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Low Evidence of Radiation Therapy in Prostate Cancer

A Plea for Intensified Scientific Activity

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Acta Oncologica Vol. 43, No. 4, pp. 311–315, 2004

EVIDENCE-BASED MEDICINE

The treatment we should offer an individual patient must be the one we believe has the greatest chance of providing benefit, balanced against unwanted acute and late effects, and other costs for the individual and the society. In order to be able to make the choice, we and the patients need to know the likelihood of all relevant events; clinical research retrieves such information. The studies can be anything from descriptions of a few cases to investigations of thousands of patients that have been randomized between different treatment strategies. The scientific evidence is stronger the more patients that have been treated under controlled and documented conditions. Numerous systems have graded the strength of evidence from clinical trials (1, 2). They all rank meta-analyses of randomized trials or adequately powered and completed high-quality randomized trials at the top and case reports and expert opinions at the bottom. The meta-analyses of the randomized trials can also be of various quality with a statistical analysis of individual data from all randomized patients in all completed randomized trials as the best available evidence. Evidence-based medicine is " ... the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (3). The level of evidence for a given clinical situation and treatment must be described. Evidence-based medicine is thus not only to identify the randomized trials and analyse them properly but also to describe the best evidence that is available at a given point in time, i.e. studies providing lower scientific evidence than randomized trials must also be included. The compilation must be systematic, i.e. as complete and as stringent as possible.

No system can, however, replace a careful examination of each performed study, and the proposed ranking should not obscure the fact that we just need data valid enough for answering the scientific question we ask. There is thus no point in asking for redundant information to fulfil scientific ideals of "high evidence". For strong effects observational studies suffice. However, to document weak effects, or when the magnitude of an effect is to be measured with a high precision, validity of collected data need to be high. If we have plenitude of studies for a clinical question, however, it is self-evident that we should utilize the most valid data that have been collected. A real-life study has four important potentially detrimental validity threats: large attrition, quality-differences in measuring outcome between the groups we compare, inadequate comparisons and erroneous statistical modelling (4).

Evidence-based medicine might be seen as a requisite to learn and integrate the most valid data that have been collected (and published) into clinical practice; scattered clinical impressions should not obscure available scientific evidence. To practise evidence-based medicine is further to provide recommendations based upon the scientific evidence of the magnitude of the gains identified, balanced against unwanted effects and (especially when the effects are modest) costs.

SYSTEMATIC OVERVIEWS IN RADIATION ONCOLOGY

Several years ago, The Swedish Council of Technology Assessment (SBU) made an extensive systematic overview of the effects of radiotherapy in several tumour types. The overview then filled many gaps of unprecise knowledge, and it has been much appreciated by the international community (5–7). Many unanswered clinically important questions were identified. The SBU-group have later performed a similar systematic overview concerning the effects of

 ISSN 0284-186X
DOI: 10.1080/02841860410032867

chemotherapy (8). Difficulties in transferring the evidence from available studies to recommendations were identified and discussed (2). Experts, even if having all available evidence at hand, make different interpretations. The information may not be clear-cut enough, e.g. since long-term follow-up information about unwanted effects frequently is lacking (9).

In the light of rapidly evolving knowledge in radiation oncology an update of the previous radiotherapy report by SBU was considered urgent. The results from studies published from 1994 through 2001 or 2002 were collected and examined. The report was recently published and it was immediately made available to an international public (10–23). It has been greatly welcomed by the ESTRO project on QUAntification of Radiation Therapy infrastructure and Staffing needs (QUARTS), indicating a future substantial international impact.

Prostate cancer was one of 15 tumour types included in the SBU evaluation but was not published with the others. The incidence of prostate cancer is rapidly increasing, likely primarily an effect of screening, and it is presently the most common cancer in many Western countries. Radiation therapy is a frequently used treatment modality, why it must be considered of greatest importance to critically review available evidence and make it publicly available. The reason for not publishing the chapter about prostate cancer with the other chapters was that it was not yet finalized and that it was considered not appropriate to delay publication of the others.

The SBU process is very careful and strictly predefined to secure quality so that as unbiased conclusions as possible can be made. A primary reviewer together with a group of specialists evaluate the literature and extract appropriate information from all relevant articles. Their description is then evaluated by national and international experts in the field. After modifications, the text is again evaluated by a second group of international experts and national non-experts skilled in clinical medicine and various methodologies, and finally by members of the scientific board of SBU. The conclusions of each chapter are then approved by the SBU board. Such a rigorous process was not completed for prostate cancer. It was known prior to the work that the number of radiation trials in prostate cancer having a valid comparative design was very limited; an extensive search for trials confirmed this. It was then decided to make an effort to describe the best available evidence. This ambitious task substantially increased the workload, and the work was simply not ready in time.

In this issue of Acta Oncologica the reviewers account their reading of the literature on radiation therapy and prostate cancer (24). The presentation has been subject to peer review-as always is the routine prior to acceptance of an article in Acta Oncologica. During this process, many valuable comments, also including how individual trials should be interpreted, were made. The original overall conclusions were, however, not modified from what was accepted by the SBU board. It was considered valuable to publish this extensive work so that clinicians and researchers would get a possibility to study a reading of a large part of the literature (24).

Evidence of radiation therapy in prostate cancer

Has the review become complete and are the conclusions appropriate? It would be unfair to describe this work as complete. Not all performed studies can reasonably be identified in the literature searches, and it would be an unproportionate task to, for example, identify further hospital-based studies. Among the many trials published, a few may erroneously have been excluded. Since the far majority of the studies have a design that makes findings inconclusive, it is also an extremely intricate task to make the most appropriate interpretations, both of the individual trials, as given in the many tables, and for the compiled data. If we follow the ranking proposed by Bentzen (1), level II evidence is actually only present for reduced incidence of gastrointestinal complications after three-dimensional (3D) conformal radiotherapy (two randomized trials comparing conventional radiotherapy with 3D-CRT found reduced complications, however, one evaluating acute toxicity and one late unwanted effects; the evidence is thus not of level I as recently stated (25) (see (24)). There is also reasonable evidence (possibly level II, again not level I, the study has validity problems (26)) that an increase in the prescribed dose improves the failure-free rate in a subgroup of patients. Improved dose distributions may convince fellow radiation oncologists, and thus the experts, but a proven effect on patient-related outcomes must be shown to convince the non-experts (25, 27). Recently, it was also shown in a large randomized trial, confirming observational study results, that prophylactic whole-pelvic radiation followed by a boost to the prostate improved progression-free survival compared with prostate only radiotherapy in patients with localized prostate cancer and intermediate to high risk of lymph node involvement (all patients also received androgen suppression) (28). This randomized trial gives, again, level II evidence. In an evidence-based estimate of appropriate radiotherapy utilization rate for prostate cancer, level II evidence was present only for palliative radiotherapy; the levels were considered to be III or IV for all radiations against the prostate/pelvic volumes (29).

However, valid conclusions can be made also in many other aspects not ranked level I or II. For example, cohort studies have beyond reasonable doubt taught us that radical prostatectomy gives an excess risk of erectile dysfunction and radiotherapy against the prostate an excess risk of faecal leakage. This evidence is only ranked level III, as is the evidence that smoking causes lung cancer. However, to ask for randomized placebo-controlled studies investigating

whether radical prostatectomy causes erectile dysfunction, radiotherapy fecal leakage or smoking lung-cancer would add nothing scientifically, apart from being unethical. We know the answer is 'yes', highlighting the weakness of an absolute ranking system for validity as opposed to a system measuring validity relative to the question asked.

For a treatment with curative intention, a man with newly detected localized (T1-2) prostate cancer without unfavourable prognostic signs can choose between radical prostatectomy and radical radiotherapy. Concerning radical prostatectomy, we know that a man will increase his survival chances by the surgery, and we are beginning to understand how large his gain on average will be (30). For radiotherapy we simply do not yet know if it influences the expected survival.

In a well-performed randomized clinical trial (30), radical prostatectomy as compared with watchful waiting (no initial treatment with curative intention) halved the risk of dying of prostate cancer (T1-2, G1-2); a finding by and large identical to a compilation of non-randomized patient series. Over time, the difference between the radical-prostatectomy and watchful-waiting groups increases, suggesting that the absolute difference in survival between groups will increase when five as well as ten more years of follow-up are added – prostate-cancer deaths happen up to 23 years after diagnosis (31). Moreover, there are no indications that radical prostatectomy influences intercurrent mortality, the absolute difference in overall survival subsequently is virtually identical to the difference in prostate-cancer mortality.

For radiotherapy we have no comparative trial with watchful waiting that has been published, but results from ongoing Scandinavian trials are awaited. A compilation of non-randomized patient series showed a higher (not lower) prostate-cancer-specific mortality after radiotherapy as compared to watchful waiting (32). This finding may, however, fully be explained by an inadequate comparison; tumour volume may be higher or tumour characteristics more unfavourable when radiotherapy is initiated as compared to watchful waiting. However, if there is, say, three years between diagnosis and start of radiotherapy an 'inversed lead time' effect may arise spuriously increasing the observed cancer-specific mortality (33). Nevertheless, if a tumour is not sterilized, radiotherapy may have induced mutations that make the tumor more aggressive than before. We need better evidence before we can say that radiotherapy shortens or lengthens the expected survival in patients with localized favourable prostate cancer.

Concerning long-term unwanted effects, there is a sharp boundary between radiotherapy and radical prostatectomy. The radiotherapy previously used causes fecal leakage, soiling, socially bothersome flatulence, defecation urgency and abdominal pain – these symptoms do not occur after radical prostatectomy (34–40). Both radical prostatectomy and radiotherapy cause erectile dysfunction, probably of a similar magnitude with present techniques, and radical prostatectomy induces long-term urinary incontinence more often than radiotherapy. Fecal leakage is a bothersome symptom occurring after radiotherapy to the small pelvis (38, 40). Thus, radiotherapy induces a unique set of bothersome side effects and has an uncertain effect on survival; presently it is hard to find evidence to recommend radiotherapy before radical prostatectomy in favourable T1-2 tumours, except for patients who are afraid of a large surgical trauma. The technology develops swiftly, modes for imaging and delivery of radiation get better every year improving the possibilities to diminish the risk of side effects. Robot-assisted laparascopic radical prostatectomy and other new operative techniques likewise give new possibilities to decrease the risk of sexual dysfunction and urinary incontinence.

Capsule penetrating prostate cancer (T3) cannot be excised radically with radical prostatectomy. Theoretically, this patient group and those who have had a non-radical prostatectomy as well as those recurring after surgery only have one treatment modality for cure; viz. radiotherapy. We have, again, no comparative trials investigating the effects on prostate cancer mortality by radiotherapy in these clinical situations. However, multiple series show a low continuous serum-PSA level after radiotherapy for such patients (see (24)), indicating that tumor sterilization can be achieved. Since this can not presently be achieved by any other means, a trial comparing radiotherapy with no radiotherapy would be impossible, and unethical. The situation is analogous to that in many other tumour types in patients presenting with locally inextirpable tumours without evidence of distant metastases. Thus, it is reasonable to recommend patients with e.g. capsule penetrating prostate cancer radiotherapy – if the patients' preference is to optimize chances of survival even though he faces a risk of late complications.

WHO TO BLAME?

Who should then be blamed for the comparatively low level of evidence concerning the effects on prostate cancer by radiation therapy and what are the conclusions for the present and future patients? Many share the responsibility to advance knowledge. The patients themselves are the least to blame; 'after appropriate information about a trial they generally accept participation, including randomization' (41). Actually, there has been a trend among patients to ask for a trial, recognizing that trial participation may mean that you get a better treatment than in routine care (42). Every doctor responsible for a patient has to ask himself whether the patient may be suitable for an ongoing trial and then take the extra time to inform the patient. The ongoing trial (SPCG-7), comparing no radiotherapy but an anti-androgene with radiotherapy and an anti-androgene, recruits well, but not all eligible patients. Too frequently, no

trial is available even if uncertainties about the best treatment is present. Physicians in a position to be responsible for, let say urologic tumours at a department, particularly at university hospitals but also at other hospitals, have the obligation to keep the care at the highest standard but also to advance knowledge. Quite frequently these doctors adopt, modify or develop a new technique, and then treat their suitable patients. When the experience is sufficient and the results apparently favourable, a retrospective analysis is done, written-up and published. Frequently, the series continue, often without any formally approved trial (43, 44) and another publication follows a few years later. There are numerous examples of this in prostate cancer radiotherapy, and these 'devoted' clinicians are among the ones to blame for not advancing knowledge. An extensive investigation by the Swedish Cancer Society also stated that 'convinced, almost converted investigators' have frequently prevented accurate evaluations (45). Prostate cancer is a good example of this. However, radiation therapy research faces many other difficulties (see (45)), and responsible for the lack of proper development of knowledge also includes department heads, hospital and health care managements, research organisations and others. There is a disproportion in the number and quality of studies performed in medical oncology and radiation oncology, mainly reflecting research activities by pharmaceutical companies. Also surgical oncology faces the same scarcity of data (46, 47). By the time this editorial and the prostate cancer overview is published, we may know with very high accuracy from a large randomized trial whether or not docetaxel influences survival in hormone refractory metastatic prostate cancer patients. If an effect, also a small one, is shown, this treatment will likely be part of routine care at most hospitals within short, due to marketing activities. When will we reveal, with the same level of precision and validity, much greater incremental gains on survival from different surgical and radiation therapies in primary prostate cancer? Until then, we are left with major uncertainties when to recommend a particular therapy for an individual patient, and researchers performing systematic overviews are faced with major practical difficulties synthesizing the literature-accounted evidence. Only firm evidence about specific treatment effects obtained from large populations under controlled conditions will allow us to further individualize treatment-strategy by, e.g. information from imaging and molecular profiling of the tumour (48–50).

REFERENCES

1. Bentzen SM. From clincal trials to clinical practice: A user's guide to evidence-based oncology. Eur J Cancer Suppl 2003; 1: 77–91.
2. Nygren P, Glimelius B. The Swedish Council on Technology Assessment in Health Care (SBU) report on Cancer Chemotherapy–Project objectives, the working process, key definitions and general aspects on cancer trial methodology and interpretation. Acta Oncol 2001; 40: 155–65.
3. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evience-based medicine: What it is and what it is not. Br Med J 1996; 312: 71–2.
4. Steineck G, Kass PH, Ahlbom A. A comprehensive clinical epidemiological theory based on the concept of the source person-time and four distinct study stages. Acta Oncol 1998; 37: 15–23.
5. SBU – The Swedish Council on Technology Assessment in Health Care. Radiotherapy for cancer. Volume 1. Acta Oncol 1996; 35 (suppl 6): 1–100.
6. SBU – The Swedish Council on Technology Assessment in Health Care. Radiotherapy for Cancer. Volume 2: A critical review of the literature. Acta Oncol 1996; 35 (suppl 7): 1–152.
7. Frödin JE, Jonsson E, Möller T, Werkö L. Radiotherapy in Sweden – a study of present use in relation to the literature and estimate of future trends. Acta Oncol 1996; 35: 967–80.
8. Glimelius B, Bergh J, Brandt L, et al. The Swedish Council on Technology Assessment in Health Care (SBU) systematic overview of chemotherapy effects in some major tumour types – summary and conclusions. Acta Oncol 2001; 40: 135–54.
9. Steineck G, Bergmark K, Henningsohn L, al-Abany M, Dickman PW, Helgason A. Symptom documentation in cancer survivors as a basis for therapy modifications. Acta Oncol 2002; 41: 244–52.
10. Zackrisson B, Mercke C, Strander H, Wennerberg J, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in head and neck cancer. Acta Oncol 2003; 42: 443–61.
11. Ask A, Albertsson M, Järhult J, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in oesophageal cancer. Acta Oncol 2003; 42: 462–75.
12. Glimelius B, Grönberg H, Järhult J, Wallgren A, Cavallin-ståhl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol 2003; 42: 476–92.
13. Sirzen F, Kjellen E, Sörenson S, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in non-small cell lung cancer. Acta Oncol 2003; 42: 493–515.
14. Strander H, Turesson I, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in soft tissue sarcomas. Acta Oncol 2003; 42: 516–31.
15. Rutqvist LE, Rose C, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in breast cancer. Acta Oncol 2003; 42: 532–45.
16. Einhorn N, Trope C, Ridderheim M, Boman K, Sorbe B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in ovarian cancer. Acta Oncol 2003; 42: 562–6.
17. Einhorn N, Trope C, Ridderheim M, Boman K, Sorbe B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in uterine cancer (corpus uteri). Acta Oncol 2003; 42: 557–61.
18. Einhorn N, Trope C, Ridderheim M, Boman K, Sorbe B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in cervical cancer (cervix uteri). Acta Oncol 2003; 42: 546–56.
19. Widmark A, Flodgren P, Damber J, et al. A systemic overview of radiation therapy effects in urinary bladder cancer. Acta Oncol 2003; 42: 567–81.
20. Berg G, Blomquist E, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in brain tumours. Acta Oncol 2003; 42: 582–8.
21. Gustavsson A, Osterman B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in non-Hodgkin's lymphoma. Acta Oncol 2003; 42: 605–19.

22. Gustavsson A, Osterman B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. Acta Oncol 2003; 42: 589–604.
23. Falkmer U, Järhult J, Wersäll P, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in skeletal metastases. Acta Oncol 2003; 42: 620–33.
24. Nilsson S, Widmark A, Norlén BJ. A systematic overview of radiation therapy effects in prostate cancer. Acta Oncol 2004; 43: 316–81.
25. Bentzen SM. High-tech in radiation oncology: should there be a ceiling? Int J Radiat Oncol Biol Phys 2004; 58: 320–30.
26. Zietman AL. Dose escalation in localized prostate cancer: make no assumptions. Int J Radiat Oncol Biol Phys 2002; 54: 635–6.
27. Johansson KA, Mattsson S, Brahme A, Carlsson J, Zackrisson B, Turesson I. Radiation therapy dose delivery. Acta Oncol 2003; 42: 85–91.
28. Roach M, 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003; 21: 1904–11.
29. Foroudi F, Tyldesley S, Barbera L, Huang J, Mackillop WJ. Evidence-based estimate of appropriate radiotherapy utilization rate for prostate cancer. Int J Radiat Oncol Biol Phys 2003; 55: 51–63.
30. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002; 347: 781–9.
31. Adolfsson J, Oksanen H, Salo JO, Steineck G. Localized prostate cancer and 30 years of follow-up in a population-based setting. Prostate Cancer Prostatic Dis 2000; 3: 37–42.
32. Adolfsson J, Steineck G, Whitmore WF. Recent results of management of palpable clinically localized prostate cancer. Cancer 1993; 72: 310–22.
33. Steineck G, Adolfsson J. Bias due to observation of different parts of a nonconstant hazard curve over time. Urology 1996; 48: 105–9.
34. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002; 347: 790–6.
35. Bacon CG, Giovannucci E, Testa M, Glass TA, Kawachi I. The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. Cancer 2002; 94: 862–71.
36. Little DJ, Kuban DA, Levy LB, Zagars GK, Pollack A. Quality-of-life questionnaire results 2 and 3 years after radiotherapy for prostate cancer in a randomized dose-escalation study. Urology 2003; 62: 707–13.
37. Nguyen LN, Pollack A, Zagars GK. Late effects after radiotherapy for prostate cancer in a randomized dose-response study: results of a self-assessment questionnaire. Urology 1998; 51: 991–7.
38. Hanlon AL, Watkins Bruner D, Peter R, Hanks GE. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: Comparing late bowel and bladder quality of life symptoms to that of the normal population. Int J Radiat Oncol Biol Phys 2001; 49: 51–9.
39. Yeoh EE, Botten R, Russo A, et al. Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. Int J Radiat Oncol Biol Phys 2000; 47: 915–24.
40. al-Abany M, Helgason AR, Ågren-Cronquist A-K, Lind B, Mavroidis P, et al. Dose to the anal sphincter region and risk of fecal leakage. Acta Oncol 2004; 43: 117–8.
41. Comis RL, Miller JD, Aldige CR, Krebs L, Stoval E. Public attitudes toward participation in cancer clinical trials. J Clin Oncol 2003; 21: 830–5.
42. Cassileth B. Clinical trials: Time for action. J Clin Oncol 2003; 21: 765–6.
43. Glatstein E. What is research? Int J Radiat Oncol Biol Phys 2001; 51: 288–90.
44. Zackrisson B, Mattsson S, Kjellén E, Glimelius B. and the Swedish Cancer Society Investigation Group. Research and development of radiation therapy in clinical routines. Acta Oncol 2003;42:115–122.
45. Mattsson S, Brahme A, Carlsson J, et al. Swedish Cancer Society radiation therapy research investigation. Acta Oncol 2002; 41: 596–603.
46. Medical Research Council. Clinical research-crisis and costs (in Swedish). MFR Report 5, 1998.
47. Swedish Cancer Society. Investigation concerning clinical treatment studies. Cancerfonden, 1999 (in Swedish).
48. Forssell-Aronsson E, Kjellén E, Mattsson S, Hellström M. and the Swedish Cancer Society Investigation Group. Medical imaging for improved tumour characterisation, delineation and treatment verification. Acta Oncol 2002; 41: 604–14.
49. Turesson I, Carlsson J, Brahme A, Glimelius B, Zackrisson B, Stenerlow B. and the Swedish Cancer Society Investigation Group. Biological response to radiation therapy. Acta Oncol 2003; 42: 92–106.
50. Coleman CN. International Conference on Translational Research ICTR 2003 Conference Summary: marshalling resources in a complex time. Int J Radiat Oncol Biol Phys 2004; 58: 307–19.