REVIEW ARTICLE

Radiotherapy and Hormone Treatment in Prostate Cancer

The Use of Combined External Beam Radiotherapy and Hormonal Therapy in the Management of Localized and Locally Advanced Prostate Cancer

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SUMMARY

Background: Prostate cancer has the highest incidence of any type of cancer in Germany; an estimated 67 000 new diagnoses of prostate cancer will be made in 2016. In the current German S3 guideline for the treatment of prostate cancer, radiotherapy—sometimes in combination with androgen deprivation therapy (ADT)—is one of the two recommended options for treatment with curative intent (the other is radical prostatectomy). There have been many publications on this subject, yet it is still often unclear in routine practice how ADT should be administered, and for how long.

Methods: This review is based on publications retrieved by a selective literature search, with special attention to controlled trials.

Results: For low risk patients, radiotherapy without ADT is indicated (evidence level 1). Patients with localized prostate cancer and an intermediate risk benefit from radiotherapy combined with a four-to-six-month course of ADT. In this situation, a higher radiation dose might be an effective substitute for ADT (evidence level 1–2). For patients at high risk, radiotherapy combined with long-term hormonal treatment is the standard therapy, as it significantly improves all oncological end points (evidence level 1). For example, in the largest randomized and controlled trial, this form of treatment reduced cancer-specific mortality from 19% to 9%. Higher radiation doses of 66–74 Gy and longer ADT can improve local control at the cost of increased urethral toxicity.

Conclusion: Androgen deprivation combined with external beam radiotherapy is a curative standard option for patients with prostate cancer who are at high risk of recurrence. The modern radiotherapeutic techniques that are now available, such as intensity-modulated radiotherapy, enable a further improvement of the risk/benefit ratio.

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Prostate cancer is the most common malignant tumor in men in Germany. Its estimated incidence for 2016 is 66 900 men. Among all cancers, mortality due to prostate cancer in 2012 was in third place, with 12 957 patients (1).

Because of the poorer prognosis of patients with a high risk profile (*Table 1*) treatment remains a challenge. Radical prostatectomy ($\pm$ adjuvant or salvage radiotherapy) and a combination of radiotherapy and androgen deprivation therapy (ADT) are an option for primary therapy. The current guideline does not recommend further treatment options—such as cryotherapy, high-intensity focused ultrasound, and other procedures—outside prospective studies (2).

No data of a satisfactory evidence level are available with a view to a therapeutic recommendation for the combination of interstitial brachytherapy with ADT. A randomized trial is being conducted, but its results have not yet been published (3). Treatment with protons or heavy ions is currently available in very few centers and has not been conclusively evaluated (4). Data on ADT combined with proton or heavy-ion therapy are lacking completely. The American Society for Radiation Oncology (ASTRO) has also confirmed that the role of these qualities of rays remains unclear in the treatment of prostate cancer (5). Furthermore, the currently available data on hypofractionation—that is, radiotherapy using higher daily individual doses and a lower total number of radiation fractions—are inconsistent (6–8). Two new randomized trials (the CHHIP Trial, including 3162 patients; and the HYPRO Trial, including 820 patients) have shown that hypofractionation is not inferior to conventional approaches and can therefore provide a treatment alternative. The study results are expected to be published in early 2016.

Research question

The multitude of publications on combined radiation and hormone therapy often prompts uncertainties when defining the indication. We aim to alleviate this situation by summarizing the results of randomized studies in this article.

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TABLE 1

Risk groups according to the National Comprehensive Cancer Network and D'Amico (e1)

Risk group	Low risk of recurrence	Moderate risk of recurrence	High risk of recurrence
NCCN			
Tumor stage	cT1c–cT2a and	cT2b–2c and/or	cT3 or
PSA value	<10.0 ng/mL and	>0.0–20.0 ng/mL and/or	>20.0 ng/mL or
Gleason score	<7	= 7	8–10
D'Amico			
Tumor stage	cT1c–2a and	cT2b and/or	cT2c–cT3 or
PSA value	<10.0 ng/mL and	>10.0–20.0 ng/mL and/or	>20.0 ng/mL or
Gleason score	<7	= 7	8–10

NCCN, National Comprehensive Cancer Network (www.nccn.org); PSA, prostate specific antigen

Method

The recommendations are based on studies that correspond to the highest available evidence level. The cited literature is the result of a selective search in the medical databases PubMed, Embase, and Cochrane Library. We used the following search terms or limitations for search terms for the time period 2000–2015 individually and in combination: “prostate cancer”, “androgen deprivation”, “hormonal therapy”, “radiotherapy”, “irradiation”, “radiation”, “randomized trial”, “review”, “evidence based medicine”.

Results

In what follows we summarize the results of randomized trials that provide answers to the question of the indication on the basis of risk factors and the duration of ADT, as well as explaining possible side effects and their management.

External beam radiotherapy uses photons generated by a linear accelerator (LINAC) and is often referred to as three-dimensional conformal radiotherapy (3D-CRT). Standard treatment entails fractionated therapy using individual doses of 1.8–2.0 Gy and total dosages of 74.0–80.0 Gy. Intensity modulated radiotherapy (IMRT) is a form of improved 3D-CRT, in which continual changes to the photon beam mediated by thin movable leaves of lead ensure that different volumes of the irradiated area receive different doses. This approach spares the surrounding healthy tissue and optimally covers the target area. Randomized studies comparing 3D-CRT and IMRT are lacking. Several cohort studies including 6102 and 7244 patients who had received either IMRT or 3D-CRT showed a significant reduction in acute and late gastrointestinal

toxicity and the rates of proctitis/hemorrhage as a result of IMRT (24 month incidence: 18.8% versus 22.5% [9]). Late genitourinary sequelae did not differ (9, 10). In Germany, IMRT has become widespread in the treatment of prostate cancer and can be regarded as the new standard. *Table 2* compares the results of dose escalation studies with those of more recent therapeutic studies; the literature selection concentrates on studies including large numbers of participants (>100 patients).

In order to ensure the correct positioning of patients during radiotherapy, image-guided radiotherapy (IGRT) (11–13) is increasingly used in Germany. Determining the exact position of the prostate by using implanted gold markers within the prostate, ultrasound, or computed tomography immediately preceding irradiation increases the precision of the treatment.

Irradiation of the pelvic lymphatic drainage pathways in case of a risk of lymph node metastases

None of the randomized trials so far has shown that irradiating the pelvic lymphatic drainage pathways is associated with an improved oncological result. The largest randomized study (RTOG-94–13) in 1323 patients with prostate cancer and a follow-up period of 7 years did not find a clear benefit for pelvic irradiation (14).

In case of lacking lymph node staging, the risk of lymph node involvement (LN risk) was calculated by using the following formula, which Roach developed in 1994 (15): $\text{LN risk (\%)} = 2/3 \text{ PSA} + ([\text{GS}-6] \times 10)$ (PSA, the initially measured value of prostate specific antigen; GS, Gleason score).

The calculations of Nguyen (16) and Yu (17) were also used. According to a comparative analysis, the

TABLE 2

Comparison of phase III studies of dose escalation in three-dimensional conformal radiotherapy with studies of new radiotherapeutic techniques

	Study	Pat.	Dose (Arm A /B) (Gy)	BR (arm A/B) (%)	GI-tox. $\geq$ °II (%) arm A/B	GU-tox. $\geq$ °II (%) arm A/B	FU
Randomized studies, 3D-CRT	M.D. Anderson (e2, e3)	301	70/78	50/27*	13/26*	8/13	9.0 years
	Dutch study (e4)	669	68/78	53/46*	35/25*	41/40	70 months
	PROG 95–09 (e5, e6)	393	70.2/79.2	32.4/16.7*	13/24	24/29	8.9 years
	GETUG 06 (e7)	444	70/80	39/28*	14/19.5	10/17.5*	61 months
	MRC RT01 (e8, e9)	843	64/74	40/29*	24/33	8/11	63 months
New therapeutic techniques (e.g., IMRT, IGRT)	Sharma et al. (e10)	123	76	–	8	–	5 years
	Zelevsky et al IGRT (e11)	186	86.4	13.0	1.0	10.4	24 months
	Zelevsky et al. non-IGRT (e11)	190	86.4	22.3	1.6	20.0	49 months
	Vora et al. (e12)	416	75.6	15.4	24	29	5 years
	Vesprini et al. IGRT/IMRT (e13)	362	75.6–79.8	24	14	33	58 months
	Eade et al. (e14)	216	74–78	6.5	2.4	3.5	43 months

Pat., number of patients; BR, biochemical recurrence; GI-tox., gastrointestinal toxicities; GU-tox., genitourinary toxicities; FU, follow-up; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; IGRT, image-guided radiotherapy; PROG, Proton Radiation Oncology Group; GETUG, Groupe d'Etude des Tumeurs Uro-Génitales; MRC RT, Medical Research Council RT01
* significant differences

Roach formula yielded the best results, however, and is therefore the analytic tool of choice (18).

External beam radiotherapy ± androgen deprivation therapy

External beam radiotherapy is the only curative therapeutic option, which in randomized trials showed superior efficacy compared with sole androgen deprivation therapy. More than 2300 patients who had been randomized to ADT or a combination of irradiation and ADT were found to have significantly superior results with additional radiotherapy (Table 3):

- Biochemically no evidence of disease (bNED)
- Metastasis free survival (MFS)
- Prostate cancer specific survival (PCSS) or
- Prostate cancer specific mortality (PCSM)
- Overall survival (OS).

The rate of distant metastases for ADT only was almost three times that of combination treatment (6% versus 17%) (DART01 Study). The largest study, which included 1205 randomized patients, showed a reduction in prostate cancer specific mortality as a result of additional irradiation, from 19% to 9% (19–21).

ADT was given as neoadjuvant treatment, in parallel with and/or adjuvant to percutaneous irradiation. The medications used were androgen receptor blockers (for

example, bicalutamide) or gonadotropin releasing hormone (GnRH) agonists (such as goserelin) or antagonists (for example, degarelix). The combination of radiotherapy with newer medications, such as CYP17A1 inhibitors (for example, abiraterone acetate) cannot be wholly recommended as no randomized studies exist for this drug that have shown equivalent or better efficacy.

In patients with an enlarged prostate—for example >60 mL with accompanying symptoms—neoadjuvant ADT can be used to reduce the prostate volume. Studies have shown that a reduction of up to 50% is possible (22). This results in lower dose exposures to the bowel and bladder (23).

Two randomized studies investigated the question of the duration of neoadjuvant ADT. The Trans-Tasman Radiation Oncology Group (TROG 96.01) studied in 802 patients with moderate and high risk profiles the option of additional neoadjuvant ADT of two months' or five months' duration before they had 66 Gy radiotherapy. The second study randomized patients to three months or eight months of maximal androgen blockage in combination with 66 Gy radiotherapy. Both studies showed a significant improvement in biochemical control, MFS, and PCSS if the lowest PSA value had

TABLE 3

Randomized studies of combined radiotherapy ± androgen deprivation therapy

Study	Pat.	Arm A	Arm B	bNED (%) arm A/B	PCSM (%) arm B/B	OS (%) arm A/B	FU
PR3/PR07 (20, e15)	1205	RT + ADT lifelong	ADT	93.2/80	9/20	74/66	7 y
SPCG-7/SFUO-3 (21)	875	RT + ADT lifelong	ADT	74.1/25.3	11.9/23.9	69.4/60.6	7.6 y
DART01/05 GICOR (e16)	365	RT + 4 mth ADT	RT + 28 mth ADT	81/90	–	86/95	5.2 y
D'Amico (e17)	206	RT + 6 mth ADT	RT	81/46	3.9/13.4	74/61	8.2 y
Jones et al. (30)	1979	RT + 4 mth ADT	RT	59/74	4/8	62/57	9.1 y
RTOG 86–10 (e18)	471	RT + 4 mth ADT	RT	35/20	23/36	42.6/33.8	13.2 y
RTOG 85–31 (e19)	977	RT + ADT lifelong	RT	77/62	16/22	49/39	9.6 y
RTOG 92–02 (e20)	1554	RT + 24 mth	RT + 4 mth ADT	48.1/31.9	11.3/16.1	51.6/53.9	11.2 y
Bolla et al. (e21)	415	RT + 36 mth ADT	RT	47.7/22.7	10/30	58.1/39.8	9.1 y
Bolla et al. (38)	970	RT + 36 mth. ADT	RT + 6 mth ADT	78.3/58.9	3.2/4.7	84.8/81	6.4 y

Pat., number of patients; bNED, biochemically no evidence of disease (biochemical absence of recurrence);

PCSM, prostate cancer specific mortality; OS, overall survival; FU, follow-up;

Mth, months; y, years; RT, radiotherapy; ADT, androgen deprivation therapy

Fields with green borders represent significant differences. Fields containing red text show non-significant differences.

reached 1.0 ng/mL or 0.4 ng/mL (24–27). By contrast, the RTOG Study-9910 compared eight weeks versus 28 weeks of neoadjuvant ADT. Compared with the studies cited above, the relevant oncological endpoints after 10 years of follow-up did not differ (28). This means that no generalizable advantage for a longer duration of neoadjuvant ADT can be stipulated.

In interpreting the results, it should be borne in mind that the total irradiation doses administered in the studies are not regarded as high enough from today's perspective. A recent dose escalation study of six versus 18 months of ADT ± zoledronate and a dose of 66 Gy, 70 Gy or 74 Gy or high-dose-rate (HDR) brachytherapy showed significantly improved local control for increasing doses and with longer ADT. Urethral toxicity increased, however (29).

In all randomized studies that compared combination treatment with radiotherapy only and adjuvant ADT, results improved especially in patients with a moderate or high risk profile. For the former, short-term ADT lead to significantly more instances of biochemical absence of recurrence and PCSM. For locally limited prostate cancer with risk factors, two studies found a benefit for short-term ADT for four to six months in addition to radiotherapy compared with radiotherapy alone for all relevant endpoints (bNED,

PCSM, and OS) (30, 31). A comparison of the results of short-term ADT with the results of dose escalation shows that dose escalation improved biochemical control to at least the same degree. Accordingly, the irradiation dose can be increased to >74 Gy as an alternative to short-term ADT lasting four to six months. By contrast it was found that patients with a low risk profile did not benefit from additional ADT.

The Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) have conducted studies in high-risk patients whose results substantially influenced the therapeutic standards (Table 3). The key message is the significant superiority of long term hormone treatment for 24–36 months for all oncological endpoints in patients with a high risk profile. The results of a recently presented study in which ADT was given for a total of 18 months were not inferior to ADT given for a longer period. Until the final publication of that study, however, the current standard of 24–36 months will remain valid.

With regard to overall survival, the studies' results are not consistent. The result of the RTOG Study 86–10 is a surprise in that the overall survival was not significantly improved in the treatment arm for the combination of radiotherapy and ADT. The reason for this is

likely to be the fact that most patients in this study had high risk factors and four months of ADT is not enough in this group of patients.

What deserves critical comment, however, is the fact that the selection of study endpoints is controversial. Many authors give the highest priority to overall survival, whereas other authors regard cancer-specific or metastasis-free survival as more important for the patient.

New randomized studies designed to optimize treatment of patients with high-risk prostate cancer investigated the role of local therapy + ADT and additional medical tumor treatment with local therapy + ADT alone. The GETUG-12 Study compared the combination of radiotherapy + ADT for three years + 4 cycles of Docetaxel/Estramustine with radiotherapy + ADT alone. 413 patients experienced significantly improved recurrence-free eight-year survival when they were additionally given chemotherapy (62% versus 50%) (32). The RADAR Study mentioned above did not find any additional benefit for zoledronate therapy with a combination of radiotherapy and ADT. After 7.4 years, 18 months of ADT and zoledronate showed a significant advantage with regard to bNED (74% versus 65.8%) and the need for secondary tumor therapy compared with six months' ADT (15.3% versus 25.6%) (33).

Side effects of radiotherapy

The treatment of radiation induced side effects should always be undertaken in collaboration with Radiation Oncologists in order to combine experiences optimally and ensure a high effectiveness of side effect management for the patient.

Mild or moderate side effects during and after radiotherapy (acute side effects) are irritative genitourinary (dysuria, pollakiuria, nocturia, increased urge to urinate) and gastrointestinal symptoms (increased urge to defecate, passing of mucus and, more rarely, rectal bleeding). These occur depending on the data collection method (EORTC-RTOG scale or Common Terminology Criteria of Adverse Events [CTCAE]) at a rate of 9–49%, whereas severe acute side effects affect only 1–3% of patients. All acute side effects usually cease quickly after the therapy has been concluded. Severe late genitourinary or gastrointestinal side effects—such as higher-grade incontinence, urethral structures, or persistent hemorrhages—have become rare after modern external beam radiotherapy (0.1–6%). Patient-based risk factors for the increased risk of radiation induced acute and late side effects are older age, large rectal volume, previous abdominal surgery, diabetes mellitus, hemorrhoids, and inflammatory bowel disorders. Equally, previous genitourinary symptoms, transurethral resection of the prostate, and acute genitourinary side effects during radiotherapy are risk factors for late side effects after radiotherapy. Erectile dysfunction after sole radiotherapy is a common side effect (20–30%), which in most cases can be treated successfully by administering phosphodiesterase

(PDE)-5 inhibitors (34). In 2012, Budäus et al. published a comprehensive summary of the causes and risk factors of radiation induced side effects (35).

The side effects listed here, but also milder symptoms that may concern the patient, are often easily managed by using simple conventional methods or medications. For severe side effects, hyperbaric oxygen therapy is a therapeutic option in severe proctitis that has been investigated in a randomized study (evidence level 1) (36).

Radiotherapy may increase the risk of developing secondary malignancies. This late side effect becomes clinically relevant only after more than 10–15 years. Current data do not allow any definite conclusions about the extent of this risk after localized radiotherapy for prostate cancer. A matched-pair analysis of 2120 patients each after radical prostatectomy or radiotherapy found only after 10 years a significant difference in the rate of secondary malignancies (hazard ratio 4.9 for bladder cancer and lymphoproliferative disorders). If modern therapeutic techniques such as brachytherapy or IMRT were used, however, the risk did not increase significantly, even after 10 years (37). Regarding this, the interdisciplinary discussion with the patient should neither favor definitive radiotherapy nor radical prostatectomy.

Side effects of androgen deprivation therapy

The use of ADT has a substantial rate of side effects. Common side effects (>10%) include hot flashes and attacks of sweating, loss of libido, tiredness/fatigue, headache, weight gain, gynecomastia, and erectile dysfunction. Important for patients' quality of life—in addition to the rarer (<1%) mood swings/depression, loss of muscle mass, osteoporosis, micturition problems, and impaired vision—is the even rarer (<1%) febrile neutropenia. The differences in quality of life for six or 36 months of ADT do not reach significance (38). Rare but serious cardiovascular side effects—for example, myocardial infarction, sudden cardiac death, and stroke—have been reported in association with long-term ADT. Cardiovascular mortality in men with congestive heart failure or myocardial infarction in their medical histories was investigated in a retrospective analysis of 591 men who had received ADT for a median of four months, in addition to brachytherapy. The study showed a significant increase in mortality (22.7% versus 11.7%) (39). Similar data have been reported after a median duration of six months of ADT combined with radiotherapy (19.5% versus 14.3%) (40). Recent meta-analyses have given rise to the suspicion that the administration of luteinizing hormone-releasing hormone (LHRH) analogues raises the risk of cardiovascular death particularly in patients with pre-existing severe cardiovascular disorders. Two recent meta-analyses found a significantly increased risk of cardiovascular death (e22) and an increased risk for cardiac events (e23). By contrast, a meta-analysis of randomized studies of cardiovascular deaths after ADT did not ascertain any increase in cardiovascular mortality

KEY MESSAGES

- Modern techniques such as intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have an improved therapeutic index (the ratio of effects to side effects) (evidence level 2+ to 3).
- Radiation and hormonal therapy have shown significant advantages for all oncological endpoints over hormonal therapy or radiotherapy alone in localized prostate cancers with risk factors or locally advanced cancers (evidence level 1+).
- For patients with a low risk profile, ADT has not been found to offer any therapeutic benefit in addition to radiotherapy.
- Radiation induced side effects should always be treated in collaboration with a radiation oncologist, in order to aggregate experiences in an optimal way and ensure high effectiveness of the side effect management for the patient.
- ADT probably increases the risk of fatal cardiovascular events for patients taking luteinizing hormone-releasing hormone (LHRH) analogues and who have a history of severe previous disorders (coronary heart disease, congestive heart failure, myocardial infarction).

(e24). Data from RTOG studies did not show increased cardiovascular mortality either (e25). In at-risk patients, a cardiological consultation should be conducted and, if required, radiotherapy with LHRH antagonists or antiandrogens should be given.

Since androgen deprivation treatment with LHRH analogues can also increase the risk of metabolic syndrome or diabetes mellitus, regular control of laboratory variables is required (e26). Because of the two risks mentioned, the US Food and Drug Administration (FDA) published a warning in 2010. This was—among others—based on a recommendation of the American Heart Association, the American Cancer Society, and the American Urological Association, and the support of the American Society for Radiation Oncology (e27).

Conflict of interest statement

PD Dr Böhmer has received conference delegate fees and travel expenses as well as lecture honoraria from Takeda Pharma GmbH. He is the principal investigator of an EORTC phase III study of prostate cancer that receives funding from Ferring Arzneimittel [Medicines] GmbH.

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Supplementary material
For eReferences please refer to:
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Supplementary material to:

Radiotherapy and Hormone Treatment in Prostate Cancer

The Use of Combined External Beam Radiotherapy and Hormonal Therapy in the Management of Localized and Locally Advanced Prostate Cancer

by Dirk Böhmer, Manfred Wirth, Kurt Miller, Volker Budach, Axel Heidenreich, and Thomas Wiegel

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