Stereotactic Body Radiotherapy (SBRT) For Primary Management of Early-Stage, Low-Intermediate Risk Prostate Cancer

Report of the ASTRO Emerging Technology Committee (ETC) September 19, 2008

Emerging Technology Committee Co-Chairs

Andre A. Konski, M.D., M.B.A., Fox Chase Cancer Center
Paul E. Wallner, D.O., 21st Century Oncology Inc.

Evaluation Subcommittee Co-Chairs

Eleanor E. R. Harris, M.D., H. Lee Moffitt Cancer Center
Robert A. Price Jr., Ph.D., Fox Chase Cancer Center

Task Group Leader

Mark Buyyounouski, M.D., M.S., Fox Chase Cancer Center

Task Group Members

Robert Miller, M.D., Mayo Clinic and Mayo Foundation
Tracey Schefter, M.D., University of Colorado Health Services
Wolfgang Tome, M.D., University of Wisconsin
Robert A. Price Jr., Ph.D., Fox Chase Cancer Center
Ishmeal Parsai, Ph.D., University of Toledo, College of Medicine

I. INTENDED USE OF TECHNOLOGY

A. Definition of Stereotactic Body Radiotherapy

In this report, stereotactic body radiotherapy (SBRT) is being evaluated exclusively in the definitive treatment of primary prostate cancer. The term *stereotactic* refers to precise positioning of the target volume within three-dimensional space. The target volume is usually localized in space using some external frame of reference which can be related to the treatment machine. The term *body* is used to distinguish the technique from the current terminology of stereotactic radiosurgery (SRS) employed for radiation treatment of central nervous system lesions with a full course of therapy consisting of five or fewer treatments. Stereotactic positioning can be precise and as a result, stereotactic radiotherapy commonly employs higher doses per fraction and fewer fractions (hypofractionation) than conventional radiation. As defined by the CPT® Editorial Panel of the American Medical Association, SBRT consists of a total course of therapy comprising five or fewer treatments.

II. DESCRIPTION OF TECHNOLOGY

A. Target localization and tracking

An overriding principle of radiotherapy is to maximize the dose of radiation delivered to the tumor while sparing normal tissue to the greatest extent possible. This ideally increases the tumor control probability (TCP) and decreases the normal tissue complication probability (NTCP). In the case of the hypo-fractionation related to SBRT, this principle becomes ever more important since any inaccuracy in patient setup can have potentially severely harmful consequences in terms of expected TCP and induced

normal tissue complications, since a small number of high dose/fraction treatments are employed.

SBRT enables delivery of radiation more precisely at the tumor with a high graduation of dose between the tumor and normal tissue. A precise ability to localize the target tumor is essential to fully benefit from hypofractionation techniques. Several different techniques have been developed to measure and account for interfraction and intrafraction motion as well as target tracking and more precise immobilization than had previously been available or even essential. These devices and techniques will be the subject of subsequent ETC reports and are beyond the scope of this particular evaluation.

B. Treatment Delivery

A significant requirement of SBRT is tight comformality of the prescription isodose shell to the tumor volume with sharp dose fall off. Kavanagh et al. (2003) suggest that this may be accomplished by implementing multiple, nonopposing and often noncoplanar arcs, spread in a large solid angle with fairly equal weighting to minimize the entrance dose and ultimately the volume of the irradiated normal tissue. Using this technique, the proportion of scatter contribution will also be reduced.

Chang et al. (2007) in a review on this subject suggest that a clinical factor in deciding the number of beam directions and the relative beam weights is the entrance dose and that it should be kept to a modest level to prevent potential severe skin toxicity while keeping a uniform isotropic dose falloff. The beam's eye-view for each beam coincides with the planning target volume (PTV) outline leading to a lower prescription isodose line of 60 percent to 80 percent providing 95 percent PTV coverage, rather than what is typically seen with conventionally fractionated radiotherapy. In assessment and

evaluation of dosimetric properties of the SBRT plans, three major criteria are considered: conformity index, high-dose spillage, and intermediate dose-spillage. The conformity index is defined as the ratio of the volume of the isodose shell that provides 95 percent PTV coverage to the PTV volume. It is generally recommended that this ratio be kept to less than 1.2 to minimize the volume of tissue receiving an ablative dose. High-dose spillage takes into account areas of hot spots and the recommendation is that those areas remain within the PTV. Any area receiving greater than 105 percent of the prescription dose is considered a high-dose spillage area. Intermediate-dose spillage, which is responsible for most of the toxicity associated with SBRT, is evaluated using one or both the following methods: 1) keeping dose to any point 2 cm away from the PTV surface below a limit that is a function of the PTV volume, and 2) the region of intermediate-dose spillage is defined as the ratio of 50 percent isodose coverage to the PTV volume.

In delivering SBRT, many commercially available systems are used. Sophisticated image guidance is a common feature to these treatment systems. Systems equipped with Image Guided Radiation Therapy (IGRT) minimize the uncertainty associated with tumor localization. Most delivery systems also allow integration of patient immobilization devices. The most prevalent treatment systems used in the US are the Novalis® (Brain LAB, AG, Feldkirchen, Germany.), the TomoTherapy® Hi-Art® System (TomoTherapy, Inc., Madison, WI), the Varian Trilogy® (Varian Medical Systems, Inc., Palo Alto, CA), the Elekta Synergy® (Elekta, Inc., Norcross, GA), the Siemens Oncor® and Artiste® (Siemens Medical Solutions USA, Inc., Malvern, PA) , and the CyberKnife® Robotic Radiosurgery System (Accuray, Inc., Sunnyvale, CA).

The Novalis® system uses a 6 MV linear accelerator with micro-multileaf collimators ranging in leaf thickness from 3 to 5.5 mm. Two KVp orthogonal X-ray cameras are mounted on the system to track bony landmarks or implanted fiducials in relation to the DRR's generated from CT simulation. The patient is then aligned in the treatment position in accordance with identified positions of markers.

The TomoTherapy® system uses a megavoltage CT to continuously image the patient with the table continuously moving when IMRT is delivered throughout a full range of 360 degree rotations using a binary multileaf collimator system.

The Varian Trilogy® and Elekta Synergy® both use a cone beam CT to provide real time image guidance for repositioning. Elekta has recently acquired a company (3D Line Medical Systems USA, Norcross, GA) whose product was a full stereotactic radiosurgery system for cranial and extra-cranial radiotherapy treatments. The system is composed of a Micro MLC system with leaf thicknesses of 3 mm, 5 mm or 7 mm, head and body frames for positioning and localization (CT/MR & Angiography), dynamic patient support assembly with all translational, rotational, pitch, yaw and roll movement, and an integrated optical tracking system for positioning. Additionally, an inverse treatment planning package with intensity modulated arc therapy (IMAT) capability, unique to 3D line with optimization routines for SRS techniques, is included.

The Siemens system is different in that the CT unit is linked to the accelerator via a shared tabletop and it travels along rails. Once CT imaging is completed the table top rotates to the linear accelerator for treatment delivery, thereby providing a near real-time localization for treatment delivery.

The CyberKnife® uses a frameless image-guided process to direct a robotic arm with a linear accelerator attached to it, along six spatial axes delivering dose to the target. Translational and rotational movements of this robotic radiosurgery are much broader and impossible to match with existing designs of linear accelerators. Two orthogonal diagnostic x-ray cameras are mounted on the ceiling to provide real time imaging for tracking. Implanted fiducials or reliable bony landmarks are used to localize the tumor in real-time for treatment delivery.

C. Rationale for Prostate Stereotactic Body Radiotherapy

Prostate cancer potentially lends itself to the use of SBRT because the majority of cases present with disease clinically localized in the prostate, providing a well-defined structure for target localization. Additionally, the biologic nature of prostate cancer has been hypothesized to benefit from the use of fewer, larger fractions. The greatest challenges to the delivery of SBRT for prostate cancer are accurate prostate stereotaxis, prostate motion, and avoidance of surrounding normal tissues such as the bladder and rectum, as well as the selection of an appropriate dose/fractionation schedule.

D. Radiobiology (Early versus Late Effects and the Alpha/Beta Ratio)

Conventional prostate radiotherapy is delivered in fraction sizes of 1.8 to 2.0 Gy. This method of fractionation emerged from the observation that late complications of radiotherapy have been reduced without an apparent compromise in local control. This approach is supported by the radiobiological nature of surrounding normal tissues such as the rectum. The sensitivity of tissue to fractionation can be expressed as the alpha/beta ratio.

Tissues with a small alpha/beta ratio (i.e., two to four) are more sensitive to changes in fractionation than tissue with a large alpha/beta ratio (i.e., > 8). Tissues with a low alpha/beta ratio are commonly referred to as "late-responding" because sequelae of treatment are generally seen years following treatment. Increasing the number of fractions generally spares late-responding tissues. Tumors are generally less sensitive to the effects of fractionation due to relatively large alpha/beta ratios more characteristic of "early-responding" tissues. Therefore, increasing the number of fractions used for prostate radiotherapy should spare the "late-responding" rectum, while impacting minimally on the tumor.

With the aforementioned concepts in mind, hypofractionation presents several potential advantages. Ideally, tumor control may be increased for a given level of late complications. Conversely, late complications may be reduced for a given level of tumor control. Fewer fractions would increase patient convenience compared to standard external beam radiotherapy treatment courses that extend for seven to nine weeks. Hypofractionation may also result in increased cost-effectiveness by potentially decreasing the cost of a course of treatment. Prostate cancer may not be typical of other tumors and may not be an early-responding tissue. Instead it may be a late-responding tissue for which increasing fractionation may provide a sparing effect that limits or reduces the therapeutic ratio. If this is true, hypofractionation may be more effective for cell killing.

E. The Alpha/Beta Ratio for Prostate Cancer

The alpha/beta ratio for prostate cancer is hypothesized to be low. In 1999, Brenner and Hall (Brenner and Hall 1999) hypothesized that the alpha/beta ratio for prostate cancer may be small because prostate tumors contain unusually small proportions of cycling cells (Haustermans, Hofland et al. 1997). They estimated the alpha/beta ratio for prostate cancer to be 1.5 Gy (95 percent confidence interval: 0.8-2.2 Gy) by using clinical data to assume the linear and quadratic components of cell killing. Low dose-rate brachytherapy (Stock, Stone et al. 1998) results, used to estimate the linear (alpha, dose protraction-independent) component, together with external beam radiotherapy (Hanks, Schultheiss et al. 1997) data were used to derive an estimate of the alpha/beta ratio for prostate cancer. This method has been repeated by several authors (Duchesne and Peters 1999; Brenner 2000; King and Mayo 2000; D'Souza and Thames 2001; Fowler, Chappell et al. 2001; King and Fowler 2001; Logue, Cowan et al. 2001; Dale and Jones 2002; King and Fowler 2002; Lee 2002; Amer, Mott et al. 2003; Kal and Van Gellekom 2003; Lindsay, Moiseenko et al. 2003; Nahum, Movsas et al. 2003; Wang, Guerrero et al. 2003). Using this method, most studies support this hypothesis and suggest the alpha/beta is low, probably 1 to 4 Gy (Brenner 2003; Brenner 2004). If the alpha/beta is low for prostate cancer this would support SBRT at the risk of increased late side effects. But, if the alpha/beta is not low, SBRT may increase the risk for late toxicity from a radiobiological perspective without improving the therapeutic ratio.

Some of the problems with the estimates of the alpha/beta ratio include: non-uniform dose distributions, tumor heterogeneity, varying relative biologic effectiveness (Dale and Jones 2002), varying overall treatment times, and heterogeneity in tumor

hypoxia. The linear quadratic model is a simple application that does not take into account other fractionation-related phenomena such as reoxygenation, redistribution, and repopulation. King and Mayo (King and Mayo 2000) looked at a heterogeneity model and challenged that the alpha/beta is closer to 5 Gy but subsequent studies have identified problems with heterogeneity modeling that have lowered this value. (King and Fowler 2001) Dale and Jones have indicated that if allowances are made for the increased relative biologic effectiveness (RBE) of I125 and Pd103 then the alpha/beta ratio may be 1.0 Gy (Dale and Jones 2002). With respect to estimates derived from inter-institutional and brachytherapy versus external beam radiotherapy comparisons, the best addressing data is Brenner-Martinez (Brenner, Martinez et al. 2002) where no inter-institutional comparisons and no comparisons of brachytherapy and external beam radiotherapy were made. This yielded a value for alpha/beta of 1.2 Gy (95 percent CI 0.03 – 4.1 Gy). A similarly low alpha/beta ratio of 1.5 Gy (95% CI 1.2–1.8) has been supported by larger studies (Fowler, Chappell et al. 2001).

Fowler et al. have modeled various hypofractionation regimens using the linear quadratic model with the assumptions that the alpha/beta ratio for prostate tumors is in the range of 1 to 2 Gy, and warn against the use of too few fractions (< 5) because this may limit the possibility of reoxygenation or redistribution of tumor cells into more sensitive phases of the cell cycle. (Fowler, Ritter et al. 2003)

F. The Alpha/Beta Ratio of The Rectum

The alpha/beta ratio of the rectum is as important as the prostate alpha/beta ratio in understanding what hypofractionation regimens will be beneficial or detrimental. The

alpha/beat ratio for the rectum is not known precisely. The generic value used for late responding tissue such as the rectum is 3 Gy. In rodents, analyses of different experiments for late rectal damage by Brenner et al. (Brenner, Armour et al. 1998) yielded 4.6 Gy (95 percent C.I. 4.0, 5.5). Van der Kogel et al. (van der Kogel, Jarrett et al. 1988) reported 4.1 Gy (1.5, 7.7) and Dewit et al. (Dewit, Oussoren et al. 1989) found 4.4 Gy (1.6, 7.7). Terry and Denekamp (Terry and Denekamp 1984) reported a range of 3.1 to 5.1 Gy, while Dubray and Thames (Dubray and Thames 1994) found a range of 2.7 Gy (0.9, 4.8) to 6.7 Gy (2.2, 11.7). Gasinska et al. (Gasinska, Dubray et al. 1993) found the alpha/beta ratio to be 6.4 and 6.9 Gy for two different late rectal end points in mice. In summary, animal experiments suggest an alpha/beta ratio for the rectum of 4 to 6 Gy.

Brenner estimated the alpha/beta ratio for late rectal bleeding using clinical results of hypofractionation with 1.8 Gy, 2 Gy and 3 Gy per fraction data using the standard linear-quadratic model (Brenner 2004). The incidence of Radiation Therapy Oncology Group (RTOG) grade 2 late rectal toxicity was fitted to the linear-quadratic model as a function of equivalent total dose if delivered in 2 Gy fractions using data points from rectal toxicity results from Memorial-Sloan Kettering Cancer Center (Skwarchuk, Jackson et al. 2000), RTOG protocol 9406 (Michalski, Winter et al. 2003), M.D. Anderson Cancer Center (Kuban, Pollack et al. 2003), and Akimoto et al. (Akimoto, Muramatsu et al. 2004). Using this method the alpha/beta ratio for the rectum was determined to be 5.4 +/- 1.5. This is consistent with most estimates in animals.

If the alpha/beta ratio for rectal damage is higher than that for prostate, then larger hypofractionated doses could be given with correspondingly larger clinical gains for the same constant late complication rates. (Fowler, Ritter et al. 2003) If, however, the

alpha/beta ratio of late rectal reactions were smaller than that of the prostate, the incidence of complications would be increased. The relative increase is estimated to rise by factors of 1.15 at 15 fractions or 1.25 at 5 fractions (Fowler, Ritter et al. 2003). Such low numbers of fractions is the "worst case" likely, meaning that if a given complication were normally 5 percent it could rise to 6.3 percent, when using only five fractions. (Fowler, Ritter et al. 2003)

III. EVALUATION/SUMMARY OF RESULTS OF EXISTING STUDIES

Because SBRT essentially represents an accelerated form of hypofractionation, consideration of "conventional" (greater than five fractions) hypofractionation is appropriate as a frame of reference for this evaluation of SBRT.

A. Clinical Trials of Hypofractionation

Clinical trials of hypofractionation are ongoing. Most trials have studied modest increases in daily fraction size while concerns of increased rectal toxicity predominate. Some investigators have introduced much more substantial hypofractionated regimens.

1. Cleveland Clinic

At the Cleveland Clinic, 770 consecutive patients with localized prostate cancer were treated with hypofractionated intensity-modulated radiotherapy between 1998 and 2005 (Kupelian, Reddy et al. 2002; Kupelian, Thakkar et al. 2005; Kupelian, Willoughby et al. 2007). Patients received 70 Gy delivered at 2.5 Gy/fraction to the prostate within 5.5 weeks using intensity-modulated radiotherapy (IMRT), prescribed typically to the 87 percent isodose line. The overall average of mean dose was 75.3 Gy. Therefore, the

"biologic" fraction size with intensity modulated radiotherapy would be 2.69 Gy (75.3 Gy/28 fractions). For high-risk disease (stage T3 or pretreatment PSA >10 or biopsy Gleason >7), the seminal vesicles were treated to a dose of 66 Gy. Using an alpha/beta ratio of 3.5 Gy for the prostate, the equivalent dose was calculated using the linear-quadratic model to be 83.8 Gy if delivered in 39 fractions. The equivalent dose for rectum using an alpha/beta ratio of 3.0 Gy for late reacting tissues was 84.7 Gy in 39 fractions.

Treatments were delivered with a 10-MV photon beam using dynamic multileaf collimators. A five-field beam arrangement was used (two lateral beams, two anterior oblique beams, and one anterior beam). Daily localization for treatment was performed using the B-mode Acquisition and Targeting (BAT) trans-abdominal ultrasound system, an ultrasound localization technique.

The limits that were used for the bladder were no more than 30 percent volume to receive greater than 55 Gy with a maximum level at 74 Gy, and no more than 30 percent of the rectum to receive greater than 50 Gy with a maximum dose of 74 Gy. The limits of the normal structures were met in almost all cases except those that included seminal vesicles in the target and included a larger volume of rectum. The maximum limits of the normal structures were not met and were put in to try to keep maximum doses in the normal structures as low as possible.

Updated results with a median follow-up of 45 months (maximum, 86) show that the potential overall five-year ASTRO biochemical relapse-free survival rate[1] was 82 percent (95 percent CI, 79–85 percent), and the five-year nadir + 2 ng/mL rate was 83

[1] A PSA rise by 2 ng/mL or more above the nadir PSA without backdating (Roach et al, Int J Radiat Oncol Biol Phys, 2006. Jul 15;65(4):965-74)

percent (95 percent CI, 79–86 percent). For patients with low-risk, intermediate-risk, and high-risk disease, the five-year ASTRO rate was 95 percent, 85 percent and 68 percent, respectively. The five-year nadir + 2 ng/mL rate for patients with low-risk was 94 percent, intermediate-risk 83 percent, and high-risk disease was 72 percent. The RTOG acute rectal toxicity scores were 0 in 51 percent, 1 in 40 percent and 2 in 9 percent of patients. The acute urinary toxicity scores were 0 in 33 percent, 1 in 48 percent, 2 in 18 percent and 3 in 1 percent of patients. The late rectal toxicity scores were 0 in 89.6 percent, 1 in 5.9 percent, 2 in 3.1 percent, 3 in 1.3 percent and 4 in 0.1 percent (1 patient). The late urinary toxicity scores were 0 in 90.5 percent, 1 in 4.3 percent, 2 in 5.1 percent and 3 in 0.1 percent (1 patient).

The authors concluded that the outcomes after high-dose hypofractionation are acceptable in a large cohort of patients treated with the schedule of 70 Gy at 2.5 Gy per fraction.

2. Fox Chase Cancer Center

Hypofractionation was tested recently in a randomized phase III clinical trial at Fox Chase Cancer Center and primary outcome results are maturing. The dosimetry and preliminary acute toxicity in the first 100 men treated have been reported. (Pollack, Hanlon et al. 2006). The rationale for the hypofractionation schedule used was that there would be a therapeutic gain if the alpha/beta ratio for prostate cancer was 1.5 Gy and 4.0 Gy for the rectum for late effects. The trial compared 76 Gy in 2.0 Gy fractions with 70.2 Gy in 2.7 Gy fractions, prescribed to the planning target volume. Assuming a prostate cancer alpha/beta ratio of 1.5 Gy, the delivery of 70.2 Gy in 26 fractions would be biologically equivalent to 84.4 Gy in 2.0 Gy fractions. Using the same 26-fraction

regimen and assuming an alpha/beta ratio for late effects of 4.0 Gy for the rectum, the biologically equivalent dose in 2 Gy fractions would be 78 Gy. The principal hypothesis was that the 8 Gy escalation in biologic dose between the two arms would result in a 15 percent gain in freedom from biochemical failure from 70 percent to 85 percent in intermediate and high-risk patients.

Simulation was performed with the patient supine, in an immobilization cast with a full bladder and empty rectum. Both computed tomography (CT) and magnetic resonance imaging (MRI) were used to define target and normal structures unless there was a medical contraindication to MRI. The contouring method used for the prostate, seminal vesicles, lymph nodes, rectum, bladder and other normal structures have been described in detail (Pollack, Hanlon et al. 2006). The effective PTV margins were 8-13 mm in all dimensions, except posteriorly, where 3-8 mm was acceptable. In the hypofractionated arm, the effective PTV margins were 5-10 mm in all dimensions, except posteriorly, where 2-6 mm was used. Smaller margins were used for hypofractionation based in part on the rationale that the 90 percent line in the hypofractionated plan would fall in about the same position as the 100 percent line in the conventional plans.

Rectal treatment planning constraints were defined in detail and based on prior results of the M.D. Anderson Cancer Center dose escalation trial (Storey, Pollack et al. 2000; Huang, Pollack et al. 2002). In the conventional arm, less than or equal to 17 percent of the rectum (sigmoid flexure to bottom of ischial tuberosities) should receive 65 Gy and less than or equal to 35 percent less than 40 Gy. The criteria for the bladder were relaxed because a meaningful dosimetric cut-point has not been defined. The bladder V65 Gy was 25 percent and V40 Gy 50 percent. For the hypofractionated group, the rectal

V50 Gy was 17 percent and V31 Gy 35 percent. The bladder V50 Gy was 25 percent and V31 Gy was 50 percent.

Acute side-effects were reported using modified RTOG and Late Effects Normal Tissue (LENT) Task Force criteria, modeled after that described by Hanlon et al. (Hanlon, Schultheiss et al. 1997) and later Storey et al. (Storey, Pollack et al. 2000).

The authors describe an approximately 48 percent rate of Grade 2 or higher maximum genitourinary reactions whereas the average in the other reports of hypofractionation was 35 percent (range, 28–56 percent). The slightly higher than average incidence of genitourinary reactions may be related to their use of a modified RTOG scale, the inclusion of lymph nodes in the high-risk patients and that mean biologic doses to the prostate, and hence urethra, were in excess of 80 Gy. The drop in Grade 2 or higher acute genitourinary toxicity to 10 percent by three months after the completion of radiotherapy is noteworthy. In terms of Grade 2 or higher maximum gastrointestinal reactions, the authors report 13 percent which is at the low end of the range reported by others: average 30 percent (range 14–52 percent).

Dose–volume criteria were related to treatment-related increases in acute gastrointestinal and genitourinary reactions. The only significant predictor of increased gastrointestinal reactions was the high-dose rectal constraint (V65 Gy for conventional and V50 Gy for hypofractionation); the complication risk was greater when the volume of rectum receiving these doses was higher. Acute genitourinary toxicity was found to be most dependent on the bladder volume with greater risk when the bladder volume was smaller.

The authors concluded there was a small, but significant increase in acute gastrointestinal reactions at Weeks two through four of treatment in the hypofractionation group. Overall, there was little difference in acute morbidity between the standard and hypofractionation randomization arms of the IMRT-based treatments used.

3. National Cancer Institute of Canada (NCIC)

Investigators collaborating through the Clinical Trials Group of the NCIC have reported preliminary results of a randomized trial comparing conventional (66 Gy in 33 fractions, prescribed at the isocenter) and hypofractionated (52.5 Gy in 20 fractions) regimens (Lukka, Hayter et al. 2005). This was the first randomized trial comparing a high-dose hypofractionated radiation schedule to a longer conventional-dose per fraction schedule. The primary outcome was a composite of biochemical (three consecutive PSA rises) or clinical failure. The study was designed as a non-inferiority investigation with a predefined tolerance of 7.5 percent and that a sample size of 940 men was estimated to provide approximately 80 percent power to demonstrate noninferiority.

Patients with T1-2 adenocarcinoma of the prostate were eligible. Pretreatment PSA was required to be <40ng/mL, simulated treatment volume <1,000 mL and hormone therapy was not permitted. Patients were stratified by PSA (≤15 versus > 15 ng/mL), Gleason score (<7 vs ≥7), lymph node assessment (clinical versus surgical) and treatment center (16 total).

Simulation was performed with CT with the patient supine. A four-field box radiotherapy technique was used with the target defined as the prostate with a 1.5-cm margin on all sides except posteriorly, where, at the discretion of the radiation oncologist,

the margin could be reduced to 1 cm. Shielding, where appropriate, was used to keep the PTV under 1,000 mL. Patients were treated in the supine position with a full bladder. All patients were treated with a 10-MV linear accelerator.

Genitourinary and gastrointestinal toxicity was assessed using the standardized NCIC toxicity scale and graded toxicity according to specific criteria for each symptom on a five-point scale ranging from 0 (nontoxic) to 4 (severe toxicity).

Between March 1995 and December 1998, 470 patients were randomly assigned to receive 66 Gy in 33 fractions, and 466 patients were randomly assigned to receive 52.5 Gy in 20 fractions. The median follow-up time for all patients was 5.7 years (minimum, 4.5 years; maximum, 8.3 years). At five years, the Kaplan-Meier estimates of biochemical and clinical failure in the long arm was 52.95 percent and short arm was 59.95 percent. The difference was 7.0 percent (90 percent CI, 12.58 percent to 1.42 percent). Because the lower bound is less than the predefined tolerance of 7.5 percent, they could not exclude the possibility of the short arm being inferior. Using the PSA nadir + 2 ng/mL definition of biochemical failure, 37.7 percent of patients in the long arm and 42.3 percent of patients in the short arm experienced biochemical failure.

Acute combined gastrointestinal and genitourinary toxicity was less in the conventional group: 7.0 percent of patients in the conventional group and 11.4 percent of patients in the hypofractionation group experienced grade 3 or 4 gastrointestinal or genitourinary toxicities (risk difference 4.4 percent; 95 percent CI, 8.1 percent to 0.6 percent). Combined late toxicity was comparable with 3.2 percent of patients in both treatment arms experiencing severe toxicities (risk difference 0.0 percent; 95 percent CI,

2.4 percent to 2.3 percent). Overall, genitourinary toxicity represented two thirds of these events.

4. **Christie Hospital**

Between 1995 and 1998, 705 men with T1-4N0M0 adenocarcinoma of the prostate were treated with a hypofractionated regimen consisting of (50 Gy in 16 fractions). The biologic equivalent dose in 2 Gy fractions is 66 Gy (alpha/beta = 1.5). Livsey et al (Livsey, Cowan et al. 2003) retrospectively reviewed their experience and reported toxicity and biochemical outcome.

The median pretreatment PSA was 13ng/mL (range: 0.6–270 ng/mL). Approximately one third of patients had T3-4 disease and one-third had Gleason 7-10.

Radiotherapy was delivered to a planning target volume (prostate plus all/base of the seminal vesicles dependent on risk criteria with a 1-cm margin) with a 4-field conformal technique to a dose of 50 Gy in 16 daily fractions over 22 days. Radiotherapy dose was prescribed to the isocenter and 95 percent coverage of the planning target volume was ensured. The lymph nodes were not treated and no patient received hormonal manipulation.

With a median follow-up was 48 months (range: 1–82 months), five-year freedom from biochemical failure (three consecutive PSA rises) for low-risk (T1-2, PSA ≤10, Gleason < 7) was 82 percent, intermediate-risk (one raised value) was 56 percent, and high-risk (two or more raised values) was 39 percent. RTOG Grade >2 bowel toxicity was 5 percent and bladder 9 percent.

5. Royal Adelaide Hospital (Yeoh, Fraser et al. 2003)

In Australia, investigators conducted a randomized trial comparing conventional (64 Gy in 32 fractions) vs. hypofractionated (55 Gy in 20 fractions) radiotherapy for clinically localized, early-stage (T1-T2N0M0, TNM classification) prostate cancer. The primary end-point of the study was a comparison of late radiation morbidity between the treatment groups after a minimum follow up of two years. The trial was designed to detect a difference in the frequency of mild late radiation morbidity of 20 percent (40 percent vs. 20 percent) with 90 percent power and required recruiting 110 patients in each treatment schedule. Based on the linear-quadratic formulation and an alpha/beta ratio of 3 Gy for late radiation effects, the hypofractionated regimen is approximately equitoxic with the conventional regimen (64 Gy in 32 fractions). Yoeh et al. (Yeoh, Fraser et al. 2003) reported an interim analysis of the first 120 consecutive patients in this Phase III trial.

No patients had a serum PSA level >80 ng/mL or had received antiandrogen therapy. Sixty-one patients received conventional fractionation and 59 hypofractionation. The radiation dose in the patients was prescribed to the isocenter of either a three-field (anterior and two posterior oblique/lateral) or four-field (antero-posterior and laterals) computer-generated plan that encompassed the prostate gland only, with a 1.5-cm 95 percent isodose margin and was delivered using external beam megavoltage (6–23 MV) photons. Posterior field shielding was not used. The median volume encompassed by the 50 percent isodose of the radiation fields was 855 cc (range: 542–1391).

Gastrointestinal symptoms were evaluated by questionnaire and included: stool frequency, stool consistency, rectal pain, rectal mucous discharge, urgency of defecation

and rectal bleeding. Genitourinary symptoms were also evaluated by questionnaire and included: frequency of micturition by day, frequency of micturition by night, hematuria, urgency of micturition and dysuria. After a median follow-up of 43.5 months (range 23–62), there was no difference in clinically significant toxicity or any of the measures of treatment efficacy between the two radiation dose schedules. There was no significant difference in actuarial four-year biochemical relapse-free survival, 85.5 percent for the conventional dose and 86.2 percent for the hypofractionated.

6. Gunma University, Japan

Akimoto et al reviewed their toxicity results delivering 69 Gy in 3 Gy fractions (three times weekly) in 52 patients with clinically localized prostate cancer (Akimoto, Muramatsu et al. 2004). The equivalent total dose for administration of a fractional dose of 2 Gy was 83 Gy (prostate alpha/beta = 3 Gy). A four-field, 10MV technique was used without rectal blocking or explicit dose-volume histogram based criteria. The average field size was 6.5 X 8.2 cm. An immobilization device was used and patients were treated with an empty rectum. All patients receive neoadjuvant, concurrent and adjuvant androgen deprivation therapy consisting of a luteinizing hormone-releasing agonist plus an anti-androgen.

Toxicity was graded using the toxicity criteria of the RTOG. The late RTOG Grade 2 complication rate was 25 percent with a mean follow up of 31 months. Notably, this was identical to that reported by the M.D. Anderson Cancer Center using a three-dimensional conformal radiotherapy to 78 Gy in conventional 2 Gy fractions. One patient who developed rectal bleeding that needed laser coagulation and blood transfusion for

control was considered to have Grade 3 rectal bleeding. No patient developed Grade 4 or worse rectal bleeding.

The V30, V50, V80 and V90 and a history of diabetes mellitus were the factors most closely associated with the development of Grade 2 or worse rectal bleeding. Six (60 percent) of 10 patients with a history of diabetes mellitus developed rectal bleeding, and only 7 (17 percent) of 42 patients without a history of diabetes mellitus developed rectal bleeding. In this study, the volume receiving 50 percent (V50) of the prescribed dose or 80 percent (V80) of the prescribed dose (69 Gy) would be equivalent to 41 or 66 Gy, respectively, at 2 Gy per fraction, assuming that the alpha/beta ratio is 3 Gy for late toxicity. A V50 > 40% or V80 > 25 percent correlated positively with the occurrence of Grade 2 or worse rectal bleeding and was statistically significant.

B. Clinical Reports of Stereotactic Body Radiotherapy

1. Korean Institute of Radiological and Medical Sciences (KIRMS)

Reports of clinical experiences have been limited. The largest report to date originates from the KIRMS in Seoul, Korea (Park, Kim et al. 2006; Choi, Cho et al. 2007). Choi et al. reported on the results of 44 patients treated for low to high risk prostate cancer with CyberKnife® SBRT. This report, available in abstract form only, details the results at 13 months of follow-up of the treatment of ten patients with low-risk prostate cancer (PSA less than 10, Gleason less than 6, stage T1b-T2a), nine intermediate-risk prostate cancers (PSA 10-20, Gleason 7), and 25 high-risk patients (PSA $\geq$ 20, or Gleason $\geq$ 8). The patients received stereotactic treatment with a CybeKnife® unit to a total dose of 32-36 Gy in 4 fractions, with the exception of one

patient who received 24 Gy in 3 fractions. Overall survival at three years was 100 percent, with a three-year biochemical failure-free rate of 78 percent. Fourteen patients experienced grade 1 or 2 acute rectal toxicity, and 17 patients experienced grade 1 or 2 bladder toxicity. There were no grade 3 or greater acute toxicities. No report is made on chronic toxicity.

2. Virginia Mason Medical Center, Seattle, WN (VMMC)

Berit Madsen, M.D., from VMMC in Seattle presented early results in manuscript form on the treatment of 40 patients on a Phase I/II trial of stereotactic hypofractionated radiation therapy for the prostate using a linear accelerator and fiducial marker system (Madsen, Hsi et al. 2007). The patients received 33.5 Gy in 5 fractions, the equivalent of 78 Gy in 2 Gy fractions, assuming an alpha-beta ratio of 1.5 Gy, with noncoplanar fields. There was daily stereotactic localization of the prostate using radio-opaque fiducial markers implanted at the prostate apex, base, and mid-gland. A margin of 4-5 mm from block edge to the prostate was used for treatment. PTV margins were not specified. Six beam angles were employed for treatment. The patients enrolled in the trial were patients with low-risk disease by the Partin criteria, with a combined Gleason score of 6 or less, PSA 10 or less, and clinical stage of T2a or less. The median prostate volume was 56.4 cc. Patients were placed on a diet to minimize gas and took daily simethicone to reduce rectal dilatation and movement during treatment. Before each fraction, orthogonal images were obtained and analyzed for the position of the fiducial markers. An automated computer program (Isoloc 5.2; Northwest Medical Physics Equipment, Linwood, Washington) was used to calculate the necessary off-set between fiducials at the time of

treatment and at the time of simulation. This was used to calculate appropriate couch movements to properly localize on the actual treatment isocenter. Typical treatment time was in the 20-40 minute range. Median follow-up was 41 months. Acute toxicity was 49 percent grade 1 or 2 genitourinary toxicity; 39 percent grade 1 or 2 gastrointestinal toxicity. There was a single grade 3 genitourinary toxicity. Late toxicity grade 1 or 2 was 45 percent in genitourinary and 37 percent in gastrointestinal. No late grade 3 or higher toxicity was reported. 23 percent of patients who were potent before treatment developed erectile dysfunction. Median time to PSA nadir was 18 months. Forty-eight month biochemical freedom from relapse was 70 percent using the former ASTRO definition[2] and 90 percent by the alternative nadir plus 2 ng/mL definition. The authors' conclusions were that SBRT for localized prostate cancer was feasible with little acute or late toxicity.

3. Radiation Medical Group of San Diego, CA

The Radiation Medical Group of San Diego has reported early clinical observations regarding stereotactic body radiotherapy using a CyberKnife® system presented at ASTRO 2007, "Virtual HDR Cyberknife prostate treatment: Toward the development of Noninvasive HDR dosimetry delivery and early clinical observations" (Fuller, Lee et al. 2007). Patients received 38 Gy in 4 fractions. Ten consecutive IRB-approved patients who had undergone SBRT planning were then compared with HDR brachytherapy plans. Plans were initially compared using the stereotactic DVH's versus those of HDR. Five of the plans were then recalculated in order to match the maximum urethra dose to examine the possibility of dose escalation of the stereotactic group for an isotoxicity effect level for the urethra. The authors' conclusions were that isodose

[2] Three consecutive PSA rises after a nadir with the date of failure as the point halfway between the nadir date and the first rise or any rise great enough to provoke initiation of therapy. (Int J Radiat Oncolo Biol Phys. 1997 Mar 15;37(5):1035-41)

coverage was similar for each modality and that higher doses were possible with SBRT while keeping urethral doses constant. Very preliminary results were reported with a median pretreatment PSA level of 6.9 prior to treatment and at four-month follow up after treatment it had decreased to 0.7 ng/ml in the first eight patients. Toxicity was not detailed.

4. 21st Century Oncology, Inc., Fort Myers, FL

Linear accelerator-based SBRT to the prostate using the Trilogy® system was reported from Fort Myers, Fla., by Mantz (Mantz, Fernandez et al. 2007). In this abstract, presented at ASTRO 2007, "A Phase II Trial of Trilogy-Based Prostate SBRT: Initial Report of Favorable Acute Toxicity Outcomes," 22 patients were reported of which 18 had been followed for at least one month. Patients in this study received a total dose of 36.25 Gy prescribed to the prostate in 5 fractions on an every-other-day schedule. Protocol inclusion criteria required T1c to T2a stage, PSA less than 10, Gleason score 6 or less, prostate volume less than 60 cc, and an IPSS voiding score of less than 18. The common toxicity criteria for adverse effects version 3.0 was used to assess toxicity at intervals from one to twelve months after treatment. During treatment, three patients reported dysuria and five urinary hesitancy, all grade 1 toxicities. At one month, one patient reported continued dysuria and hesitancy, and four patients reported frequency and urgency. During treatment, five patients reported diarrhea and two reported proctitis. At one month, one patient reported continued proctitis, grade 1. For patients followed more than three months, they returned to baseline urinary and rectal function. No reporting of clinical outcomes was made.

5. Stanford University

Pawlicki (Pawlicki, Cotrutz et al. 2007) from Stanford University has reported the technical aspects of the Stanford experience in treating patients with prostate cancer with SBRT beginning in 2003. Between 2003 and 2007, 23 patients had been treated. Acute toxicity consisted of grade 1 genitourinary toxicity and an average of grade 1.3 gastrointestinal toxicity, with no grade 3 toxicity in either category. Long-term toxicity results are not available. PSA values have declined in the cohort of patients treated, but, once again, long-term treatment information is unavailable. Patients treated consisted of T1c or T2a patients with a PSA of less than 10 and Gleason score of 6 or less with a primary score of 3 or less. The dose schedule is 7.25 Gy per fraction times 5 fractions for a total dose of 36.25 Gy and treatment was administered every other day. Patients are treated with implantable gold fiducials for daily localization, as well as intra-fraction tracking performed every 30 to 90 seconds during treatment.

IV. CLINICAL DATA OVERVIEW

Preliminary results, primarily available only in abstract form and consisting of reports of clinical experiences from single institutions, show that SBRT for the prostate is technically feasible, with little reported acute morbidity. Very early results, of limited statistical power, suggest that treatment will induce an initial PSA response of a magnitude equivalent to that seen with conventionally fractionated radiotherapy. Data are not available regarding long-term disease control, survival, and chronic toxicity. In the absence of randomized trials and mature, long-term follow-up data, a conservative estimation of consequences of non-use of SBRT would be a continuation of treatment following standard, accepted fractionation schemes with realization of the associated TCP and NTCP values.

V. FUTURE POTENTIAL BASED ON CLINICAL DEVELOPMENT

Assuming favorable outcomes from the maturation of long-term data from the aforementioned randomized studies, one can envision a significant change in the landscape of external beam prostate radiotherapy. The departure from 7-9 weeks of daily treatments to five or fewer fractions for SBRT will certainly allow for an increased throughput of patients through an appropriately equipped facility. If it is found that SBRT of the prostate results in improved cell killing or an improved therapeutic ratio, it is likely that this technique will gain favor in the radiotherapy community.

A. Prediction of Social Implications

Prostate cancer is the most common malignancy in men. The American Cancer Society estimated 218,890 new prostate cancers in 2007, comprising 29 percent of new cancers in men. The majority of these cancers are nonmetastatic at the time of diagnosis (91 percent according to the 2007 National Cancer Institute Reports) thus are amenable to local treatment modalities for potential cure. Currently, the standard local treatment options include radical prostatectomy, prostate brachytherapy (seed implantation or high dose- rate interstitial regimens), external beam prostate irradiation alone (from a variety of radiation sources), and combinations of external beam radiation and brachytherapy as a boost. Conventional courses of external beam irradiation have typically been given over six to eight weeks of daily fractions, five days per week.

Dose escalation has been an ongoing focus of national cooperative clinical trials and institutional studies in an effort to improve upon local-regional control rates and ultimately upon survival outcomes while at the same time maintaining acceptable levels

of morbidity. Concurrently, efforts to achieve greater precision in prostate organ targeting in order to reduce the dose to the adjacent rectum and bladder have risen from new technological advancements, including IMRT with image-guidance and internal fiducial systems implanted in the prostate gland that allow the dose delivered to be localized to the organ on a daily basis. Such technologies improve upon the accuracy of real-time dose delivery while adding complexity, time and cost to the treatment process.

Some patients with early-stage prostate cancers may be candidates for observation alone (no therapeutic intervention) and those appropriate groups remain to be defined. However, the majority of patients in the United States with organ-confined prostate cancer will either require or desire therapeutic intervention. As described in this report, the general concept of hypofractionation for prostate cancer has its origins in the radiobiological premise that prostate cancers may express a low alpha/beta ratio, more similar to late reacting normal tissues, and thus the therapeutic ratio may be enhanced by delivering fewer larger fractions, while maintaining acceptable late normal tissue toxicities. While the therapeutic benefit is of primary importance, hypofractionation regimens that shorten overall treatment time may be desirable for both the radiation oncology facility and the patient, both of which may gain in terms of convenience and cost-effectiveness. These advantages exist only if the new hypofractionation regimens are truly more cost-effective with equivalent or improved clinical effectiveness. In addition, these regimens are largely unverified in any venue other than relatively small single-institution trials with generally short follow up. In particular, the studies of highly accelerated hypofractionation (SBRT) regimens (such as 32 to 38 Gy in 4 to 5 fractions, as opposed to 52 Gy in 20 fractions or other schemas with daily doses per fraction less

than 300 cGy) have been reported exclusively as small manuscripts or abstracts from single institutions, with small numbers of patients and short follow up.

In the ultimate sought-after goal of comparable clinical outcomes for local control, survival and toxicity, then conventional and accelerated hypofractionation schemas may provide significant reductions in the overall cost of prostate cancer radiation treatment, and greatly reduced overall treatment times favored by patients as well. Regimens involving 4 or 5 fractions, as compared to conventional regimens requiring 35 to 40 fractions, may have significant impact on patients' ability to continue working with minimal impact on productivity and resources, as long as acute toxicities and recovery times are not extended. Preliminary data suggest this is not the case, but additional studies are required to verify these preliminary observations. Longer follow up is required to confirm clinical outcomes and quality of life measures. Such results can only be achieved if treatment accuracy, especially with respect to minimizing normal tissue dose-volumes, is strictly achieved. Prostate hypofractionation is an arena in which advanced technology is required to produce acceptable outcomes, and should not be attempted without some mechanism for optimization of immobilization and precise daily real-time organ localization, for which there are several commercially available solutions. Parameters for optimal dose per fraction, normal tissue dose constraints at hypofractionated dose levels, PTV definitions and dose distribution standards remain to be established. Ground work for these parameters has been laid in previous trials of dose escalation, prostate IMRT and even seed implantation techniques.

As these various hypofractionation regimens evolve, it is important to document via adequately powered clinical trials their relative efficacy and toxicity. This is

particularly important in the setting of a shift in paradigm based on biological modeling, to ensure that outcomes are at least equivalent to the long-established conventional fractionation regimens. Currently evidence does not exists to establish that the hypofractionated techniques, especially with acceleration, e.g. SBRT, have been proven to be equivalent to standard fractionation radiation treatments. However, the overall potential benefits in terms of clinical outcomes, cost-effectiveness and patient convenience are promising aspects of this paradigm shift that warrant further investment and investigation.

B. Analysis of Potential Clinical Issues

ASTRO maintains the position that new technologies and modifications of existing technologies representing significant paradigmatic shifts in treatment approach should be implemented into clinical practice in such a manner as to ensure safety, efficacy and, ideally, cost-effectiveness. Current conventionally-fractionated courses of radiotherapy for prostate cancer at escalated doses are among the longest treatment courses for any disease, creating a major impetus to find effective shortened regimens. Hypofractionation with stereotactic body localization for prostate cancer has the potential to shorten overall treatment times, improving upon immediate quality of life for patients due to reduced time commitment to treatment, and may improve upon cost-effectiveness if this technique is less costly to administer than conventionally-fractionated courses of radiation treatment. However, if these benefits come at the cost of higher local recurrence rates and/or higher late toxicity rates, these events will adversely impact upon patients' quality of life and incur increased costs longer term for treatment of recurrences

and complications. As this report outlines, the vast majority of clinical data related to prostate hypofractionation regimens have not used super-high doses per fraction, but rather doses per fraction of less than 3 Gy, which only moderately accelerates dose delivery in comparison to conventional fractionation. SBRT hypofractionation regimens currently under investigation, using doses per fraction of 7 to 9.5 Gy, have only extremely short follow-up times and small numbers of patients treated. These data are inadequate at this time to demonstrate either significant efficacy or toxicity rates.

The potential biological advantages of hypofractionation, as well described in this report, are based on modeling of the linear-quadratic formula for the α/β ratio for prostate cancer cells and normal tissues such as bladder and rectum. This model may not adequately address the complexities of tumor and normal tissue response, and, therefore, may not accurately be able to predict the dose per fraction that may be safely administered. Dose escalation randomized trials, generally using conventional-fractionation schemes, have shown increased rectal toxicity at higher doses. Trials that have compared different techniques, such as 2D versus 3D versus IMRT, have further demonstrated that normal tissue toxicity can be reduced at similar dose levels or with dose-escalation using the more precise image-based and target localization treatment techniques. These trials highlight the need to reduce the normal tissue dose-volumes in order to safely escalate dose without increasing toxicity. However, many of these studies have five-year follow up, while normal tissue toxicities may still appear at later time points, so the true rate of late effects is probably not yet known for the higher total doses. In addition, daily dose delivery imprecision in conjunction with reduced margins around the prostate has the potential to result in poorer local control. Studies have shown that

simply tightening margins to reduce normal tissue dose-volumes without image guidance or other methods to verify daily positioning results in higher rates of PSA failures.

Uncertainties regarding the assumptions underlying the biological advantages of prostate hypofractionation have been proposed. The α/β ratio for prostate cancer may not be as low as some studies have suggested, when hypoxia and other factors are considered. It may not be the case that all risk groups will benefit equally; in fact, the intermediate-risk group has shown the most benefit from dose escalation in randomized trials, with less benefit to high- or low-risk groups. If biologic differences account for such variable outcomes, the same may be true for hypofractionation. To date, a variety of hypofractionation regimens have been used and the optimal schema remains undefined. The interactions between androgen ablation and hypofractionation have also not been adequately addressed.

Technological advances such as stereotactic body radiotherapy combined with optimum immobilization and organ localization may allow refinements in dose delivery precision to achieve the goal of minimal margins around the target structure while permitting dose acceleration. Clinical implementation of this technique will require a consistent investment in new technologies capable of achieving this precision, or poorer local control rates will probably result. These techniques are typically more time-consuming for the radiation oncologist and staff, involving the need for extensive contouring and closer oversight on treatment by the physician, as well as daily localization procedures on the part of the therapists. This increased time commitment should be offset by the fewer number of fractions used. The authors of this report believe further clinical trials addressing the uncertainties in the clinical implementation of

this new approach to prostate cancer treatment should be conducted.

The technique holds sufficient promise to warrant further investigation. If proven efficacious and safe, conventional and/or accelerated hypofractionation may provide social and economic benefits to prostate cancer patients as well.

Disclaimers and Notifications

- *This document was prepared by the Emerging Technology Committee of the American Society for Therapeutic Radiology and Oncology.*
    - *Prior to initiation of this evaluation project, all members of the Emerging Technology Committee (ETC) and of the Task Group performing the evaluation were required to complete Conflict of Interest statements specifically related to the devices or procedures involved. These statements are maintained in the file at ASTRO Headquarters in Fairfax, VA and pertinent conflict information will be published with the report. Individuals with disqualifying conflicts are recused from participation in ASTRO emerging technology assessments.*
    - *The primary role of the ETC is to provide technology assessments regarding emerging technologies to various stakeholders within and outside the Society. It is not the role of the Committee to develop or defend code definitions, valuation recommendations, or other payment policy development functions.*
    - *ASTRO Emerging Technology Reports present scientific, health and safety information and may to some extent reflect scientific or medical opinion. They are made available to ASTRO members and to the public for educational and informational purposes only. Any commercial use of any content in this report without the prior written consent of ASTRO is strictly prohibited.*
    - *ASTRO does not make or imply any warranties concerning the safety or clinical efficacy of the devices reviewed in this report. ASTRO assumes no liability for the information, conclusions, and findings contained in its Emerging Technology Reports.*
    - *This Report is subject to the ASTRO copyright restrictions.*
    - *ASTRO considers any consideration of its technology assessment reports to be voluntary, with the ultimate determination regarding any technology's application to be made by the practitioner, in consultation with the patient, in light of each patient's individual circumstances in accordance with applicable law. Decisions*

regarding coverage of a technology, device or procedure are made by payors and government agencies in accordance with applicable legal standards and their decision-making processes. In addition, this technology assessment describes the use of devices or procedures; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored. In that assessment development involve a review and synthesis of the latest literature, a technology assessment also serves to identify important questions and settings for further research.

REFERENCES

(2007). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. L. A. G. Ries, D. Melbert, M. Krapchoet al. Bethesda, MD, National Cancer Institute.

Akimoto, T., H. Muramatsu, et al. (2004). "Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding." Int J Radiat Oncol Biol Phys **60**(4): 1033-9.

Amer, A. M., J. Mott, et al. (2003). "Prediction of the benefits from dose-escalated hypofractionated intensity-modulated radiotherapy for prostate cancer." Int J Radiat Oncol Biol Phys **56**(1): 199-207.

American*Cancer*Society (2007). Cancer Facts and Figures 2007. Atlanta, GA, American Cancer Society. **2007**.

Balter J and Wright N. et al., (2003) Demonstration of accurate localization and continuous tracking of implantable wireless electromagnetic transponders Int J Radiat Oncol Biol Phys 57, Issue 2, pp. 264-S265

Brenner, D., E. Armour, et al. (1998). "Sublethal damage repair times for a late-responding tissue relevant to brachytherapy (and external-beam radiotherapy): implications for new brachytherapy protocols." Int J Radiat Oncol Biol Phys **41**(1): 135-8.

Brenner, D. J. (2000). "Toward optimal external-beam fractionation for prostate cancer." Int J Radiat Oncol Biol Phys **48**(2): 315-6.

Brenner, D. J. (2003). "Hypofractionation for prostate cancer radiotherapy--what are the issues?" Int J Radiat Oncol Biol Phys **57**(4): 912-4.

Brenner, D. J. (2004). "Fractionation and late rectal toxicity." Int J Radiat Oncol Biol Phys **60**(4): 1013-5.

Brenner, D. J. and E. J. Hall (1999). "Fractionation and protraction for radiotherapy of prostate carcinoma." Int J Radiat Oncol Biol Phys **43**(5): 1095-101.

Brenner, D. J., A. A. Martinez, et al. (2002). "Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue." Int J Radiat Oncol Biol Phys **52**(1): 6-13.

Chang, BK, Timmerman, RD. (2007) Prost Stereotactic Body Radiation Therapy: A Comprehensive Review. American Journal of Clinical Oncology. 30(6):637-644.

Choi, C., C. Cho, et al. (2007). "Stereotactic Radiation Therapy of Localized Prostate Cancer Using Cyberknife." Int J Radiat Oncol Biol Phys **69**(3): S375.

D'Souza, W. D. and H. D. Thames (2001). "Is the alpha/beta ratio for prostate cancer low?" Int J Radiat Oncol Biol Phys **51**(1): 1-3.

Dale, R. G. and B. Jones (2002). "Is the alpha/beta for prostate tumors really low? In regard to Fowler et al., IJROBP 2001;50:1021-1031." Int J Radiat Oncol Biol Phys **52**(5): 1427-8; author reply 1428.

Dewit, L., Y. Oussoren, et al. (1989). "The effect of cis-diamminedichloroplatinum(II) on radiation damage in mouse rectum after fractionated irradiation." Radiother Oncol **16**(2): 121-8.

Dubray, B. M. and H. D. Thames (1994). "Chronic radiation damage in the rat rectum: an analysis of the influences of fractionation, time and volume." Radiother Oncol **33**(1): 41-7.

Duchesne, G. M. and L. J. Peters (1999). "What is the alpha/beta ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy." Int J Radiat Oncol Biol Phys **44**(4): 747-8.

Fowler, J., R. Chappell, et al. (2001). "Is alpha/beta for prostate tumors really low?" Int J Radiat Oncol Biol Phys **50**(4): 1021-31.

Fowler, J. F., M. A. Ritter, et al. (2003). "What hypofractionated protocols should be tested for prostate cancer?" Int J Radiat Oncol Biol Phys **56**(4): 1093-104.

Fuller, D. B., C. Lee, et al. (2007). "Virtual HDR Cyberknife prostate treatment: Toward the development of Non-invasive HDR dosimetry delivery and early clinical observations." Int J Radiat Oncol Biol Phys **69**(3): s358.

Gasinska, A., B. Dubray, et al. (1993). "Early and late injuries in mouse rectum after fractionated X-ray and neutron irradiation." Radiother Oncol **26**(3): 244-53.

Hanks, G. E., T. E. Schultheiss, et al. (1997). "Optimization of conformal radiation treatment of prostate cancer: Report of a dose escalation study." Int J Radiat Oncol Biol Phys **37**: 543-550.

Hanlon, A. L., T. E. Schultheiss, et al. (1997). "Chronic rectal bleeding after high dose conformal treatment of prostate cancer warrants modification of existing morbidity scales." International Journal of Radiation Oncology Biology Physics **38**(1): 59-63.

Haustermans, K., I. Hofland, et al. (1997). "Cell kinetic measurements in prostate cancer." Int J Radiat Oncol Biol Phys **37**: 1067-1070.

Huang, E. H., A. Pollack, et al. (2002). "Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer." Int J Radiat Oncol Biol Phys **54**(5): 1314-21.

Kal, H. B. and M. P. Van Gellekom (2003). "How low is the alpha/beta ratio for prostate cancer?" Int J Radiat Oncol Biol Phys **57**(4): 1116-21.

Kavanagh BD, Timmerman RD, Benedict SH, et al. (2003) How should we describe the radiobiologic effect of extracranial stereotactic radiosurgery: equivalent uniform dose or tumor control probability? Med phys. 30:321-324.

King, C. R. and J. F. Fowler (2001). "A simple analytic derivation suggests that prostate cancer alpha/beta ratio is low." Int J Radiat Oncol Biol Phys **51**(1): 213-4.

King, C. R. and J. F. Fowler (2002). "Yes, the alpha/beta ratio for prostate cancer is low or "methinks the lady doth protest too much...about a low alpha/beta that is"." Int J Radiat Oncol Biol Phys **54**(2): 626-7; author reply 627-8.

King, C. R. and C. S. Mayo (2000). "Is the prostrate alpha/beta ratio of 1.5 from Brenner & Hall a modeling artifact." Int J Radiat Oncol Biol Phys **47**(2): 536-9.

Kitamura K, Shirato H, Seppenwoolde Y, et al. (2002) Three-dimensional intrafractional movement of prostate measured during real-time tumor-tracking radiotherapy in supine and prone treatment positions. Int. J. Radiol. Oncol. Biol. Phys. 53 1117–23

Kuban, D., A. Pollack, et al. (2003). "Hazards of dose escalation in prostate cancer radiotherapy." Int J Radiat Oncol Biol Phys **57**(5): 1260-8.

Kupelian, P. A., C. A. Reddy, et al. (2002). "Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localized prostate cancer." Int J Radiat Oncol Biol Phys **53**(4): 904-12.

Kupelian, P. A., V. V. Thakkar, et al. (2005). "Hypofractionated intensity-modulated radiotherapy (70 gy at 2.5 Gy per fraction) for localized prostate cancer: long-term outcomes." Int J Radiat Oncol Biol Phys **63**(5): 1463-8.

Kupellian P, Willoughby R, Meeks S. (2005) Intraprostatic fiducials for localization of the prostate gland: Monitoring intermarker distances during radiation therapy to test for marker stability, Int. J. Radiat. Oncol. Biol. Phys. Volume 62, Issue 5, Pages 1291-1296

Kupelian, P. A., T. R. Willoughby, et al. (2007). "Hypofractionated intensity-modulated radiotherapy (70 gy at 2.5 gy per fraction) for localized prostate cancer: cleveland clinic experience." Int J Radiat Oncol Biol Phys **68**(5): 1424-30.

Lee, W. R. (2002). "In regard to Brenner et al. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio) similar to late-responding normal tissue." Int J Radiat Oncol Biol Phys **53**(5): 1392; author reply 1393.

Lindsay, P. E., V. V. Moiseenko, et al. (2003). "The influence of brachytherapy dose heterogeneity on estimates of alpha/beta for prostate cancer." Phys Med Biol **48**(4): 507-22.

Livsey, J. E., R. A. Cowan, et al. (2003). "Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis." Int J Radiat Oncol Biol Phys **57**(5): 1254-9.

Logue, J. P., R. A. Cowan, et al. (2001). "Hypofractionation for prostate cancer." Int J Radiat Oncol Biol Phys **49**(5): 1522-3.

Lukka, H., C. Hayter, et al. (2005). "Randomized trial comparing two fractionation schedules for patients with localized prostate cancer." J Clin Oncol **23**(25): 6132-8.

Madsen BL, His RA, et al. (2007). "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 **67**(4): 1099-105.

Mantz, C. A., E. Fernandez, et al. (2007). "A Phase II Trial of Trilogy-Based Prostate SBRT: Initial Report of Favorable Acute Toxicity Outcomes." Int J Radiat Oncol Biol Phys **69**(3): s334.

Michalski, J. M., K. Winter, et al. (2003). "Preliminary evaluation of low-grade toxicity with conformal radiation therapy for prostate cancer on RTOG 9406 dose levels I and II." Int J Radiat Oncol Biol Phys **56**(1): 192-8.

Nahum, A. E., B. Movsas, et al. (2003). "Incorporating clinical measurements of hypoxia into tumor local control modeling of prostate cancer: implications for the alpha/beta ratio." Int J Radiat Oncol Biol Phys **57**(2): 391-401.

Park, K., K. H. Kim, et al. (2006). "Feasibility of cyberknife for the treatment of localized prostate cancer: Preliminary results." Eur Urol Suppl **5**(2): 132.

Pawlicki, T., C. Cotrutz, et al. (2007). "Prostate cancer therapy with stereotactic body radiation therapy." Front Radiat Ther Oncol **40**: 395-406.

Pollack, A., A. L. Hanlon, et al. (2006). "Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial." Int J Radiat Oncol Biol Phys **64**(2): 518-26.

Seiler P G, Blattmann H, Kirsch S, et al. (2000) A novel tracking technique for the continuous precise measurement of tumour positions in conformal radiotherapy Phys. Med. Biol. 45 N103–N110

Shirato H et al. (2000a) Physical aspects of a real-time tumor-tracking system for gated radiotherapy, Int. J. Radiat. Oncol. Biol. Phys. 48 1187–95

Skwarchuk, M. W., A. Jackson, et al. (2000). "Late rectal toxicity after conformal radiotherapy of prostate cancer (I): multivariate analysis and dose-response." Int J Radiat Oncol Biol Phys **47**(1): 103-13.

Stock, R. G., N. N. Stone, et al. (1998). "A dose-response study for I-125 prostate implants." Int J Radiat Oncol Biol Phys **41**(1): 101-8.

Storey, M. R., A. Pollack, et al. (2000). "Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial." Red Journal **48**: 635-642.

Storey, M. R., A. Pollack, et al. (2000). "Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial." Int J Radiat Oncol Biol Phys **48**(3): 635-42.

Terry, N. H. and J. Denekamp (1984). "RBE values and repair characteristics for colo-rectal injury after caesium 137 gamma-ray and neutron irradiation. II. Fractionation up to ten doses." Br J Radiol **57**(679): 617-29.

van der Kogel, A. J., K. A. Jarrett, et al. (1988). "Radiation tolerance of the rat rectum to fractionated X-rays and pi-mesons." Radiother Oncol **12**(3): 225-32.

Wang, J. Z., M. Guerrero, et al. (2003). "How low is the alpha/beta ratio for prostate cancer?" Int J Radiat Oncol Biol Phys **55**(1): 194-203.

Wang L, Jacob R, Chen L, et al. (2004) Stereotactic IMRT for prostate cancer: Setup accuracy of a new stereotactic body localization system. Journal of Applied Clinical Medical Physics, Vol. 5, No. 2.

Willough TR, Kupelian P. (2006) Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer, Int J Radiat Oncol Biol Phys 65 Issue 2, pp. 528-534

Yeoh, E. E., R. J. Fraser, et al. (2003). "Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial." Int J Radiat Oncol Biol Phys **55**(4): 943-55.