Curative Treatment of Prostate Cancer

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Key Words

Prostate cancer · Radical prostatectomy · Adjuvant treatment · Evidence-based medicine

Abstract

The guidelines for the curative treatment of prostate cancer presented by the German Society of Urology are discussed. They are based on the current knowledge of the outcomes of surgical and radiotherapeutic treatment for prostate cancer. Radical prostatectomy is recommended as the first-line treatment for organ-confined prostate cancer in patients with an individual life expectancy of at least 10 years. Radiotherapy can be considered as an alternative treatment modality, although current knowledge does not allow a definite assessment of the relative value of radiotherapy compared to radical prostatectomy. Locally advanced cT3 prostate cancer is overstaged in about 20% and curative treatment is possible in selected cases. Guidelines represent rules based on the available evidence. This implies that exceptions must be made whenever appropriate and that guidelines have to be reviewed regularly as new information becomes available.

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Zusammenfassung

Die Leitlinien der Deutschen Gesellschaft für Urologie zur kurativen Therapie des Prostatakarzinoms werden diskutiert. Sie beruhen auf dem gegenwärtigen Wissensstand über die Ergebnisse der operativen und strahlentherapeutischen Behandlung. Demnach wird die radikale Prostatektomie als primäre Standardtherapie für alle Patienten mit organbegrenztem Tumor, die eine individuelle Lebenserwartung von mindestens 10 Jahren haben, empfohlen. Die Strahlentherapie kann dabei als Alternative gelten, jedoch ist bislang eine klare Beurteilung der relativen Wertigkeit der Strahlentherapie im Vergleich zur operativen Therapie noch nicht möglich. Lokal fortgeschrittene Tumoren (cT3) sind bei 20% pT2 (overstaging), so dass eine Kuration in selektionierten Fällen möglich ist. Leitlinien sind Regeln, die aufgrund des verfügbaren Wissensstandes erstellt werden. Dies beinhaltet, dass erforderliche Ausnahmen gemacht werden können und dass Leitlinien immer wieder überarbeitet werden müssen, wenn neue Erkenntnisse dies erfordern.

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Introduction

Prostate cancer has received increased attention in the developed industrial nations during the last two decades for several reasons. It has a high incidence among populations with a long life expectancy and it therefore has an important impact on the quality of life of a population that can expect to live 7 or 8 decades. With a high prevalence of latent prostate cancer in the elderly, the lifetime cumulative risk of overt prostate cancer is about 10% up to the age of 75 in the United States [1].

Advances in the early diagnosis of prostate cancer have been due to the detection of a reliable serum marker, the prostate-specific antigen (PSA), in 1979 [2] and the use of ultrasound-guided systematic prostate biopsies. The widespread use of PSA for the detection of prostate cancer has led not only to an increase in its incidence but also to a shift towards the diagnosis of more organ-confined stages of the disease. More recently, the diagnosis of prostate cancer has further been improved by the differentiation between total and free PSA [3].

At the same time, progress in urologic surgery and in perioperative intensive care management has advanced the frontiers of urological operative management principles, and transformed radical prostatectomy from a highly specialized to a routine procedure in experienced hands. Simultaneously, radiotherapy has also made considerable advances in its management possibilities of prostate cancer by refinements of dosimetry with modern imaging techniques, megavolt X-rays and effective radioactive isotopes. Improved results are reported for modern, conformal percutaneous radiotherapy. A new interest in interstitial radiotherapy has been kindled by the advent of palladium in the form of commercially available seeds.

Competing Treatment Modalities

The increased incidence and the widespread availability of specialized treatment modalities has focussed the discussion on who to treat and how to treat. It is imperative that the results of controlled multicenter trials or from metaanalyses of many large trials are used to provide the evidence that is needed to answer these questions. Due to a relative paucity of mature trials so far, and the long disease course of prostate cancer, several questions which are under discussion cannot be answered with certainty at this stage.

One of these important questions concerns the relative roles of radiotherapy and surgery in the treatment of

organ-confined prostate cancer, another circumstance under which 'watchful waiting' can be considered a reasonable strategy. While watchful waiting remains an option in patients with life expectancies of less than 10 years, an international consensus seems to emerge that prostate cancer should be actively treated in patients young enough to live another decade.

The relative roles of radiotherapy versus radical prostatectomy are under continuing intensive discussion. However, at present it cannot be decided with absolute certainty which of the two treatment modalities, if any, is better in long-term patient survival, since randomized prospective long-term outcome trials that would permit a clear conclusion in this respect are not available so far. However, the metaanalysis of Adolfsson [4] clearly indicates an advantage for radical prostatectomy.

The outcome of surgery and radiotherapy in the treatment of prostate cancer can be assessed at the clinical, the pathological and the biochemical levels. Clinical assessment is based on patient survival, evidence of local recurrence by DRE and on the diagnosis of metastases by standard evaluation. Pathological results refer to the evidence of cancer tissue in post-treatment biopsies and are important in the follow-up of radiotherapeutic modalities. Biochemical treatment results refer to post-treatment PSA measurements and their significance in assessing treatment success or failure.

After radical prostatectomy, the clinical results are excellent in that long-term survival at 10 and 15 years has been reported to be 92–97 and 86–94%, respectively [5]. At the same time, 15–27% of patients with organ-confined tumors will develop local recurrence and, of these, 16% will die of prostate cancer within a 10-year period and up to 70% later [5, 6]. Similarly, in a multi-center analysis of 2,758 men with T1 and T2 prostate cancer after radical prostatectomy, 10-year survival rates of 94, 80 and 77% were reported for grade 1–3 tumors, respectively [7]. Clearly, with small organ-confined cancers tumor differentiation is the most important prognostic factor after radical prostatectomy.

The aim of radical prostatectomy is the complete removal of the localised prostate cancer. Problems of clinical staging lead to a certain degree of failure in achieving this goal. Systematic pathological evaluation of radical prostatectomy specimens allows tumor classification into the three surgical categories of organ confined (intracapsular), specimen-confined (extracapsular with negative surgical margins) and those with positive surgical margins. Only organ-confined prostate cancers with a low Gleason score can reliably be cured by radical prostatecto-

my [8]. Organ-confined prostate cancers used to range between 37 and 50% in older radical prostatectomy series [9, 10]. More recently, due to the stage shift with a higher proportion of T1c patients and improved surgical technique, the rate of positive margins has decreased [8]. The frequency of extracapsular disease is related to tumor stage: 68% in T2b, 33% in T2a disease and still 26% in T1b, thus depending on tumor volume [10]. Penetration of the prostatic capsule carries an unfavorable prognosis with a progression rate of 46% within 10 years [11]. With organ-confined tumors, the risk of postoperative progression of the disease depends on preoperative PSA, tumor DNA ploidy and pathological grade [12].

Ideally, after complete radical prostatectomy for organ-confined disease, PSA should be undetectable in the serum. Persistence and a rise in post-surgery PSA above 0.1 ng/ml is considered evidence of disease. The long-term failure rate at 10 years after radical prostatectomy is related to the incidence of early postoperative PSA detection in the serum, and amounts to 12% for organ-confined, 30% for specimen-confined and 60% for positive-margin cases [13]. In a more recent analysis, the risk of progression with margin-positive disease has been calculated to be 27% within 5 and 46% within 10 years after radical prostatectomy [8].

When post-surgery PSA persistence is considered a criterion of not declaring 'no evidence of disease' (NED) status after radical prostatectomy, in some series only 40% of pT2 will have NED 10 years after radical prostatectomy as compared to 90% based on survival without clinical evidence of disease [14]. Similarly, for pT2A and pT2B disease, PSA-inclusive NED at 10 years of 76 and 52% has been reported [15]. The preoperative PSA level seems of predictive importance since at 10 years after radical prostatectomy, 90% of patients with a preoperative PSA <4 ng/ml will have an undetectable PSA, while with a preoperative PSA of 10–20 ng/ml only 56% of patients will achieve this goal [15]. Thus, major predictive factors for the success of radical prostatectomy for localized prostate cancer are tumor stage, Gleason score and initial PSA.

There is no doubt that radiotherapy is an efficient treatment and does achieve cure in localized prostate cancer. External beam radiotherapy with a dose of 60–70 Gy is delivered to the true pelvis and the prostate itself. No benefit could be demonstrated for extended field irradiation including pelvic lymph nodes. Clinically, external beam radiotherapy has been reported to achieve 10-year survival rates for T1/2 prostate cancer of 65–86%, and of 62% at 15 years [5], however, in patients treated by surgical pelvic lymphadenectomy with negative lymph nodes.

Local failure occurs in up to 20% of cases [16–18], metastatic disease in up to 30% [5].

Pathological results of radiotherapy can be assessed by posttreatment biopsies of the prostate. The rate of positive biopsies after radiation treatment varies widely between 18 and 90%, depending on the selection of patients for biopsy, the technique used and the time after radiation treatment [19, 20]. However, 70% of patients with cT1 or cT2 disease treated by radiotherapy can have a negative biopsy at 2 years. While clinical survival can be much longer, local failure and metastatic disease have been reported to occur in 45–66% and 60–80% of cases with positive biopsies [19–21].

PSA is reduced significantly after radiation treatment. There is no consensus regarding the PSA nadir following radiation treatment which can be considered the mark of successful cure. While it is usually set at <1 ng/ml, some set it as low as <0.5 ng/ml.

While radiotherapy has few immediate complications and side effects and seems therefore less invasive to the patient, it does have a definite long-term morbidity. Complications are dose- and field-related and improved techniques will in future undoubtedly improve posttreatment morbidity. Severe and moderate complications occur in 3 and 7%, respectively. Patients who have undergone transurethral resection are at risk of developing incontinence or strictures. Radiation cystitis and proctitis occur in 5–6% each. Impotence is a problem in 15–40% of patients. It is important to realize that the posttreatment problems of radiation often tend to increase with time.

The renewed interest in brachytherapy as a treatment modality for prostate cancer is based on the development of radioactive seeds with short half-lives such as palladium and transrectal or perineal implantation techniques with modern imaging techniques. Interstitial radiotherapy of prostate cancer itself was used at the beginning of this century and later as the surgical implantation of gold seeds [22]. Often, brachytherapy is combined with external beam radiotherapy and treatment results are thus difficult to compare. With modern image-based posttreatment dosimetry, it has become apparent that the distribution of the radiation dose applied with seed implantation varies widely [23]. The complications are similar to those of external radiotherapy, if somewhat less pronounced. As with external beam radiotherapy, treatment results are difficult to assess and the discussion depends on the interpretation of posttreatment biopsies and PSA. PSA-progression-free survival is greater in patients treated by radical prostatectomy in comparison to patients treated by brachytherapy [24, 25]. However, treatment figures for

brachytherapy are low and larger trials will be needed before this treatment modality can be definitely assessed.

While Paulson's study on the relative outcomes of radical prostatectomy and radiotherapy published in 1982 [26] already showed an advantage for the treatment by radical prostatectomy, this study has been severely criticised for methodological reasons. However, a more recent metaanalysis showed an advantage for radical prostatectomy as well [27]. Radiotherapy trials often suffer from a selection bias in that patients with locally more advanced disease and patients with other severe medical problems who are not candidates for radical prostatectomy are referred for radiotherapy and are included in outcome trials. While postprostatectomy results can easily be defined in their curative success by PSA measurement, the problem of assessing curation after radiotherapy is difficult and always comes back to progression-free survival. The value of radical prostatectomy is clearly defined as a curative treatment for organ-confined disease, that of radiotherapy much less. This dilemma cannot be solved at present. Thus, it will be some more years before the ongoing dispute about the relative roles of radiotherapy and radical surgery in prostate oncology will be settled.

Selecting Treatment Options

Organ-confined prostate cancer is potentially curable by complete surgical removal of the whole prostate gland together with the seminal vesicles. While this is technically possible, the results of the procedure depend on whether cure has been achieved and on the long-term morbidity of the operation in terms of incontinence and impotence.

The major drawback of the surgical approach to prostate cancer is that preoperative staging has definite limitations in its accuracy and that clinical staging will not reliably differentiate between T2 and T3 disease. It is also not possible to confidently exclude lymph node metastases in every case.

Radiotherapy can achieve cure and its results are better for small prostate cancers as well. The prediction of treatment results is more difficult and complications in the individual are unpredictable in the long run.

With these limitations in mind, guidelines for the management of prostate cancer will have to focus on the following points. Which patients and what tumor stages are successfully and best treated surgically? Which surgical procedures should be employed? When should radiotherapy be recommended?

Patient Selection for Radical Prostatectomy

General Considerations

General considerations underlying the selection of patients for radical prostatectomy as the first line of treatment are those of life expectancy based on empirical considerations and individual factors in view of biological versus chronological age and comorbidity. It is accepted that radical prostatectomy should only be considered for individuals whose remaining life expectancy is or exceeds 10 years.

The general life expectancy of a 72-year-old man in the United States in 1991 was just over 10 years [28]. Similar life expectancies apply to Western Europe. However, there are many individuals whose general health and family history of longevity suggests a longer life expectancy so that the decision to operate should be based on the individual state of health and personal situation. Significant comorbidity, especially cardio- and cerebrovascular disease, must be taken into account as it has a clear impact on survival in men aged 65–75 years [29].

Specific Considerations

The single most important specific consideration which is important for patient selection for radical prostatectomy is tumor stage. Other prognostic factors which are known to have a definite impact on postoperative long-term survival such as Gleason score and PSA must also be included in the decision-making process.

Preoperative tumor staging based on PSA, transrectal ultrasonography and nuclear bone scanning will result in a stage assessment that includes a definite margin of error. While nuclear bone scans are not required if PSA is <10 ng/ml [30], there is no definite value in using CT or MRI imaging at all since the sensitivity and specificity in detecting lymph node metastases is low. Understaging of clinical T1/T2 disease occurs in 30–40% of cases [31, 32]. This staging error will have an impact for individual patients as well as for the overall results of radical prostatectomy.

Nevertheless, the decision to operate will by necessity be based on clinical staging. Preoperative prognostic factors are clinical stage, Gleason score and PSA [8, 33, 34].

The main indication for radical prostatectomy is clinically organ-confined disease (T1 and T2). There is no definite consensus about the value of radical surgery in T3 disease and its role in patients with lymph node involvement is disputed. Patients with metastatic disease definitely are not candidates for radical prostatectomy.

Organ-Confined Disease

T1aN0

Patients with an incidental carcinoma of the prostate found in less than 5% of the tissue resected at transurethral resection generally have a reasonably good prognosis and can therefore be offered different treatment options. A significant difference in long-term survival between watchful waiting and radical prostatectomy in these patients does not become apparent before 10 and 15 years [35, 36]. Patients with a life expectancy of 10 years or more should be offered radical prostatectomy; external beam radiotherapy is an alternative. Patients who do not meet these criteria can be followed with watchful waiting.

T1bN0

These patients with an incidentally discovered prostatic carcinoma of more than 5% of the tissue resected have a considerable tumor volume. Watchful waiting in these patients carries a much less favourable prognosis than in stage T1a patients. These patients should therefore all be offered curative treatment. They are definitely candidates for radical prostatectomy if they meet the general criteria of life-expectancy and comorbidity. Again, percutaneous radiation is an alternative.

T1cN0

Patients with an elevated PSA and a nonpalpable tumor diagnosed by random biopsies form a large and increasing group of men diagnosed with prostate cancer today. This increase in the PSA-based detection of clinically inapparent tumors accounts for the stage shift in diagnosis that has been observed. T1c patients are often relatively young patients with long life expectancy. At the same time these patients are those who are most concerned about postprostatectomy impotence. While preservation of potency is a major issue in this group of patients, they are most definitely candidates for radical prostatectomy, and should be offered a nerve-sparing procedure. While principally radiotherapy is an alternative in these patients as well, a successful nerve-sparing radical prostatectomy offers a high chance of cure with no long-term liabilities in terms of later complications.

T2N0

Patients with clinically palpable and organ-confined disease can be treated by radical prostatectomy, bearing in mind the problems of clinical understaging. Disease in both lobes of the prostate (T2b) carries a less favorable

prognosis. However, complete removal of the prostate in organ-confined disease offers the best chance of cure. 10-year survival rates after radical prostatectomy in this group of patients ranges between 85 and 90% [37–40]. PSA-based progression-free rates at 5 years range between 69 and 85% [41].

Again, radiotherapy is an alternative. While the disputed study of Paulson et al. [26] suggested better survival rates for T2 patients treated by radical prostatectomy in comparison to those treated by radiotherapy, this issue is at present undecided [42].

Locally Advanced Disease

T3N0

The value of radical prostatectomy for this group of patients is doubtful since the risk of micrometastases is considerable, and many patients will have positive lymph nodes. The chance of curative treatment is therefore low in the majority of patients with T3 disease.

Radical prostatectomy improves local control and thus quality of life in T3 patients, and for this reason patients in this group may be considered for radical prostatectomy on an individual basis. Following radical prostatectomy, it seems prudent to treat these patients adjuvantly with hormonal deprivation [43]. However, results from several clinical studies suggest that cancer-specific survival may be increased. Reported clinical progression-free survival rates at 5 and 10 years of patients with T3N1/2 disease treated by radical prostatectomy with pelvic lymphadenectomy and androgen deprivation were 41–83 and 25–71%, respectively [44–49].

Similarly, radiotherapy as a localized treatment will not be curative for the majority of these patients. Local control may possibly be improved by adjuvant radiotherapy after radical prostatectomy for pT3 disease [50].

Techniques and Problems of Radical Prostatectomy

The standard technique of radical prostatectomy is the retropubic approach, either with an ascending or descending technique. Alternatively, radical perineal prostatectomy is favored by some urologists and laparoscopic retropubic radical prostatectomy today is also becoming an alternative.

Radical Retropubic Prostatectomy

This technique is the worldwide standard approach. It has the advantage of allowing a pelvic lymphadenectomy at the same time and providing good exposure. Perioperative mortality today ranges between 0 and 1.5% in large series [51, 52]. Anastomotic insufficiency occurs in 1.2–4% of cases [53, 54].

Incontinence remains a controversial issue in that the assessment is not standardized. While rates of severe postoperative incontinence will generally be low, the rates of minor incontinence will vary widely depending on the definition of continence used, and whether data are assessed by urologists or taken from patient surveys. Long-term postoperative incontinence persisting after appropriate physiotherapy after 1 year has been reported to be 7.7% in a large US survey, in which a total of 3.6% of patients were completely incontinent following radical prostatectomy [55]. Improvement in continence function continues postoperatively over 12–24 months [56]. Surgical treatment for incontinence should therefore not be undertaken for at least 1 year after radical prostatectomy.

Radical Perineal Prostatectomy

This approach is favored by some urologists because it supposedly provides an access for radical prostatectomy that reduces postoperative morbidity. A lower intraoperative blood loss has been reported in comparison to retropubic radical prostatectomy [57]. The argument against the perineal approach is that tumor control is less likely to be achieved in all cases. However, there are no randomized studies substantiating this view, and tumor control rates which are the same as after retropubic radical prostatectomy have been reported [58]. However, for lymphadenectomy a second procedure is required, and some of the potential advantages of the perineal approach are foregone.

Laparoscopic Radical Retropubic Prostatectomy

This is a new technique which has recently been introduced. It offers good exposure and reduced peri- and postoperative morbidity while allowing the performance of a pelvic lymphadenectomy at the same time. While this technique promises positive new developments, it is too early to make definite judgements at present.

Nerve-Sparing Technique

Nerve-sparing radical prostatectomy can be routinely done in all younger patients and those who express concern about postoperative impotence. However, in many

cases of T2b or most of T3 disease this may not be possible without compromising the goal of complete tumor excision. While postoperative potency will generally depend on the patient's age and preoperative sexual function, it can be preserved for some patients if the neurovascular bundle on the side contralateral to the tumor in T2a disease is spared [59]. Contraindications are capsular penetration and tumor close to the apex [60]. The preservation of potency is achieved in 41% if one and in 63% if both neurovascular bundles are preserved [61].

Conclusions

While especially the issue of the role of percutaneous radiotherapy and interstitial brachytherapy has not been clearly defined from a surgical point of view, it is clear that radical prostatectomy is a curative treatment with excellent survival rates for organ-confined prostate cancer. Thus, patients with a life expectancy of at least 10 years and T1 or T2 disease should be treated by radical prostatectomy. Patients with pT3 disease will be included in the group of cT2 patients due to errors of staging. For these, adjuvant treatment strategies need to be investigated systematically.

In contrast to surgery, radiotherapy does have the definite potential to cure locally advanced prostate cancer. In localized prostate cancer, however, it must be considered an alternative treatment option as long as definite long-term outcome data are missing, and should certainly be offered to all patients who are not candidates for radical prostatectomy.

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