11. **Prostate Cancer**

Introduction

Prostate cancer is a major health problem, being the most common male cancer in Western countries. The steep increase in incidence is mainly due to increased public awareness and the introduction of screening programmes. The management of patients with localized disease is still controversial. The treatment options span from early initial aggressive local therapy, such as various forms of radiotherapy or radical surgery to deferred treatment ("watchful waiting"). Treatment strategies will most certainly continue to vary considerably around the world. Well-differentiated carcinomas frequently run an indolent course and watchful waiting may be the "treatment" of choice, especially for patients with an expected survival of less than 10 years. However, deferred treatment has been shown to have a poor outcome for poorly differentiated tumours, and in these cancers, if still localized, curative treatment has generally been considered more beneficial than watchful waiting.

Radiotherapy, administered with various techniques, has been in routine use as a curative treatment modality for more than four decades. With the advent of improved technology, including imaging and computer-based dose-planning systems, a dramatic development has taken place. Radiation treatment is now as frequently used as surgery in Sweden. Before the advent of prostate specific antigen (PSA), only crude assessments could be done concerning local control and freedom from metastasis. Although it has sometimes been questioned as a surrogate marker for cure, ample data show that achievement of a post-treatment nadir value of ≤ 0.5 ng/mL correlates fairly well with long-term disease-free survival.

Several treatment alternatives are available in radiation oncology. The two main modalities are external beam radiotherapy and brachytherapy. These can be combined with each other or with medical treatment such as androgen deprivation. Brachytherapy can be administered with radioactive permanent seed implants or with temporary implants using modern

afterloading techniques. During the last years, concepts such as 3D-conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT) and dose escalation have been introduced in the management of prostate cancer. The aim of this systematic review has been to describe the outcome of each and one of these techniques and to, when possible, compare the outcome data with each other and with those of surgery.

Summary of the earlier report, SBU 129/2

Conclusions

- The literature provides no apparent evidence to motivate radiotherapy, or any treatment, for highly differentiated T0 tumours. Some findings suggest that radiotherapy or surgery may be indicated for poorly differentiated tumours. The literature however shows no differences in tumour effects between these two methods for treating T0 tumours. Radiotherapy is milder and less mutilating.
- Conclusions can not be drawn from the literature concerning whether surgery (radical prostatectomy) or external radiotherapy is preferable for T1 and T2 tumours. Most probably, some patients are more suitable for surgery, others for radiotherapy. More patients are, nevertheless, candidates for radiotherapy.
- The value of external radiotherapy for T3 tumours is documented.
- Radiotherapy is valuable as palliative treatment for T4 tumours.
- Radiotherapy may be valuable as localized, symptomrelieving treatment for generalized prostate cancer. Treatment given via a few high fractions saves patients time, hospitalization, and resources.
- Concerning individualized treatment, the differentiation grade is important for the choice of treatment method, mainly in early, but even in late clinical stages. This may involve choosing between radiotherapy and endocrine therapy, or even choosing between radiotherapy

and surgery. The value of external radiotherapy increases as the differentiation grade of the tumour decreases. It is essential to treat patients at facilities that have the diagnostic potential to establish the differentiation grade of tumours.

- The value of postoperative radiotherapy has not yet been demonstrated at any clinical stage of prostate cancer.
- Treatment results from interstitial brachytherapy alone appear to be clearly inferior to the results from other methods. The value of combining intertitial/external radiotherapy should be studied further.

Discussion

The literature survey was performed at a time when the value of predictive factors such as pretreatment serum PSA and the Gleason scoring system were still not used or even fully known. This hampers the interpretation of the treatment results, especially when making comparisons with respect to efficacy between RT and surgery.

Furthermore, PSA determination for assessing outcome was not in routine use and no consensus was at hand in 1996 concerning the upper limit of PSA for defining cure. No consensus had been reached concerning the definition of recurrent disease. These facts all hampered meaningful comparisons between treatment results from different centres and between RT and surgery.

The report did not encompass therapy results with heavy ions such as protons, neutrons and pions.

The majority of treatments that had been reported up until 1996 were based on observational data and phase II trials. Only one study had been published on randomization between RT and radical surgery. This study has, as mentioned in the report, several severe flaws and the main question, whether prostatectomy is superior to RT, or vice versa, cannot be answered.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients).

	1 = high	2 = moderate	3 = low	Total
M	–	–	–	**–**
C	–	2/770	2/208	**4/978**
P	2/284	1/120	–	**3/404**
R	6/43 754	14/3 479	24/3 390	**44/50 623**
L	–	–	–	**–**
O	2	–	–	**2**
Total	**10/44 038**	**17/4 369**	**26/3 598**	**53/52 005**

Assessment of new literature

Search methods and selection

Since no randomised outcome studies were found on radiation monotherapy in patients with low-risk localized disease, an extended search was performed to include all scientific clinical articles published in the English literature. More than five thousand titles dealing with radiation therapy and prostate cancer were retrieved. The vast majority of articles were later excluded from further analysis due to various reasons (articles without original data and/or published before 1994 and/or with insufficient information on criteria for patient inclusion and treatment outcome, irrelevant articles and congress abstracts or case reports). The full articles on more than seven hundred references were then retrieved. Of these, more than four hundred were excluded due to lack of original data, insufficient data for analysis, lack of pre-treatment prognostic factors and/or outcome criteria, incomplete reviews of the literature, earlier reports on individual studies. The remaining three hundred retrieved articles were judged adequate for complete analysis and were, thus, included in this evidence based overview.

Due to the substantial number of articles and to editorial reasons, the complete review of Prostate Cancer will appear in a separate Appendix to Volume 2. This Appendix will be published before summer 2003.

Conclusions and comments

- There are no randomised studies that compare the outcome (disease-free survival and overall survival) of surgery (radical prostatectomy) to either external beam radiotherapy or brachytherapy for patients with clinically localized low-risk (PSA < 10, GS ≤ 6, ≤ T2b) prostate cancer. However, with the advent of widely accepted prognostic markers for prostate cancer (pre-treatment PSA, Gleason score, and T-stage), such comparisons have been made possible. There is substantial documentation from large single-institutional and multi-institutional series on patients with this disease category showing that the outcome of external beam radiotherapy and brachytherapy are similar to those of surgery. ([27]R1, [10]R1, [32]R1, [45]R1, [41]R1, [7]R1, [47]R1, [14]P1, [44]R1).

- There is fairly strong evidence that patients with localized, intermediate risk and high risk (pre-treatment PSA ≥ 10 and/or GS ≥ 7 and/or > T2) disease, i.e. patients normally not suited for surgery, benefit (freedom from failure and freedom from distant metastases) from higher than conventional total dose. No overall survival benefit has yet been shown. ([40]C1,[46]C1, [51]R1, [21]R1, [14]P1, [4]P1, [28]R1, [31]R1, [2]R1, [3]R1, [25]R1, [24]P1).

- Dose escalation to patients with intermediate risk or high risk disease can be performed with 3D conformal radiotherapy (photon or proton) boost, with Ir-192 high dose rate brachytherapy boost, or brachytherapy boost with permanent seed implantation. Despite an increased risk for urinary tract and/or rectal side effects, dose-escalated therapy can generally be safely delivered with all three techniques. The support for this conclusion is substantial. ([48]C1, [46]C1, [50]R1, [5]R1, [33]P1, [43]P1, [37]P1, [15]P1, [41]R1, [17]R1, [53]P1, [35]R1, [12]R1, [1]C2, [19]R1, [18]R1, [23]R1, [16]P1).

- There is some evidence that 3D conformal radiotherapy results in reduced late rectal toxicity and acute anal toxicity compared with radiotherapy administered with non-conformal treatment volumes. (C1[26], [11]C1)

- There is some evidence that postoperative external beam radiotherapy after radical prostatectomy in patients with pT3 disease prolongs biochemical disease-free survival (DFS) and that the likelihood of achieving long-term DFS is higher when treatment is given in an adjuvant rather than a salvage setting. A breakpoint seems to exist around a PSA level of 1.0 ng/mL, above which the likelihood for eradication of the recurrence of cancer diminishes. There are no randomised studies yet and no firm conclusions can be drawn. Such studies are ongoing. ([52]R1, [38]R1, [13]R1, [54]R1, [34]R1, [8]R1, [49]R1, [36]R1).
- After prostatectomy, endocrine therapy prior to and during adjuvant radiotherapy may result in longer biochemical disease-free survival than if only adjuvant radiotherapy is given. No impact on overall survival has been shown. ([9]C1).
- There is fairly strong evidence that short-term endocrine therapy prior to and during radiotherapy results in increased disease-free survival, increased local control, reduced incidence of distant metastases and reduced cause-specific mortality in patients with locally advanced disease. ([39]C1, [42]M1, [29]C2).
- There is some evidence that short-term endocrine therapy prior to and during radiotherapy results in increased overall survival in a subset (Gleason score 2–6) of patients with locally advanced disease. ([39]C1, [42]M1).
- There is strong evidence that adjuvant endocrine treatment after curative radiotherapy results in improved local control, increased freedom from distant metastases, and increased disease-free survival in patients with loco-regionally advanced and/or high-risk disease. ([30]C1, [6]C1, [20]C2, [42]M1, [22]C1, [55]C3).
- There is moderately strong evidence that adjuvant endocrine treatment after radiotherapy results in longer overall survival compared with radiotherapy alone in patients with loco-regionally advanced disease. ([6]C1, [20]C2, [42]M1, [30]C1).

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