The German S3 Guideline Prostate Cancer

Aspects for the Radiation Oncologist

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This report summarizes the relevant aspects of the S3 guideline prostate cancer for the radiation oncologist. Treatment decision and dose prescription are discussed, as well as technical performance of external beam radiotherapy and brachytherapy. The relevant literature is cited to allow an overview of the current recommendations.

Key Words: Prostate cancer · Radiation oncology · German S3 guideline

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Die deutsche S3-Leitlinie Prostatakarzinom. Radioonkologische Aspekte

Dieser Bericht fasst die relevanten Aspekte der S3-Leitlinie Prostatakarzinom für den Strahlentherapeuten zusammen. Indikationsstellung und Dosisverschreibung werden ebenso diskutiert wie die technische Durchführung der perkutanen Bestrahlung und die Brachytherapie. Die relevante Literatur gibt einen Überblick über die aktuellen Empfehlungen.

Schlüsselwörter: Prostatakarzinom · Strahlentherapie · Deutsche S3-Leitlinie

Introduction

The "Interdisciplinary guideline (quality level S3) for the early detection, diagnosis and therapy of prostate cancer" [2, 16, 22] was established in cooperation of several national societies (DGU, DEGRO, AWMF, BDU, BVDST, DGHO) supported by the "Ärztliches Zentrum für Qualität in der Medizin (ÄZQ)" and the German Cancer Aid ("Deutsche Krebshilfe e.V."). It is an instrument based on evidence and consensus to improve the early detection, diagnosis and therapy of prostate cancer. The following report summarizes the relevant aspects for the radiation oncologist.

The German S3 guideline uses the following categories:

- localized prostate cancer: stages T1–2 N0 M0,
- locally advanced prostate cancer: stages T3–4 N0 M0,
- advanced prostate cancer: stages N1–3,
- metastasized prostate cancer: stage M1.

The localized prostate cancer is classified into three prognosis groups according to risk factors [6], which is well established in clinical practice:

(1) low risk: prostate-specific antigen (PSA) < 10 ng/ml and T1c–T2a and Gleason Score < 7,

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(2) intermediate risk: PSA ≥ 10 and < 20 ng/ml or T2b or Gleason Score = 7,
(3) high risk: PSA ≥ 20 ng/ml or > T2b or Gleason Score > 7.

Treatment Decision for the Newly Diagnosed, Nonmetastasized Prostate Cancer

Randomized phase III studies comparing all curative treatment options for prostate cancer are not available at present. Retrospective analyses demonstrated that external-beam radiotherapy with sufficiently high doses, permanent low-dose-rate (LDR) brachytherapy and radical prostatectomy yield comparable results regarding PSA control [20]. Therefore, external-beam radiotherapy (± endocrine therapy) is considered to be a primary treatment option. Permanent LDR brachytherapy is an equivalent option for the low-risk group of patients (< T2c, Gleason Score < 7, PSA < 10 ng/ml). External-beam radiotherapy with endocrine therapy or combined with a high-dose-rate (HDR) boost is a primary treatment option for patients with locally advanced prostate cancer. There was consensus that all patients with prostate cancer who qualify for curative treatment should be offered the opportunity to discuss advantages or disadvantages of surgery and radiotherapy with an urologist and a radiation oncologist. The discussion of potential side effects should always include the functional domains of micturation, gastrointestinal symptoms, and sexual dysfunction.

Technical Performance of External-Beam Radiotherapy

Before initiation of radiotherapy, patients with a Gleason Score ≥ 8 or cT3/4 stadium should undergo magnetic resonance imaging (MRI), first, to evaluate local tumor extension and pelvic lymph node status and, second, for treatment-planning purposes. Additionally, a bone scan should be done in these patients and patients with a PSA ≥ 10 ng/ml or bone pain. Because of limited sensitivity and specificity of the imaging studies, the use of externally validated nomograms is recommended as well.

Radiation therapy shall be based on computed tomography (CT) and three-dimensional planning. In low-risk patients, a dose of at least 70–72 Gy shall be given. In the intermediate-risk situation, an intensified regimen should be applied either by radiation dose escalation or additional short-term endocrine treatment for 6 months [7, 14, 19]. In patients with a high risk of relapse, endocrine therapy is obligatory [5]. In several phase III trials, prolongation of the overall survival was shown after treatment with combined radiation and endocrine therapy in comparison to radiotherapy alone in patients with locally advanced and high-risk prostate cancer (EORTC 22863, RTOG 85-31, RTOG 86-10, RTOG 92-02 [4, 13, 24, 28]). Moreover, a significantly better overall survival was achieved after radiotherapy in combination with endocrine therapy in comparison to endocrine therapy alone in patients with locally advanced prostate cancer [33].

Dose prescription shall be in line with the four available randomized trials (MD Anderson 70 vs. 78 Gy [18], Netherlands 68 vs. 78 Gy [23], United Kingdom 64 vs. 74 Gy [8], MGH Boston/Loma Linda 70 vs. 79 Gy [38, 39]). To date, optimal dose prescription in localized prostate cancer on the one hand and locally advanced prostate cancer on the other hand, is not precisely determined and is in the range of 72–79 Gy depending on fractionation, overall treatment time, etc. A dose escalation of > 79 Gy is not recommended in clinical routine practice [38]. Dose escalation in general requires modern radiation oncology concepts to minimize side effects, e.g., immobilization, preparation of bowel and bladder, thin-slice imaging, inverse treatment planning, image-guided radiotherapy (IGRT), and intensity-modulated radiotherapy (IMRT; e.g., [1, 3, 17, 21, 25, 37]). In spite of the availability of several randomized trials the question of radiation of the pelvic lymph nodes is not definitely answered yet. This situation is reflected in diverging national recommendations in other countries.

Radiation Treatment after Radical Prostatectomy

A radical prostatectomy in the cT1–T2 situation results in a pT3 stage in 25–40% of the cases [34]. Meanwhile, the results of three randomized trials (SWOG [31], EORTC [4] and ARO [34, 35]) with focus on adjuvant radiotherapy in the pT3 situation are available. Radiation treatment with 60–64 Gy improves local relapse-free survival at 5 years by about 20%, whereas the Kaplan-Meier estimates diverge already 2–3 years after treatment for metastases-free survival and 5–6 years after treatment for overall survival [31]. A 20% advantage after 5 years was also seen in patients reaching a PSA < 0.1 ng/ml after radical prostatectomy [34, 35]. The SWOG study [31] showed a significant prolongation of overall survival after adjuvant radiotherapy of about 2 years after a median follow-up of almost 13 years. The highest benefit after adjuvant radiation treatment was seen in patients with a pT3 tumor and positive margins (30% higher biochemical no-evidence-of-disease [NED] rates after 5 years) [32, 34, 35]. Therefore, the patient shall be informed about adjuvant radiotherapy in a pT3 R1 situation. This recommendation was given the highest grade of strength, i.e., "shall". Patients with pT3 R0 and other risk factors should be advised about adjuvant radiotherapy. In addition, patients with a pT2 R1 situation should be treated with adjuvant radiotherapy according to the subgroup analysis of the EORTC study, which showed similar effects as in pT3 R1 tumors [32].

An alternative to adjuvant radiotherapy within 3–4 months after surgery is the salvage radiotherapy (SRT) initiated after a PSA rise or persistent postoperative PSA value [29, 34, 35]. SRT should be initiated as early as possible (PSA ≤ 0.5 ng/ml) due to the fact that biochemical NED improves by 10–20% as compared to initiation of SRT at a PSA > 0.5 ng/ml [29, 34, 35]. In cases with low PSA values the target volume should be typically restricted to the prostatic bed. However, this does not exclude an extension of the target volume to the pelvic lymph nodes in selected cases. SRT is typically performed with higher radiation doses (≥ 66 Gy).

Chronic late effects are slightly higher than in the adjuvant situation. Finally, it should be mentioned, that it is clinically often difficult to differentiate between local relapse and incipient distant metastases because of the limited sensitivity of the imaging modalities in patients with low PSA values, to date.

Brachytherapy

LDR monotherapy is a primary option for patients with PSA < 10 ng/ml, Gleason Score < 7 and cT1c–T2a tumors. Randomized trials comparing the different therapeutic concepts do not exist, but there are large cohort studies with PSA-free survival rates comparable to a treatment with radical prostatectomy or external-beam radiotherapy [27, 30, 36] and low toxicity rates [26]. The prescribed dose for LDR brachytherapy with iodine-125 (^{125}I) seeds is 145 Gy. Optimal implantation is accomplished when 100% of the prescribed dose reaches at least 90% of the prostate volume. In case of combination of LDR brachytherapy with external-beam radiotherapy, the prescribed dose for ^{125}I seeds is 100–120 Gy. In addition, 45–50 Gy are given by external-beam radiotherapy. Patients with localized prostate cancer and high-risk factors shall not receive LDR monotherapy.

HDR brachytherapy in combination with external-beam radiotherapy is an option for radiation dose escalation. HDR brachytherapy is typically applied in two courses with an interval of 1 week and doses of 2 × 8–10 Gy in combination with a 45- to 50-Gy external-beam radiotherapy [9–12, 15]. Due to biochemical relapse-free rates of > 85% after 5 years, this combination is a primary option for treatment of intermediate- and high-risk localized prostate cancer and locally advanced prostate cancer. Only little is known about the combination with endocrine therapy; therefore, no recommendations are available. Also, there is not sufficient data about HDR monotherapy available, which should therefore be used within clinical studies only.

Synopsis

Radiotherapy is an equivalent alternative to radical prostatectomy for patients with localized and locally advanced prostate cancer. Local dose escalation and/or endocrine treatment improve the outcome of patients with intermediate- and high-risk tumors significantly. The role of postoperative radiotherapy after radical prostatectomy is undisputed. In the future, the German S3 guideline will be annually updated according to the principle of a "living guideline".

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