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ORIGINAL ARTICLE

Role of combined radiation and androgen deprivation therapy in intermediate-risk prostate cancer

Statement from the DEGRO working group on prostate cancer

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Abstract

Objective This article aims to provide an overview of the role of combined radiation and androgen deprivation (ADT) therapy in patients with intermediate-risk prostate cancer.

Materials and methods The current German, European, and NCCN (National Comprehensive Cancer Network) guidelines as well as relevant literature in the PubMed database which provide information on sub-classification within the intermediate-risk group and the use of ADT in terms of oncological outcome were reviewed.

Results Different recommendations for risk-group assessment of patients with localized prostate cancer are available. Subdivision of intermediate risk into a favorable and an unfavorable group seems to be justified to allow for a more individualized therapy in a quite heterogenous group of patients. So far, multiple randomized trials have shown a benefit when radiation therapy (RT) is combined with ADT. The use of dose-escalated RT without ADT also appears to be an adequate therapy associated with a very low rate of cancer-specific deaths. Therefore, taking into account the increased rate of toxicity associated with ADT, dose-escalated RT alone might be justified, especially in favorable intermediate-risk patients.

Conclusion Dose-escalated RT alone appears to be an appropriate treatment in favorable intermediate-risk patients. Addition of short course ADT (4–6 months) might improve outcomes in unfavorable intermediate-risk patients.

A previous version of this article in German language has already been published as an expert opinion article by some of the above-mentioned authors [7]. The present article is an updated and extended version.
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Introduction

With approximately 60,000 new cases yearly, prostate cancer (PC) is the most common cancer in males in Germany [1]. According to the last annual report of the German Cancer Society, 23,677 patients were treated in certified prostate cancer centers. In 36.5% of all patients, intermediate-risk PC was diagnosed. The majority of those patients (78%) were treated by prostatectomy while about 20% received definitive radiation therapy (RT) [2].

The current German S3 guideline for prostate cancer recommends for definitive RT in the intermediate-risk setting a combination of RT (74–80 Gy) with short-term androgen deprivation therapy (ADT) of 4–6 months (Table 1; [3]).

In accordance with the German S3 guideline, the European Society of Urology (EAU) and the European Society for Radiotherapy and Oncology (ESTRO) guidelines stratify the risk groups of PC on the basis of the three-step classification of D'Amico (Table 2; [3–5]).

The National Comprehensive Cancer Network (NCCN) guideline uses a similar system, however supplemented by additional sub-grouping of the Gleason grade group (Tables 2 and 3; [6]).

Materials and methods

A literature review using the PubMed databank and the up-to-date guidelines in World Wide Web was carried out. The search strategy included the terms "prostate cancer," "intermediate-risk," "androgen deprivation," "radiation therapy," "hormonal therapy," and "guideline" alone or in combination. Original articles including prospective trials, population-based analysis and retrospective analysis, reviews, and guidelines in English and German languages were included. MB, DB, and PG selected the articles respectively guidelines for inclusion. A previous version of the article in German language has already been published as an expert opinion article by some of the above-mentioned authors [7]. The present article is an updated and extended version in collaboration with the Prostate Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO) and the Working Party Radiation Oncology of the German Cancer Society (DKG-ARO).

Results

German S3, EAU-ESTRO, and NCCN guidelines were included in our review [3, 4, 6]. Furthermore, the publications of 10 randomized trials, one meta-analysis of randomized trials, one prospective cohort study as well as the results of six retrospective studies were included. All these publications provide critical information to foster discussions on the role of combined RT and ADT, potentially evolving into improved risk stratification resulting in new individualized therapeutic strategies, as presented below.

Discussion

New risk stratification in intermediate-risk prostate cancer

In contrast to the German S3 and the European EAU-ESTRO guidelines, the NCCN guidelines use a subclassification of the low-, intermediate-, and high-risk PC groups, based on increasingly more subtilized outcome analyses during the past few years. In 2012, Zumsteg et al. published a critical discussion about the general necessity of combined ADT and RT which takes into consideration the possible heterogeneity of patients with intermediate-risk PC [8]. This was exemplarily illustrated by two clinical cases: an 85-year-old patient with a T1c PC (Gleason 3 + 4 = 7 in 1/12 core biopsies and a PSA of 3.0 ng/ml) and a 45-year-old patient with a T2c PC (Gleason 4 + 3 = 7 in 12/12 core biopsies and a PSA of 19 ng/ml). Both patients would have been treated with combined RT and ADT according to the NCCN guidelines in 2012. In two randomized trials (ClinicalTrials.gov Identifier NCT00116220 and RTOG 9408), a combined treatment with 6 months of ADT and 70 Gy RT, or 4 months of ADT and 66.6 Gy, respectively, achieved an improvement of biochemical control, metastasis-free, cancer-specific, and overall survival (OS) versus RT alone (OS: 74% versus 61%, $p = 0.01$, after 8 years [NCT00116220]; OS: 62% versus 57% after 10 years, $p = 0.03$ [RTOG 9408]), at the cost of a slightly increased rate of erectile dysfunction. Interestingly, a further long-term follow-up (16.6 years) of the NCT00116220 trial failed to reproduce the improvement of OS. Moreover, a significant increase in cardiac mortality was observed in patients receiving short-term ADT. This appeared, however, to be limited to patients with a relevant cardiovascular risk profile as determined in an unplanned subgroup analysis [8–10].

For long-term ADT, an increased risk of developing ADT-associated toxicities like bone loss, metabolic syndrome, gynecomastia, muscle loss and hot flushes, reduced libido, erectile dysfunction, and an assumed increased cardiac risk is well documented [11]. Furthermore, some evidence suggests a correlation between use of ADT and de-

Table 1 Comparison of recommendations of the German S3 guideline, European EAU-ESTRO guideline, and the NCCN guideline regarding conventional fractionated definitive radiation therapy in intermediate-risk prostate cancer

Recommended treatment schedules for conventional fractionated definitive radiation therapy in intermediate-risk prostate cancer	
German S3 guideline	"Dose-escalated EBRT should be performed in IMRT technique with application of IGRT technique"
	"By use of conventional fractionated radiation therapy, patients with prostate cancer of all risk subgroups should receive a dose of minimum 74 to approximately 80 Gy"
	"Patients with localized intermediate-risk prostate cancer should receive an additional short-term ADT (4–6 months) in combination with EBRT"
	"Decisions whether to use or not an additional ADT should respect additional factors (particularly the Gleason score and comorbidities) and the results should be discussed with the patient"
EAU-ESTRO guideline	"Patients suitable for ADT should be given combined dose-escalated IMRT (76–78 Gy) with short-term ADT (4–6 months)"
	"For patients unsuitable for ADT (e.g., due to comorbidities) or unwilling to accept ADT (e.g., to preserve their sexual health), the recommended treatment is IMRT at a dose of 76–80 Gy or a combination of IMRT and brachytherapy"
NCCN guideline (version 2.2019)	*Favorable intermediate risk:*
	Expected patient survival ≥10 years: EBRT **or** brachytherapy alone
	Expected patient survival <10 years: EBRT **or** brachytherapy alone **or** observation
	Regimen for definitive conventional fractionated radiation therapy: 72–80 Gy at 2 Gy per fraction; 75.6–81 Gy at 1.8 Gy per fraction
	Unfavorable intermediate risk:
	Expected patient survival ≥10 years: EBRT plus short-term (4 months) ADT **or** EBRT plus brachytherapy plus short-term (4 months) ADT
	Expected patient survival <10 years: EBRT plus short-term (4 months) ADT **or** EBRT plus brachytherapy plus short-term (4 months) ADT **or** observation
	Regimen for definitive conventional fractionated radiation therapy: 72–80 Gy at 2 Gy per fraction; 75.6–81 Gy at 1.8 Gy per fraction

IMRT intensity-modulated radiation therapy, *IGRT* image-guided radiation therapy, *EBRT* external beam radiotherapy, *ADT* androgen deprivation therapy, *EAU* European Association of Urology, *ESTRO* European Society for Radiotherapy and Oncology, *NCCN* National Comprehensive Cancer Network

velopment of dementia [12–15]. Whether these long-term sequelae would also be applicable to the use of short-term ADT is still uncertain. Of note, a significant decline in quality of life already due to short-term ADT has been reported [16].

Zumsteg et al. proposed a treatment schedule with a more individualized application of ADT as it was developed at the Memorial Sloan Kettering Cancer Center (MSKCC). On the basis of a subdivision of the intermediate-risk PC group, an individualized therapy with either dose-intensified RT in case of favorable intermediate-risk PC and combination of RT and ADT in unfavorable intermediate-risk PC patients is used in MSKCC patients (Table 4; [8]).

The authors also published results of 1024 intermediate-risk PC patients who received 81 Gy RT with or without combined ADT which validated the new treatment stratification.

In the multivariate analysis, Gleason 4 + 3 = 7b in comparison to 3 + 4 = 7a (HR = 5.23; $p < 0.0001$), a ≥50% percentage of positive biopsy cores (PPBC) (HR = 2.72; $p = 0.0007$), or multiple intermediate-risk factors (HR = 2.20; $p = 0.008$) were significant predictors for developing distant metastases. The primary Gleason (3+4=7a versus 4+3=7b) and the PPBC were also predictors for prostate-specific mortality (Gleason: HR = 5.23; $p < 0.0001$, PPBC: HR = 4.08; $p = 0.002$). The subgroup of patients with an unfavorable intermediate-risk PC had a significant worse PSA control rate (HR = 2.37; $p < 0.0001$), rate of distant metastases (HR = 4.34; $p = 0.0003$), and a higher prostate cancer-specific mortality (HR = 7.39; $p = 0.007$) in contrast to patients with favorable intermediate-risk PC [17].

Consequently, D'Amico, the developer of the classic three-step PC risk classification, valued the new classification as a promising tool to individualize PC treatment [18].

Another validation of the new stratification was done in a retrospective analysis of 2248 PC patients, with an observed significant worse outcome for patients with unfavorable intermediate-risk PC and an outcome similar to low-risk patients in the favorable intermediate-risk PC patients. Conversely, the detected outcomes in unfavorable intermediate-risk PC patients resembled those of high-risk PC patients [19]. These results suggest that patients with favorable intermediate-risk PC should rather be treated like low-risk patients, while in case of an unfavorable intermediate-risk constellation, treatment might be escalated for instance by addition of short-term ADT. This subdivision into favorable and unfavorable intermediate-risk PC settings allows

Table 2 Comparison of the German S3 guideline and the European EAU-ESTRO guideline versus risk stratification in the NCCN guideline

German S3 guideline and EAU-ESTRO guideline		NCCN guideline (version 2.2019)	
Low-risk	PSA ≤10 ng/ml + Gleason-Score ≤6 + T1-T2a	**Very low-risk**	PSA <10 ng/ml + Grade Group 1 + T1c + Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core + PSA density <0.15 ng/ml/g
		Low-risk	PSA <10 ng/ml + Grade Group 1 + T1-T2a
Intermediate-risk	PSA >10 ng/ml to 20 ng/ml OR Gleason score 7 OR T2b	**Intermediate-risk** Has no high- or very-high-risk features and has one or more intermediate-risk factor (IRF): – T2b-T2c – Grade Group 2 or 3 – PSA 10–20 ng/ml	*Favorable intermediate* 1 IRF + Grade Group 1 or 2 + Percentage of positive biopsy cores <50% *Unfavorable intermediate* 2 or 3 IRFs +/OR Grade Group 3 +/OR Percentage of positive biopsy cores ≥50%
High-risk	PSA >20 ng/ml OR Gleason score ≥8 OR T2c-T4	**High-risk**	PSA >20 ng/ml OR Grade Group 4 or 5 OR T3a
		Very high-risk	Primary Gleason pattern 5 (5+x=...) OR T3b-T4 OR >4 cores with Grade Group 4 or 5

EAU European Association of Urology, *ESTRO* European Society for Radiotherapy and Oncology, *IRF* intermediate-risk factor, *NCCN* National Comprehensive Cancer Network

Table 3 Definition of histological grade groups

Definition of histologic Grade Group		
ISUP Grade Group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

ISUP International Society of Urological Pathology

for a more subtilized, risk-adapted approach, also avoiding overtreatment and hence, possible treatment-related morbidity. Consequently, the new stratification of intermediate-risk PC was implemented in the NCCN guidelines (Table 2; [6]).

Dose-intensified radiation therapy in combination with or without androgen deprivation therapy

Several randomized trials repeatedly showed an improved oncological outcome for the combination of RT + ADT.

Table 4 Memorial Sloan Kettering Cancer Center treatment algorithm for definitive radiotherapy in patients with intermediate-risk prostate cancer

Memorial Sloan Kettering Cancer Center treatment algorithm	
Favorable intermediate-risk prostate cancer	Unfavorable intermediate-risk prostate cancer
Clinical characteristics:	*Clinical characteristics:*
One intermediate-risk factor	Several intermediate-risk factors
AND Gleason score of 3 + 4 = 7 or less	OR Gleason score of 4 + 3 = 7
AND <50% positive biopsy cores	OR ≥50% positive biopsy cores
Recommended radiation options:	*Recommended radiation options:*
Dose-escalated external beam radiotherapy alone	Dose-escalated external beam radiotherapy and short-term androgen deprivation
Brachytherapy alone in select cases (e.g., ≤3 positive cores, none with >50% involvement)	Combined brachytherapy and external beam radiotherapy with or without short-term androgen deprivation therapy

Considering today's standard of care, the applied radiation doses in these trials were apparently moderate, apart from other technical shortcomings affecting and compromising RT tolerance. Hence, it is not clear whether an application of higher RT doses with presently available modern RT techniques outbalances the need for a cytoreductive combination with ADT to achieve similar outcomes. As early as in 2009, a meta-analysis of dose-intensified RT in all risk groups was able to show an improvement in biochemical control [20].

Therefore, the data of the EORTC 22991 trial using a combination of different RT doses (70 Gy, 74 Gy, or 78 Gy) with a short-term ADT of 6 months in intermediate- and high-risk patients are of special interest. Patients in the control arm received the respective RT doses without ADT. Regardless of the applied RT dose, the additional use of ADT resulted in improved biochemical control and clinical progression-free survival. These data confirmed the benefit of a combination of ADT even with dose-intensified RT. However, a significant deterioration of sexual function and activity was registered for addition of ADT and no OS benefit was detectable. A clear drawback of this trial is the biochemical control endpoint and the relative short follow-up duration [21].

The former retrospective monocentric trial by Zumsteg et al. showed comparable results of RT (>81 Gy) with or without combined short-term ADT. Intermediate-risk patients also benefited from additional ADT in matters of biochemical control, metastasis-free survival, and prostate-specific survival [22].

However, it is important to bear in mind the potential higher rate of toxicities and decline in quality of life associated with an additional ADT. In particular, there is a risk of overtreating intermediate-risk PC patients if additive prognostic factors are ignored [11, 16].

Here, the recently published RTOG 0126 trial provides important evidence for individualized treatment in intermediate-risk PC patients, especially when addressing the question of necessity of additional ADT. The trial randomized exclusively patients with intermediate-risk PC between standard-dose RT with 70.2 Gy in 39 fractions versus dose-intensified RT with 79.2 Gy in 44 fractions. No ADT was applied. After a median follow-up of 8.4 years, there was no significant difference in terms of the primary endpoint OS (75% in control arm versus 76% in experimental arm, $p = 0.98$). However, a significant improvement of biochemical control (biochemical recurrence after 8 years 35% [70.2 Gy] versus 20% [79.2 Gy], $p < 0.001$) and lower rate of metastases (6% [70.2 Gy] versus 4% [79.2 Gy] after 8 years, $p = 0.05$) was observed in the dose-intensified RT group. Consequently, patients with dose-intensified RT need less salvage therapies. Besides providing the first randomized evidence for decreasing the rate of metastases with the use of dose-escalation in intermediate-risk PC patients, the results showed promising biochemical control without using ADT. The rates of metastases (4%) and cancer-specific mortality (2%) are comparable to the rates in the RTOG 9910 trial (10 years follow-up, metastases: 6% and cancer specific-mortality: 5%). This trial tested the duration of ADT (16 versus 36 weeks) in combination with standard-dose RT (70.2 Gy) [23, 24].

These findings justify the assumption that at least a subgroup of intermediate-risk PC patients could be adequately treated with dose-intensified RT without ADT, thus avoiding the toxicities and the decline in quality of life associated with ADT [16].

In this context, the results of a recently published randomized phase III trial (HYPO-RT-PC) comparing ultra-hypofractionation (42.7 Gy in 7 fractions) with conventionally fractionated dose-intensified RT (78 Gy in 39 fractions) are interesting. 89% intermediate-risk and 11% high-risk PC patients were treated in both arms without additional ADT. With a reported 5-year failure-free survival of 84% (95% CI 80–87) in both arms and an 5-year OS of 94% (95% CI 92–96) in the ultra-hypofractionation group versus 96% (95% CI 95–98) in the conventionally fractionated group, the data show a promising oncological outcome without using ADT in mostly intermediate-risk patients [25]. Data on

ultra-hypofractionation with 5 fractions are also available and appears promising [26].

On the other hand, reported higher rates of toxicity after dose-intensified RT schedules are not neglectable. Within the RTOG 0126 trial, a higher rate of late toxicities in the dose-intensified group was observed (15% versus 21% $p=0.006$ ≥grade 2 GI and 7% versus 12%, $p=0.003$ GU toxicity). However, increased rates of toxicity are frequently associated with the use of simple radiation techniques, whereas modern RT techniques like intensity-modulated RT (IMRT) and image-guided RT (IGRT) are able to more effectively shield organs at risk. In RTOG 0126, only a third of patients were treated with modern IMRT techniques [23, 27, 28].

Individualization of therapy in intermediate-risk prostate cancer

A recently published analysis of the National Cancer Data Base (NCDB) examined the data of 18,598 patients with favorable intermediate-risk PC and corroborated the assumption that additional ADT in favorable intermediate-risk patients could be omitted. All patients received an exclusive external beam radiation therapy (EBRT) with a dose >75.6 Gy or a combination of EBRT and brachytherapy. Some patients also received ADT (ADT use declined from 43.5% in 2004 to 39.5% in 2007). With a follow-up of 8 years, there was no OS difference between the groups with or without additional ADT. The multivariate analysis also showed no significant influence of additional ADT [29].

Recently, Rodda et al. and Morris et al. published data of a randomized trial comparing dose escalation with external beam RT boost versus brachytherapy boost. One group received EBRT with 46 Gy and a boost of 32 Gy. In the other group, the 46 Gy EBRT was followed by a brachytherapy boost with I-125 seeds (minimum dose of 115 Gy). Furthermore, in all patients, an additional 12 months' ADT was applied. In the brachytherapy arm, a significant improvement of biochemical control was observed, whereas brachytherapy was associated with higher rates of acute and late genitourinary toxicities and a decline in quality of life [30–33].

A further retrospective analysis of the NCDB analyzed 14,126 patients with intermediate-risk PC. For the treatment, a median RT dose of 75.6 Gy was used and 46% of patients received additional ADT. The intermediate-risk group was not further subdivided into favorable or unfavorable patients. Again, the addition of ADT showed no significant OS benefit (HR = 0.98, $p=0.56$). An additional subgroup analysis was, however, able to detect an OS benefit by use of ADT in patients meeting all three intermediate-risk criteria (HR = 0.61, $p=0.026$) [34].

These findings affirm that unfavorable groups of intermediate-risk PC patients benefit from the application of ADT, outweighing adverse events associated with hormonal therapy.

On the basis of the present data, a modified treatment recommendation as introduced by the NCCN guidelines and the MSKCC concept seems to be a promising tool for more adequately addressing an individualized choice of treatment within the large group of intermediate-risk PC patients (Tables 1 and 3; [6, 8]).

Analogous to the stratification presented above, favorable intermediate-risk PC patients could be treated exclusively with dose-intensified RT, whereas unfavorable patients would benefit from a combination therapy of RT and (at least short-term) ADT. Additional factors like age, general condition, comorbidities, and the assumed life expectancy are meaningful cofactors for treatment decisions. So far, the German S3 guideline and the European EAU-ESTRO guideline do not yet consider this subdivision into favorable and unfavorable intermediate risk and the respective consequences for a more individualized treatment (Table 2; [3, 4]). Thus, currently the treating physician has different treatment options, each confirmed by the divergent guideline recommendations, reflected by a wide spectrum of possible therapies in intermediate-risk PC patients. A recent NCDB analysis on the use of ADT as an adjunct to RT for intermediate- and high-risk PC revealed quite heterogenous results.

In intermediate-risk PC, the application of ADT decreased from 50% in 2004 to 38% in 2012. Regional differences in ADT prescription were reported and no correlation of ADT application with existence of comorbidities was detected. On the other hand, with 91% of cases, the concept of dose-intensified RT seems to be a common practice in the US [35].

Lastly, with continuously growing evidence of discrimination factors and especially by the help of advanced genomic profiling, the choice of therapy will be further refined [36].

In this context, eagerly awaited evidence will be provided by the RTOG 0815 trial of dose-intensified RT with or without ADT in intermediate-risk PC [37].

Conclusion

RT with and RT without ADT are treatment options for patients with intermediate-risk PC. New stratification concepts, as implemented in the NCCN guideline but not currently used in the German S3 and European EAU-ESTRO guidelines, are promising developments toward a more individualized treatment as demonstrated by several clinical analyses and a few randomized trials. Hence, dose-escalated

RT alone in favorable intermediate-risk and its combination with short-course ADT (4–6 months) in unfavorable intermediate-risk patients seems to be an adequate individual treatment option. The pending results of the RTOG 0815 trial should foster the evidence for risk-adapted treatment decisions in intermediate-risk prostate cancer. Lastly, the authors propose to update the German and European guidelines accordingly.

Compliance with ethical guidelines

Conflict of interest A.-C. Müller and D. Zips mention the cooperation with Siemens Healthcare, Philips, and Elekta in a research project. M. Beck, D. Böhmer, D.M. Aebersold, C. Albrecht, M. Flentje, U. Ganswindt, S. Höcht, T. Hölscher, P. Niehoff, M. Pinkawa, F. Sedlmayer, S. Zschaeck, V. Budach, T. Wiegel, and P. Ghadjar declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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