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The 15-year outcomes of high-dose-rate brachytherapy for radical dose escalation in patients with prostate cancer—A benchmark for high-tech external beam radiotherapy alone?

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ABSTRACT

PURPOSE: Dose escalation using high-dose-rate brachytherapy (HDR-BT) is an established treatment method for prostate cancer. First, long-term results were previously published (specific Kiel method). This study aims to evaluate 10-/15-year outcomes of Kiel Protocol 1 (1986–1992).

METHODS AND MATERIALS: Conformal external beam radiotherapy (EBRT) was delivered to the pelvis (50 Gy per conventional fractionation) along with an HDR boost to the prostate amounting to a combined biologic equivalent dose in 2 Gy per fraction of 117.25 Gy ($\alpha/\beta = 3$). The HDR-BT was performed in two fractions of 15 Gy to the peripheral zone of McNeal. The EBRT-clinical target volume covered the full pelvis. The analyzed cohort totaled 122 patients. The reported end points were overall/cancer-specific survival, local recurrence/distant metastasis rates, and biochemical (BC) control rates according to American Society for Therapeutic Radiology and Oncology/Phoenix definitions. All end points were calculated using the Kaplan–Meier method and the log-rank test in univariate analyses.

RESULTS: The mean follow-up time was 116.8 months. The 5-, 10-, and 15-year survival rates were 81%, 62.1%, and 45% for overall survival; 92.1%, 83.1%, and 75.3% for cancer-specific survival; 92.5%, 91.4%, and 83.9% for local recurrence–free survival; and 83.8%, 81.2%, and 69.8% for distant metastasis–free survival, respectively. American Society for Therapeutic Radiology and Oncology–defined BC tumor control rates at 5, 10, and 15 years were 81.1%, 74%, and 67.8%, respectively. According to Phoenix, the BC control rates at 5, 10, and 15 years were 77.8%, 69%, and 63.6%, respectively.

CONCLUSIONS: The long-term results for the combination of HDR-BT and EBRT continue to show excellent results, providing high equivalent dose in 2 Gy per fraction and high disease control rates. These outcomes were reproducible for the extended follow-up period ranging up to 21.9 years.

Keywords: Prostate cancer; HDR brachytherapy; Dose escalation; Long-term results

Introduction

Prostate cancer is the most common malignancy in Western and Central Europe with 202,000 cases (1) and in the United States with an incidence of 220,900 new cases/yr (2). Consequently, prostate cancer constitutes a major public health and socioeconomic problem with increasing incidence in a rapidly aging population (3). Because local therapy yields excellent long-term survival rates among patients with clinically localized disease, radiotherapy (RT) and radical prostatectomy are considered curative treatments, whereas watchful waiting and active surveillance protocols as well as primary androgen deprivation therapy may be alternatively used.

RT is recommended in modern guidelines (4, 5) as one alternative of curative intent treatments in all risk strata

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of localized prostate cancer. Especially in higher risk cohorts, interstitial high-dose-rate brachytherapy (HDR-BT) in combination with external beam radiotherapy (EBRT) is recognized as an established therapy (6–10) and has been proven to be more efficient than EBRT alone in one randomized trial (11). Radiation dose escalation for prostate cancer was tested in a series of randomized controlled prospective trials (12–14) and was shown to be beneficial in terms of biochemical failure (BF), which was defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus (15) as three consecutive rises in the prostate-specific antigen (PSA) level. However, the ''price to pay'' for this benefit in clinical outcome was a significant increase of Grade 2 or higher late rectal complications of more than 25–30% as a function of the rectal volume receiving ≥70 Gy ($V_{70rectum}$). Similar observations were made for Grade 3 or higher rectal complications. The authors stated that dose escalation is beneficial; however, techniques that limit the rectal volume receiving ≥70 Gy to <25% should be used (12). Table 1 summarizes the data of dose-escalation Phase III studies using photon beam irradiation. These results indicate a dose-effect dependency for prostate cancer and can also serve as a model for further dose escalation in the prostate.

One technically feasible option for prostate dose escalation is HDR-BT that minimizes the moving target problem. In addition, modern image-guided interstitial BT has clear advantages over intensity-modulated photon beam RT and even intensity-modulated proton beam RT in terms of reduced integral dose and can be considered for benchmarking high-tech EBRT (16). Encouraging preliminary long-term data (17) from our group have been previously published demonstrating that HDR-BT is a safe and efficient method for local dose escalation in the prostate providing excellent long-term results and when respecting specific selection criteria also being associated with relatively low severe chronic gastrointestinal (GI) and genitourinary (GU) toxicities. The adopted Kiel technique was also shown to be reproducible in two other institutions producing similarly improved 5-year outcomes (18). The present study aims to analyze and report the very long-term results of Kiel Protocol 1 at 10 and 15 years (since 1986–1992). To the best of our knowledge, these registered outcomes are first reported in the literature for HDR-BT in long-term survivors of prostate cancer.

Methods and materials

The Kiel Protocol 1 was the first successfully introduced program in the world for radical local dose escalation which incorporated image-guided transrectal ultrasound (TRUS) preplanned interstitial HDR-BT and a series of conventionally fractionated CT planned EBRT for localized prostate cancer (17).

Kiel Protocol 1 anticipated in the 1980s contemporary concepts of partial dose escalation

The concept of dose escalation in this first Kiel protocol was and remains unique in addressing partial organ dose escalation [clinical target volume (CTV) 1 = peripheral zone of McNeal], while maintaining a sufficiently high dose to the remainder of the prostate. Figure 1 depicts the target volume definitions for BT and clarifies these relationships.

The original Kiel protocol needle geometry followed a 4:2:2 system (Fig. 1) that permitted in deviation from the classic Paris system to escalate dose in the tumor-bearing peripheral prostate zone. This technique used very high contact doses in close vicinity of the applicators. This option to place otherwise inevitable cold and hot spots deliberately to create cold (sparing the urethra) and hot zones (tumor related) of radiation distribution within the target volume can be reached in the modern RT era only by very sophisticated intensity-modulated external beam techniques.

Description of the therapy protocol

The RT planning for EBRT was CT-based, and the treatment was delivered using a linear accelerator with a photon

Table 1
Randomized phase III trials testing dose-escalated conformal photon radiation vs. conventional radiotherapy

Trial	Total number of patients	Subset	Tumor control[a]		*p*-Value
			Low dose, % (Gy)	High dose, % (Gy)	
Pollack (2002)	301	High risk	43 (70)	62 (78)	0.012
Median follow-up 60 m		Low risk	ca. 75% in both arms		n.s.[b]
Peeters (2006)	669	High risk	54 (68)	64 (78)	0.01
Median follow-up 51 m		Low risk	87 (68)	84 (78)	n.s.[b]
Dearnaley (2007)	843	All risk subgroups	60 (64)	71 (74)	0.0007
Median follow-up 5 yr					0.67[c]
		High risk	43 (64)	57 (74)	0.78[c]
		Low risk	79 (64)	85 (74)	0.6[c]

[a] Tumor control = 5-year freedom from failure, including freedom from biochemical failure (FBF) in the study by Pollack *et al.* (5), FBF in the trial by Peeters *et al.* (6), and FBF in the trial by Dearnaley *et al.* (7).
[b] No statistically significant difference.
[c] Hazard risk.