. The clinical data available so far suggests that hypofractionated treatments with doses-per-fraction in the range of 2.5–10.5 Gy are equivalent in toxicity; however, longer follow-up than currently available is needed to confirm this.

The mechanism of radiation-induced erectile dysfunction is complicated and not well understood. Several factors can contribute to this effect, such as age, hormonal treatment, comorbidities, and

psychological factors. The frequency of ED after SBRT for prostate cancer was comparable with the upper end of published reports for other modalities of radiotherapy alone without androgen deprivation therapy (ADT)[19]. Age appears to be a major factor for ED among treated patients.

Efficacy of SBRT for Prostate Cancer

Tumor control for prostate cancer is usually measured by observation of the level of Prostate Specific Antigen (PSA). As most studies of SBRT for prostate cancer are recent, patient follow-up is relatively short to determine the PSA response[8–14]. Nevertheless, the published early results are encouraging. The mean PSA decreased progressively after treatment, and at 24-month follow-up, 88% and 65% of the patients achieved < 1 ng/ml and < 0.5 ng/ml, respectively[20]. In one study with long-term follow-up, the 4-year PSA relapse-free survival was 94%[14].

SBRT Boost to the Prostate

Unlike other conformal radiotherapy techniques (*e.g.,* 3D conformal (EBRT or IMRT), SBRT treatment can only be applied to small volumes. In cases that need larger treatment volumes, such as pelvic irradiation in more advanced prostate cancer, or when it is difficult to deliver the entire treatment dose with SBRT techniques, SBRT can be employed as a boost to escalate the dose to the prostate after the standard EBRT or IMRT. Only limited data is found in the literature about the use of SBRT as a boost. As shown earlier, CyberKnife is capable of delivering radiotherapy plans similar to those of HDR brachytherapy[17], which have been used as a boost after EBRT[21,22]. Therefore, following this logic, SBRT could also be used as a boost to the prostate after standard EBRT, with the additional advantage of a non-invasive treatment.

There are three feasibility studies evaluating the acute toxicity and early biological effects where SBRT was given as a boost after EBRT[23–25]. Most of the cases reported were intermediate/high-risk

diseases. External Beam Radiation Therapy (EBRT) techniques included 3D conformal radiotherapy and IMRT, the dose range was 45-50.4 Gy, and whole pelvic radiotherapy (WPRT) was delivered for some high-risk patients. Hormonal treatment was allowed. After a relatively short follow-up (10-30 months), GU and GI toxicities were in an acceptable range, and early PSA response was encouraging.

SBRT and Recurrence

The standard treatment for a local failure after prostate irradiation is asalvage surgery or a hormonal treatment for lymph node recurrence. But if surgery is contraindicated, could SBRT be an alternative treatment? There are limited published studies about SBRT in these cases, and several issues should be considered: delay of failure, previous prostate radiotherapy treatment, volume to be re-irradiated, dose and fractionation that should be used. All these concerns make the answer difficult with little and immature data available in the literature[26,27].

Conclusion

Stereotactic Body Radiation Therapy for Prostate has been recently emerged in the treatment of prostate cancer. Several trials demonstrated its feasibility, with an acceptable range of toxicity, and encouraging biological control results. It can be applied exclusively for early stage or in combination with other modalities of EBRT for more advanced disease. More prospective trials with longer follow-up are needed to confirm its efficacy and safety for considering SBRT among the treatment options for patients with localized prostate cancer.

References

[1] **Kupelian P, Kuban D, Thames H, Levy L, Horwitz E, Martinez A, Michalski J, Pisansky T, Sandler H, Shipley W, Zelefsky M, Zietman A.** Improved biochemical relapse-free survival with increased external radiation doses in patients with localized prostate cancer: the combined experience of nine institutions in patients treated in 1994 and 1995. *Int J Radiat Oncol Biol Phys* 2005; **61**(2): 415-419

[2] **Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, von Eschenbach AC, Kuban DA, Rosen I.** Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002; **53**(5): 1097-1105.

[3] **Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA, Shipley WU.** Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005; **294**(10): 1233-1239.

[4] **Brenner DJ, Hall EJ.** Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys 1999*; **43**(5): 1095-1101.

[5] **Fowler J, Chappell R, Ritter M.** Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001; **50**(4): 1021-1031.

[6] **Daşu A.** Is the alpha/beta value for prostate tumors low enough to be safely used in clinical trials? *Clin Oncol (R Coll Radiol)* 2007; **19**(5): 289-301.

[7] **Nickers P, Hermesse J, Deneufbourg JM, Vanbelle S, Lartigau E.** Which α/β ratio and half-time of repair are useful for predicting outcomes in prostate cancer? *Radiother Oncol* 2010; **97**(3): 462-466.

[8] **Madsen BL, Hsi RA, Pham HT, Fowler JF, Esagui L, Corman J.** Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. *Int J Radiat Oncol Biol Phys* 2007; **67**(4): 1099-1105.

[9] **Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM.** Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat* 2009; **8**(5): 387-392.

[10] **Bolzicco G, Favretto MS, Scremin E, Tambone C, Tasca A, Guglielmi R.** Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results. *Technol Cancer Res Treat* 2010; **9**(5): 473-477.

[11] **Boike TP, Lotan Y, Cho LC, Brindle J, DeRose P, Xie XJ, Yan J, Foster R, Pistenmaa D, Perkins A, Cooley S, Timmerman R.** Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol* 2011; **29**(15): 2020-2026.

[12] **Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M.** Stereotactic body radiotherapy as boost for organ-confined prostate cancer. *Technol Cancer Res Treat* 2010; **9**(6): 575-582.

[13] **McBride SM, Wong DS, Dombrowski JJ, Harkins B, Tapella P, Hanscom HN, Collins SP, Kaplan ID.** Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer* 2012; **118**(15): 3681-3690.

[14] **King CR, Brooks JD, Gill H, Presti JC Jr.** Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**(2): 877-882.

[15] **King CR, Lehmann J, Adler JR, Hai J.** CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. *Technol Cancer Res Treat* 2003; **2**(1): 25-30.

[16] **Hossain S, Xia P, Huang K, Descovich M, Chuang C, Gottschalk AR, Roach M 3rd, Ma L.** Dose gradient near target-normal structure interface for nonisocentric Cyber- Knife and isocentric intensity-modulated body radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; **78**(1): 58-63.

[17] **Fuller DB, Naitoh J, Lee C, Hardy S, Jin H.** Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. *Int J Radiat Oncol Biol Phys* 2008; **70**(5): 1588-1597.

[18] **Brenner DJ.** Fractionation and late rectal toxicity. *Int J Radiat Oncol Biol Phys* 2004; **60**(4): 1013-1015.

[19] **Wiegner EA, King CR.** Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2010; **78**(2): 442-448.

[20] **Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M.** Stereotactic body radiotherapy for organ-confined prostate cancer. *BMC Urol* 2010; **10**: 1.

[21] **Demanes DJ, Rodriguez RR, Schour L, Brandt D, Altieri G.** High-dose-rate intensity-modulated brachytherapy with extra- nal beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005; **61**(5): 1306-1316.

[22] **Vargas CE, Martinez AA, Boike TP, Spencer W, Goldstein N, Gustafson GS, Krauss DJ, Gonzalez J.** High-dose irradiation for prostate cancer via a high-dose-rate brachytherapy boost: results of a phase I to II study. *Int J Radiat Oncol Biol Phys* 2006; **66**(2): 416-423.

[23] **Oermann EK, Slack RS, Hanscom HN, Lei S, Suy S, Park HU, Kim JS, Sherer BA, Collins BT, Satinsky AN, Harter KW, Batipps GP, Constantinople NL, Dejter SW, Maxted WC, Regan JB, Pahira JJ, McGeagh KG, Jha RC, Dawson NA, Dritschilo A, Lynch JH, Collins SP.** A pilot study of intensity-modulated radiation therapy with hypofractionated stereotactic body radiation therapy (SBRT) boost in the treatment of intermediate- to high-risk prostate cancer. *Technol Cancer Res Treat* 2010; **9**(5): 453-462.

[24] **Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M.** Stereotactic body radiotherapy as boost for organ-confined prostate cancer. *Technol Cancer Res Treat* 2010; **9**(6): 575-582.

[25] **Jabbari S, Weinberg VK, Kaprealian T, Hsu IC, Ma L, Chuang C, Descovich M, Shiao S, Shinohara K, Roach M 3rd, Gottschalk AR.** Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. *Int J Radiat Oncol Biol Phys* 2012; **82**(1): 228-234.

[26] **Vavassori A, Jereczek-Fossa BA, Beltramo G, De Cicco L, Fariselli L, Bianchi LC, Possanzini M, Bergantin A, DeCobelli O, Orecchia R.** Image-guided robotic radiosurgery as salvage therapy for locally recurrent prostate cancer after external beam irradiation: retrospective feasibility study on six cases. *Tumori* 2010; **96**(1): 71-75.

[27] **Jereczek-Fossa BA, Beltramo G, Fariselli L, Fodor C, Santoro L, Vavassori A, Zerini D, Gherardi F, Ascione C, Bossi-Zanetti I, Mauro R, Bregantin A, Bianchi LC, De Cobelli O, Orecchia R.** Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**(2): 889-897.

العلاج الإشعاعي المجسمي: مراجعة لاستخداماته في حالات سرطان البروستات

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وحدة العلاج الإشعاعي، قسم الأشعة، كلية الطب، جامعة الملك عبد العزيز جدة – المملكة العربية السعودية

المستخلص. أحرز تقدم "ملحوظ"، خلال السنوات الأخيرة، في تقنيات أجهزة تقديم العلاج الإشعاعي، واستخداماتها في مجال علاج سرطان البروستاتا على وجه الخصوص، بسبب كثرة الإصابة وفعالية العلاج الإشعاعي. وقد تطورت استراتيجيات العلاج الإشعاعي لسرطان البروستاتا في محاور مختلفة منها: تصعيد الجرعة الإشعاعية، تقليل عدد الجلسات مع زيادة جرعة كل جلسة، العلاج الإشعاعي الداخلي ذو المعدل العالي، وإدخال التقنيات الحديثة مثل العلاج الإشعاعي ذو الكثافة المتغيرة، والعلاج الإشعاعي المجسمي. يستخدم العلاج الإشعاعي المجسمي لتقديم جرعة إشعاعية عالية للبروستاتا مع قدرة أفضل لتجنب المثانة والمستقيم، بمستوى عال من الدقة واحتياج أقل للمساحة الهامشية حول البروستاتا في عدد قليل من الجلسات، إما بشكل حصري للحالات المبكرة، أو بشكل إضافي للعلاج الإشعاعي الخارجي الاعتيادي في الحالات المتقدمة، مع آثار جانبية مقبولة ونتائج أولية مشجعة في القدرة على السيطرة على المرض. يلزم المزيد من التجارب ذات المتابعة الطويلة لتقييم المضاعفات المتأخرة،

والتحقق من فعالية العلاج في السيطرة على المرض لجعل العلاج
الإشعاعي المجسمي أحد خيارات العلاج لسرطان البروستات.