Section 8

PROSTATE CANCER

Summary and Conclusions

This synthesis of the literature on radiotherapy for prostate cancer is based on 53 scientific articles, including 4 randomized studies, 3 prospective studies, and 44 retrospective studies. These studies involve 52 005 patients.

- The literature provides no apparent evidence to motivate radiotherapy, or any treatment, for highly differentiated T0 tumors. Some findings suggest that radiotherapy or surgery may be indicated for poorly differentiated tumors. The literature however shows no differences in tumor effects between these two methods for treating T0 tumors. Radiotherapy is milder and less mutilating.
- Conclusions cannot be drawn from the literature concerning whether surgery (radical prostatectomy) or external radiotherapy is preferable for T1 and T2 tumors. 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 tumors is documented.
- Radiotherapy is valuable as palliative treatment for T4 tumors.
- Radiotherapy may be valuable as localized, symptom-relieving 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 tumor decreases. It is essential to treat patients at facilities that have the diagnostic potential to establish the differentiation grade of tumors.
- 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 interstitial/external radiotherapy should be studied further.

Introduction

Prostate cancer is the most common type of cancer among males in Sweden, with 5 155 new cases registered in 1992 (II). Mostly, older men are affected, with the median age of onset between 75 and 79 years. Mortality is high, and 2 131 men died from the disease in 1992 (III).

The prostate is located directly below the urinary bladder and in front of the rectum. The organ may be accessed and specimens taken via the rectum. The anatomic position offers special opportunities for radiotherapy and surgery, but it is difficult to treat the prostate without affecting the urinary bladder and rectum. Different classifications are used for clinical staging. The most common classification, and the one used here, is UICC 1978[1] (X), revised in 1992.

Adenocarcinoma is the dominate histologic type. The tumors are graded according to the WHO groupings of well, moderately, and poorly differentiated cancer (VI). These groupings are in basic agreement with the cytological groupings. Besides clinical staging, other important factors in determining therapy are differentiation grade and patient age.

Approximately 80% of tumors respond to hormone therapy, which has been in clinical use since the 1940s. Endocrine therapy has time-limited effects, on average 1.5 years, and is therefore always palliative. The value of early hormonal therapy is controversial because of its side effects.

This section reviews only the literature on radiotherapy as a local treatment method for prostate cancer. Treatment of metastases, primarily skeletal metastases, is addressed in Section 16.

Radiotherapy is intended as curative treatment for localized prostate cancer. The method may also be used in palliative treatment to reduce the tumor and delay clinical symptoms and local problems.

Radiotherapy may be used in combination with medications (endocrine manipulation), or sometimes in combina-

[1] Primary tumor extention of prostate cancer by T stage:
T0 = microscopic tumor growth, nonpalpable
T1 = small tumor surrounded by normal tissue
T2 = palpable tumor, confined within the prostate
T3 = palpable tumor, extends in or through the capsule
T4 = tumor invasion of adjacent structures

tion with surgery (postoperative). Individual publications seldom identify which patients receive concurrent endocrine therapy and radiotherapy, perhaps because these methods can be used independently in the same patient, sometimes for different purposes. Publications usually report where curative surgery is combined with radiotherapy.

Retrospective studies provide the main basis for determining the value of radiotherapy (and surgery) for local treatment of prostate cancer. Four randomized studies have been published, one of which compares radiotherapy to surgery. This 1982 study (1, 2) randomized early prostate cancer patients (T1, T2) between radical prostatectomy and external beam radiotherapy. The study includes only 97 patients and is methodologically weak. Two randomized studies reported on surgical treatment alone. Radical surgery versus placebo (3), and surgery with or without endocrine therapy (4). One study compared radiotherapy using wider versus more limited fields (5).

Several factors must be considered when selecting a treatment strategy for prostate cancer. Some of these factors affect the prognosis, others concern patients' probabilities for surviving treatment. The expected impact of these factors on the tumor must be considered when weighing different treatment methods. Relevant factors include clinical stage, tumor differentiation grade, tumor growth pattern, and the patient's age and general condition. For example, in a study of untreated patients (6) the progression was about 20 times greater, and cancer mortality was over 200 times higher among patients with poorly differentiated prostate cancer compared to those with well-differentiated cancer. This appears to complicate randomized studies, except for selected patient data. This may help explain why so few studies appear in the literature even though this type of cancer is common in many countries. Assessments of the results of surgery and radiotherapy appear mainly in retrospective studies.

Prostate cancer, primarily in early stages, often progresses slowly. The disease mainly affects the elderly where mortality from other diseases is high. Therefore, studies with long observation times are particularly valuable. Many studies report survival in terms of 5 or 10 years. Several large retrospective studies report longer observation times, 15 to 20 years or longer.

Nonpalpable tumors (T0)

Several studies have been done on patients with accidentally detected cancer at stage T0, where patients were observed but not treated (6–9). Several studies have reported on the use of early endocrine therapy in such a patient group. The results of treatment do not differ substantially from those in untreated patients. Considering potential side effects, there appears to be no indication for early endocrine treatment in these patients.

Patients with T0 tumors who are treated by external beam radiotherapy (10–18), like those treated by radical surgery (3, 4, 19–22) are often selected, which makes it difficult to compare between these two methods or with untreated patients.

The local recurrence rate has been reported at 0% to 20% for radiotherapy and 0% to 9% for surgery. Five-year survival has been reported at 74% to 100% for radiotherapy, and in some studies between 75% and 97% for surgery. According to the literature, these figures do not differ convincingly from those for untreated controls. Despite the problems with such comparisons, there are no indications for treating patients with T0 tumors, particularly older patients with well-differentiated tumors.

There is a substantially higher risk for recurrence with poorly differentiated tumors and with diffuse tumor growth. Poorly differentiated tumors grow rapidly and the prognosis in these patients is clearly worse if left untreated. Treatment is thought to be indicated in this patient group. The literature on this patient group suggests that treatment results in terms of survival and local recurrence are similar to those from radical surgery and radiotherapy. Since radiotherapy is more gentle, more patients are candidates for this type of treatment compared to radical surgery. Furthermore, incontinence and impotency rates are reported to be much lower after radiotherapy than after surgery.

Early/limited tumors (T1 and T2)

External radiotherapy has been used since the 1950s, while microscopically verified radical prostatectomy appeared later. Large patient studies have been reported both for radiotherapy (5, 10–18, 23–32) and for surgery (4, 19, 22, 33–35). Many studies, including this one, address the two groups (T1 and T2) together.

Compared to surgery, radiotherapy is a more gentle and less mutilating method for treating T1–T2 tumors. A problem appears in comparing these two methods, since virtually every published study has selected surgical patients according to age, general condition, and tumor differentiation grade, and/or growth. Likewise, many studies negatively select patients for radiotherapy, ie, patients who are not suitable for surgery and who have more poorly differentiated tumors. The frequency of lymph node metastases, and thereby subclinical generalization of the disease, is higher in poorly differentiated cancer. This explains why the prognosis is worse for poorly differentiated cancer as opposed to more highly differentiated cancer.

Randomized studies which compare these two methods have not been published. Except in small, selected material, such studies would be difficult to conduct for practical and ethical reasons. Likewise, no studies have been published of randomized material comparing untreated patients with those receiving surgery or radiotherapy.

Total survival statistics at 5 and 10 years are reported to be 67% to 93% and 20% to 70% respectively among patients who received radiotherapy and 74% to 94% and 42% to 78% respectively among patients chosen for surgery. Disease-free-survival following radiotherapy is reported to be between 38% and 90% at 5 years and 20% to 85% at 10 years. The proportion of patients with local recurrence following radiotherapy is reported to be between 0% and 23% in different studies. Consistently, the frequency of local recurrence following surgery is poorly reported.

A review of the literature from large studies is inconclusive as to whether surgical treatment or radiation therapy is superior in terms of survival and relapse rates. Furthermore, it should be noted that the indications for treating T1 and T2 tumors remain controversial, at least among elderly patients with well-differentiated tumors.

Postoperative radiotherapy for T1 and T2 tumors has been addressed by some studies covered in the literature review (10, 15, 36–39). The percentage of local recurrence was low, between 4% and 9%. Survival figures do not vary substantially, stage by stage, from the clinical studies reported above. No indications are reported in the literature which call for postoperative radiotherapy.

Moderate tumors (T3)

Patients have a substantially worse prognosis once tumors begin to penetrate the prostatic capsule (T3), even after limited observation time.

Several older studies report results from radical surgery. The quality of these studies is poor (19, 33, 35). Surgery is not recommended if prostate cancer has progressed beyond T2.

Results from external beam radiotherapy are reported in several large studies (5, 10–18, 25–27, 29–32, 40–43). After 5 years, total survival of 40% to 90% and disease-free survival of 41% to 72% were reported. After 10 years, total survival of 36% to 47% and disease-free survival of 20% to 46% were reported, and after 15 years the figures were 18% to 27% and 40% respectively.

One large study (40) reported a relatively low rate of clinically local recurrence, ie, 12%, 19%, and 25% at 5, 10, and 15 years respectively.

It appears that external beam radiotherapy plays an important role in T3 tumors. After lengthy periods of observation, a large portion of patients are clinically tumor-free. Therefore, it appears that radiotherapy offers good palliation, postponement of local symptoms, and the opportunity for clinical cure.

Advanced tumors (T4)

A few large studies have reported on curative radiotherapy for advanced prostate cancers that invade adjacent organs (T4 tumors) (10, 14, 15, 17, 25, 27, 28, 30, 32, 42, 43). Total survival is reported to be 10% to 51% at 5 years and 17% to 36% at 10 years. The frequency of local recurrence is higher than for T3 cancer, 19% to 40%. Most of these patients have lymph node metastases, thus generally excluding curative treatment. Local radiotherapy may shrink the tumor and in some instances provide local cure. This, per se, is a major gain since patients are freed from local discomfort. Some patients remain recurrence-free for many years following radiotherapy alone.

Based on the literature, radiotherapy is indicated for many patients with T4 tumors.

Palliative local radiotherapy

Some studies have reported on palliative local radiotherapy for advanced prostate cancer with generalized metastasis among very elderly patients, or among patients in generally poor condition (44–46). To conserve resources and to avoid hospital visits/admission, treatment based on few fractions and high single dosage was attempted in these patients. Even this type of fractionation provided good relief from symptoms related to urine flow and bleeding.

The value of radiotherapy must be recognized in cases of advanced disease and metastases where curative treatment is not meaningful, or among patients who cannot tolerate weeks of treatment due to advanced age and poor health.

Radiotherapy methods

Radiotherapy methods have been relatively uniform across the studies, even though they were conducted over a period of 35 years at numerous centers around the world, mainly in the United States and Europe. The four-field method using linear accelerators has dominated. A common method has been to deliver a lower total dose to a larger volume including the lymph nodes of the true pelvis, and thereafter a booster dose to the prostate itself.

Several studies attempted to analyze the value of irradiating the regional lymph nodes versus treating the prostate alone (5, 10, 14, 15, 18, 24, 40), but found no benefits from using the larger field, except in two studies (12, 41) that observed a tendency toward improved survival and lower relapse rates. One randomized study tested additional irradiation of the para-aortal lymph nodes (5), but observed no particular benefits from this approach.

Except for strictly palliative local radiotherapy (in advanced tumors, or among patients in poor general health) the dominant fractionation has been 1.8–2.0 Gy per day, 5 days per week. The final dosage to the prostate has varied in different studies from 50 Gy to 76 Gy. In most studies, most patients received between 65 and 70 Gy. A large US study, based on data from several centers, showed a clear dose-response relationship (47). A study of 574 patients

found the frequency of local recurrence within the radiation volume after 4 years of observation to be 24% at < 55 Gy, successively decreasing with increasing dosage to 10% at >70 Gy. Unfortunately, the information in the literature is insufficient to determine the disadvantages of higher dosages in terms of side effects.

A US study from 1986 compared treatment principles in the United States during two periods separated by a 10-year interval, 1974 and 1983 (48). The percentage of patients receiving primary radiotherapy increased from 11% to 26%, while those receiving microscopically verified radical surgery decreased from 15% to 8%.

Interstitial brachytherapy

The results of interstitial brachytherapy via permanent or temporary implantation of radioactive substances, iodine 125, gold 198, or irridium 192, has been reported in several studies (49–53), and the method continues to be used. According to the literature review, the results of interstitial treatment alone have been discouraging in terms of local recurrence and survival, clearly worse when compared to other treatment methods. One possibility would be to combine interstitial radiotherapy with external radiotherapy. This has been tested in several institutions and preliminary reports are encouraging. The extent to which this type of combination therapy will be used remains to be seen.

Literature

The articles that appear in the reference list 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

REFERENCES

1. Paulson DF, Lin GH, Hinshaw L, Stephani S, the Uro-Oncology Research Group. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. J Urol 1982; 128: 502–4. (C3/97)
2. Hanks GE. More on the Uro-Oncology Research Group report of radical surgery vs radiotherapy for adenocarcinoma of the prostate. Int J Rad Oncol Biol Phys 1988; 14: 1053–7. (O1)
3. Madsen PO, Graversen PH, Gasser TC, Corle DK. Treatment of localized prostate cancer. Radical prostatectomy versus placebo. A fifteen year follow-up. Scand J Urol Nephrol 1988; (Suppl 110): 95–100. (C3/111)
4. Byar DP. VACURG Studies of post-prostatectomy survival. Scand J Urol Nephrol 1980; 55 (Suppl): 113–6. (C2/247)
5. Pilepich MV, Krall JM, Johnson RJ, Sause WT, Perez CA, Zinninger M, Martz K. Extended field (periaortic) irradiation in carcinoma of the prostate—analysis of RTOG 75-06. Int J Rad Oncol Biol Phys 1986; 12: 345–51. (C2/523)
6. Johansson J-E, Andersson S-O, Krusemo UB, Adami H-O, Bergström R, Kraaz W. Natural history of localised prostatic cancer. Lancet 1989; 1: 799–803. (P1/223)
7. George NJR. Natural history of localised prostatic cancer managed by conservative therapy alone. Lancet 1988; 1: 494–7. (P2/120)
8. Adolfsson J, Carstensen J. Natural course of clinically localized prostate adenocarcinoma in men less than 70 years old. J Urol 1991; 146: 96–8. (P1/61)
9. Markiewicz D, Hanks GE. Therapeutic options in the management of incidental carcinoma of the prostate. Int J Rad Oncol Biol Phys 1991; 20: 153–67. (O1)
10. Rosen EM, Cassady JR, Connolly J, Chaffey JT. Radiotherapy for localized prostate carcinoma. J Rad Oncol Biol Phys 1984; 10: 2201–10. (R2/229)
11. Rangala N, Cox JD, Byhardt RW, Wilson JF, Greenberg M, Lopes da Conceicao A. Local control and survival after external irradiation for adenocarcinoma of the prostate. Int J Rad Oncol Biol Phys 1982; 8: 1909–14. (R2/128)
12. Ploysongsang SS, Aron BS, Shehata WM. Radiation therapy in prostate cancer: whole pelvis with prostate boost or small field to prostate. Urology 1992; 40: 18–26. (R2/242)
13. Amdur RJ, Parsons JT, Fitzgerald LT, Million RR. Adenocarcinoma of the prostate treated with external-beam radiation therapy: 5-year minimum follow-up. Radiother Oncol 1990; 18: 235–46. (R2/225)
14. Aristizabal SA, Steinbronn D, Heusinkveld RS. External beam radiotherapy in cancer of the prostate. The University of Arizona experience. Radiother Oncol 1984; 1: 309–15. (R3/218)
15. Sagerman RH, Chun HC, King GA, Chung CT, Dalal PS. External beam radiotherapy for carcinoma of the prostate. Cancer 1989; 63: 2468–74. (R3/239)
16. Kuten A, Nitetzky S, Tatcher M, Cohen Y, Robinson E. Experience in the treatment of localized carcinoma of the prostate by definitive external irradiation. Int Urol Nephrol 1989; 21: 325–32. (R3/116)
17. McGowan DG, Hanson J. The national Canadian study of carcinoma of the prostate treated by external beam radiation (1970–1978). J Assoc Can Radiol 1985; 36: 216–22. (R2/1.496)
18. Kurup P, Kramer TS, Lee MS, Phillips R. External beam irradiation of prostate cancer. Cancer 1984; 53: 37–43. (R3/163)
19. Boxer RJ, Kaufmann JJ, Goodwin WE. Radical prostatectomy for carcinoma of the prostate, 1951–1976. A review of 329 patients. J Urol 1977; 117: 208–13. (R3/322)
20. Elder JS, Gibbons RP, Correa Jr RJ, Brannen GE. Efficacy of radical prostatectomy for stage A2 carcinoma of the prostate. Cancer 1985; 56: 2151–4. (R3/25)
21. Nichols RT, Barry JM, Hodges CV. The morbidity of radical prostatectomy for multifocal stage I prostatic adenocarcinoma. J Urol 1976; 117: 83–4. (R3/33)
22. Middleton RG, Smith JA, Melzer RB, Hamilton PE. Patient survival and local recurrence rate following radical prostatectomy for prostatic carcinoma. J Urol 1986; 136: 422–4. (R3/153)
23. Hanks GE, Krall JM, Martz KL, Diamond JJ, Kramer S. The outcome of treatment of 313 patients with T-1 (UICC) prostate cancer treated with external beam irradiation. Int J Rad Onc Biol Phys 1988; 14: 243–8. (R2/313)

24. Zagars GK, v Eschenbach AC, Johnson DE, Oswald MJ. The role of radiation therapy in stage A2 and B adenocarcinoma of the prostate. Int J Rad Oncol Biol Phys 1988; 14: 701–9. (R2/114)
25. Perez CA, Pilepich MV, Garcia D, Simpson JR, Zivnuska F, Hederman MA. Definitive radiation therapy in carcinoma of the prostate localized to the pelvis: experience at the Mallinckrodt Institute of Radiology. NCI Monogr 1988; 7: 85–94. (R1/577)
26. Kaplan ID, Prestidge BR, Bagshaw MA, Cox RS. The importance of local control in the treatment of prostatic cancer. J Urol 1992; 147: 917–21. (R1/946)
27. Arcangeli G, Micheli A, Arcangeli G, et al. Definitive radiation therapy for localized prostatic adenocarcinoma. Int J Rad Oncol Biol Phys 1991; 20: 439–46. (R2/199)
28. Collins CD, Lloyd-Davies RW, Swan AV. Radical external beam radiotherapy for localised carcinoma of the prostate using a hypofractionation technique. Clin Oncol 1991; 3: 127–32. (R3/232)
29. Davies AH, Lydford Davies H, Ramarakha P, Durrant KD, Fellows GJ. External-beam radiation for carcinoma of the prostate. Eur Urol 1990; 18: 117–9. (R3/105)
30. van der Werf-Messing BHP, Menon RS, van Putten WLJ. Prostatic cancer treated by external irradiation at the Rotterdam Radiotherapy Institute. Strahlentherapie 1984; 160: 293–300. (R1/279)
31. Forman JD, Zinreich E, Lee D-J, Wharam MD, Baumgardner RA, Order SE. Improving the therapeutic ratio of external beam irradiation for carcinoma of the prostate. Int J Rad Oncol Biol Phys 1985; 11: 2073–80. (R2/240)
32. Nilsson I, Lindholm C-E, Landberg T, Abrahamsson P-A, Sundkvist L, Lindholm K. Radical radiotherapy in prostatic carcinoma. Acta Oncologica 1989; 28: 261–6. (R2/111)
33. Schroeder FH, Belt E. Carcinoma of the prostate: a study of 213 patients with stage C tumors treated by total perineal prostatectomy. J Urol 1975; 114: 257–60. (R3/213)
34. Gibbons RP, Correa RJ, Brannen GE, Mason JT. Total prostatectomy for localized prostatic cancer. J Urol 1984; 131: 73–6. (R3/207)
35. Tomlinson RL, Currie DP, Boyce WH. Radical prostatectomy: palliation for stage C carcinoma of the prostate. J Urol 1977; 117: 85–7. (R3/24)
36. Pilepich MV, Walz BJ, Baglan RJ. Postoperative irradiation in carcinoma of the prostate. Int J Rad Oncol Biol Phys 1984; 10: 1869–73. (R3/28)
37. Hanks GE, Dawson AK. The role of external beam radiation therapy after prostatectomy for prostatic cancer. Cancer 1986; 58: 2406–10. (R3/21)
38. Ray GR, Bagshaw MA, Freiha F. External radiation salvage for residual or recurrent local tumor following radical prostatectomy. J Urol 1984; 132: 926–30. (R3/32)
39. Gibbons RP, Cole BS, Richardson RG, et al. Adjuvant radiotherapy following radical prostatectomy: results and complications. J Urol 1986; 135: 65–8. (R2/45)
40. Zagars GK, v Eschenbach AC, Johnson DE, Oswald MJ. Stage C adenocarcinoma of the prostate. An analysis of 551 patients treated with external beam radiation. Cancer 1987; 60: 1489–99. (R1/551)
41. Beiler DD, Wright DJ, Reddy GN. Radical external radiotherapy for prostatic carcinoma. Int J Rad Oncol Biol Phys 1981; 7: 885–90. (R2/88)
42. Weshler Z, Gez E, Pfeffer MR, Ben-Yosef R, Loeventhal E. Continuous course of megavoltage radiotherapy for carcinoma of the prostate. Isr J Med Sci 1988; 24: 580–3. (R3/55)
43. Lawton CA, Glisch C, Byhardt RW, Sehring S, Hartz A, Cox JD. Extended-field radiation therapy for prostatic carcinoma with para-aortic lymph node metastsis. Am J Clin Oncol 1986; 4: 302–6. (R2/23)
44. Kynaston HG, Keen CW, Matthews PN. Radiotherapy for palliation of locally advanced prostatic carcinoma. Br J Urol 1990; 66: 515–7. (R2/26)
45. Kraus PA, Lytton B, Weiss RM, Prosnitz LR. Radiation therapy for local palliative treatment of prostatic cancer. J Urol 1972; 108: 612–4. (R3/33)
46. Fosså SD. Palliative pelvic radiotherapy in patients with hormone-resistent prostatic cancer. In: "Prostate Cancer, part B: Imaging Techniques, Radiotherapy, Chemotherapy, and Management Issues" Alan R Liss Inc 1987: 479–85. (R3/19)
47. Hanks GE. Optimizing the radiation treatment and outcome of prostate cancer. Int J Rad Oncol Biol Phys 1985; 11: 1235–45. (R1/574)
48. Schmidt JD, Mettlin CJ, Natarajan N, et al. Trends in patterns of care for prostatic cancer 1974–1983: results of surveys by the American College of Surgeons. J Urol 1986; 136: 416–21. (R1/40.827)
49. El-Mahdi AM, Kuban DA, Schellhammer PF. The treatment of choice for localized poorly differentiated adenocarcinoma of the prostate. Am J Clin Oncol 1985; 8: 477–80. (R3/71)
50. Patel J, Worthen R, Abadir R, Weaver DJ, Weinstein S, Ross Jr G. Late results of combined iodine-125 and external beam radiotherapy in carcinoma of prostate. Urology 1990; 36: 27–30. (R3/96)
51. Morton JD, Harrison LB, Peschel RE. Prostatic cancer therapy: comparison of external-beam radiation and I-125 seed implantation treatment of stages B and C neoplasms. Radiology 1986; 159: 249–52. (R3/179)
52. Syed AMN, Puthawala A, Austin P, et al. Temporary iridium-192 implant in the management of carcinoma of the prostate. Cancer 1992; 69: 2515–24. (R3/200)
53. Whitmore Jr WF, Hilaris B, Batata M, Sogani P, Herr H, Morse M. Interstitial radiation: short-term palliation or curative therapy? Urology 25 1985; (Suppl 2): 24–9. (R3/606)