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ORIGINAL ARTICLE

Curative radiation therapy in prostate cancer

ULRIKA HARMENBERG[1], FREDDIE C. HAMDY[2], ANDERS WIDMARK[3], BO LENNERNÄS[4] & STEN NILSSON[1]

[1]*Department of Oncology/Pathology, Karolinska University Hospital and Institutet, Stockholm, Sweden,* [2]*Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK,* [3]*Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden and* [4]*Department of Oncology, Sahlgrenska Hospital and Academy, University of Gothenburg, Gothenburg, Sweden*

Abstract

Radiotherapy has experienced an extremely rapid development in recent years. Important improvements such as the introduction of multileaf collimators and computed tomography (CT)-based treatment planning software have enabled three dimensional conformal external beam radiation therapy (3DCRT). The development of treatment planning systems and technology for brachytherapy has been very rapid as well. Development of accelerators with integrated on-board imaging equipment and technology, for example image-guided radiation therapy (IGRT) has further improved the precision with reduced margins to adjacent normal tissues. This has, in turn, led to the possibility to administer even higher doses to the prostate than previously. Although radiotherapy and radical prostatectomy have been used for the last decades as curative treatment modalities, still there are no randomized trials published comparing these two options. Outcome data show that the two treatment modalities are highly comparable when used for low- and intermediate-risk prostate cancer.

Keywords: *Curative radiation therapy – the rationale for dose escalation – choice of radiation boost techniques*

Several randomized trials have shown that a dose-response relationship exists for curative radiotherapy of prostate cancer. A comprehensive summary of these are found in a recent meta-analysis of Viani et al. [1]. Most outcome data are reported with respect to the D'Amico risk classification [2]. In patients with intermediate-and high-risk prostate cancer doses in the range of 70–72 Gy are generally not sufficient to achieve ablation of the tumor [3–7]. These tumors require radiation doses in the range of 78 Gy and above [1]. There also appears to be a dose-response relationship even in low-risk prostate cancer, i.e. these tumors also need dose escalation [1].

Dose escalation is currently being used with different approaches at different centers. The majority of these use external radiation therapy alone based on modern technologies such as intensity modulated radiation therapy (IMRT) and IGRT, enabling radiation doses in the range of 78–81 Gy, or even higher, with conventional fractionation combined with selected radiation boost regimens [1].

Other centers use a combination of 3DCRT, IMRT or IGRT in combination with high dose-rate (HDR) brachytherapy, the latter technique used in the context of radiation boost [8–12]. Such combined therapy achieves doses > 116 Gy [8]. Two randomized studies have compared the effect of external beam radiotherapy alone with external beam radiotherapy plus HDR brachytherapy boost [13,14]. Early data from one of these studies have been published [14]. These show the benefit of combination external beam radiotherapy plus HDR brachytherapy. However, the external radiation therapy alone utilized a lower biological dose compared with the combination therapy concept. This hampers the comparison. A systematic review with meta-regression analysis has recently been carried out in which observational studies on external beam radiation therapy (EBRT), seed implantation brachytherapy, and HDR brachytherapy were included [15]. The selection for EBRT included only studies with cohorts treated with at least 75 Gy. The conclusions drawn from this

Correspondence: Sten Nilsson, Department of Oncology, Karolinska Institutet, Stockholm, SE-17176, Sweden. E-mail: sten.nilsson@ki.se

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analysis are that the combination of external beam radiotherapy and HDR brachytherapy results in a superior biochemical control as well as overall survival [15]. However, there is still a need for randomized controlled trials comparing the outcome of radiation therapies with different dose fractionation schedules, radiation boost techniques and total doses to the prostate and organs at risk.

Neoadjuvant, concomittant and adjuvant endocrine therapy

The value of combination treatment – radiotherapy and endocrine therapy – has been studied in multiple randomized trials [16,17]. These have in various degrees shown the benefit of this concept with respect to local control, distant metastasis-free survival, disease-free survival, cancer specific mortality and overall survival. However, it is important to take some factors in consideration. The majority of trials have exclusively included patients with high-risk disease, i.e. patients with locally advanced and/or poorly differentiated cancer and/or high risk of lymph node metastatic disease. Radiotherapy was generally given at doses that, with today's knowledge, are not sufficient to achieve cure. Radiation was in most studies given with whole pelvic fields to 50 Gy and a subsequent radiation boost to the prostate [16]. One of the major arguments against the combination concept (radiotherapy combined with endocrine treatment) is that the radiotherapy used *de facto* needed androgen deprivation therapy to compensate, in part, for the inadequate radiation doses that could be achieved with the radiation therapy techniques used at that time. Some observational studies support the assumption that hormonal neoadjuvant and adjuvant treatment can be excluded from the curative treatment provided that adequate radiation therapy is given [18]. The concept of neoadjuvant, concomittant and adjuvant endocrine treatment will most certainly be challenged by the concept of curative treatment with high-dose radiotherapy as monotherapy (dose-escalated 3DCRT or IMRT/IGRT) or with combination therapy (3DCRT/IMRT/IGRT plus HDR brachytherapy boost) to the primary tumor.

Adjuvant and early salvage radiotherapy

The value of adjuvant radiotherapy after radical prostatectomy has been investigated in three large randomized trials [19–21]. Two of these have shown overall survival benefit in the order of 10%, while the third [21] is not yet mature for overall survival evaluation. All studies showed, in comparison to no postoperative radiotherapy, statistically significant differences in disease-free survival, metastasis-free survival, local progression and cancer-specific mortality at advantage for radiotherapy. The question whether the postoperative treatment is best served in a strictly adjuvant setting or if this treatment could also well be given as early salvage radiotherapy has to be answered. Randomized studies on this concept are under way. The majority of centers have not yet adopted adjuvant radiotherapy into their clinical routine practice. The main reason for this is that the results from the adjuvant trials have not been obtained until quite recently. At least half of the patients experiencing recurrence after radical prostatectomy (about 30%) should be considered for early salvage radiotherapy. Still there are no conclusive data on optimal fractionation schedule and the total dose needed in this setting. Questions also remain regarding the efficacy of salvage radiotherapy in patients who never reach undetectable prostate-specific antigen (PSA) after surgery and/or have already reached a PSA level over 1 ng/ml before salvage radiation therapy and/or with tumor invasion of seminal vesicles at surgery. Pending the results from prospective trials the nomogram by Stephenson and coworkers is useful when discussing the benefit and possible side-effects of salvage radiotherapy for patients experiencing recurrent disease [22].

Treatment of locally advanced disease – the SPCG7/SFUO3 trial

The treatment of choice in patients with locally advanced prostate cancer has over the years been endocrine therapy, either as castration therapy or treatment with antiandrogen as monotherapy. This paradigm was challenged in the Scandinavian SPCG7/SFUO3 randomized phase III trial comparing endocrine therapy with and without local radiotherapy, followed by castration on progression [23]. The trial recruited 875 patients with locally advanced prostate cancer (T3; 78%; PSA $<$ 70; N0; M0) between February 1996 and December 2002. The patients were randomly assigned to endocrine treatment alone (three months of total androgen blockade followed by continuous endocrine treatment using flutamide), or to the same endocrine treatment combined with curative radiotherapy. The primary endpoint was prostate-cancer-specific survival, and analysis was by intention to treat. After a median follow-up of 7.6 years, 79 men in the endocrine alone group and 37 men in the endocrine plus radiotherapy group had died of prostate cancer. The cumulative incidence at 10 years for prostate-cancer-specific mortality was 23.9% in the endocrine alone group and 11.9% in the endocrine plus radiotherapy group (difference 12.0%, 95% CI 4.9–19.1%), for a relative risk of 0.44 (0.30–0.66). At 10 years, the cumulative incidence for overall mortality was 39.4% in the endocrine alone group and

29.6% in the endocrine plus radiotherapy group (difference 9.8%, 0.8–18.8%), for a relative risk of 0.68 (0.52–0.89). Cumulative incidence at 10 years for PSA recurrence was substantially higher in men in the endocrine-alone group (74.7% vs. 25.9%, $p < 0.0001$; HR 0.16; 0.12–0.20). After five years, urinary, rectal, and sexual problems were slightly more frequent in the endocrine plus radiotherapy group. The addition of local radiotherapy to endocrine treatment, thus, halved the 10-year prostate-cancer-specific mortality, and substantially decreased overall mortality in patients with locally advanced or high-risk local prostate cancer.

This is the only trial that has, so far, shown an overall survival benefit in patients with localized prostate cancer and, in light of these data, endocrine treatment plus radiotherapy should be implemented as the new evidence based (level 1) standard treatment in patients with locally advanced disease [23].

Unanswered questions and developmental areas within radiation therapy of prostate cancer

As mentioned above, the early radiotherapy trials included treatment with whole-pelvic fields with a subsequent radiation boost to the prostate [16]. However, with the introduction of conformal radiation therapy techniques during the 1990s and that only patients with low risk for metastatic disease or patients with N0 disease were accepted for curative treatment, whole-pelvic radiotherapy was abandoned in most centers. With the knowledge of the shortcomings of surgical lymph node staging [24] there is now a re-awakening of adjuvant radiation treatment of regional lymph nodes, especially with the advent of conformal techniques such as IMRT and intensity modulated arc therapy (IMAT) [25] and in patients with high risk (> 15%) of having lymph node metastatic disease [26–29]. With these techniques it is now possible to administer radiotherapy to the regional lymph nodes in a more conformal manner, minimizing unwanted radiation dose to organs at risk such as bladder and bowel.

Another area that has attracted much of attention recently is radiobiology of prostate cancer and radiation dose fractionation. Ample data exist to show that this tumor differs from several others by a low level α/β value, speaking in favor of hypofractionation [8,30]. Several studies have now been designed on this concept. Arcangeli et al. have recently published data from the first randomized trial [31]. This is not yet mature for evaluation of treatment effect – other than freedom from PSA recurrence – but the data show that the toxicity of the hypofractionation schedule used is acceptable [31]. A Swedish-Danish randomized hypofractionation trial has recruited over 400 patients with intermediate-risk prostate cancer patients comparing EBRT 2 Gy per fraction to 78 Gy with 6.1 Gy in 7 fractions to 42.1 Gy (Widmark, personal communication). It is important to note that the hypofractionation concept is based on the assumption that prostate cancer is often a slowly proliferating malignancy. However, some tumors also harbor poorly differentiated cancer cells which may not be suitable for hypofractionation [32,33]. The outcome of ongoing and future trials will, hopefully, clarify which patients benefit from hypofractionation.

Radiotherapy versus radical prostatectomy

Prostate cancer is different from many other malignancies in that it is one of the few cancers in which radiotherapy is a major curative treatment option primary treatment. Radical prostatectomy is the other curative treatment modality and patients are therefore asked to participate in the decision-making between these two options. Paradoxically, there are still no comparative, randomized studies on the concept radiotherapy versus surgery as primary treatment in prostate cancer – a situation which not seldom contributes to a frustrating situation for the patient as well for his partner when choosing therapy. Active monitoring is a valid option for patients with low-risk (T1c, Gleason score $\leq 3 + 3 = 6$ and PSA ≤ 10) prostate cancer. The first study on this theme is the ProtecT (Prostate testing for cancer and Treatment) trial undertaken in the UK, in which men with clinically localized prostate cancer were randomized to radiotherapy, radical prostatectomy *or* active monitoring [34]. This study has recruited extremely well and has now been closed for inclusion according to protocol. Over 1500 participants agreed to randomization (63% of those eligible) with annual follow-up at over 90%. The first results are expected in 2015 and overall survival data will be obtained in due course.

In patients with intermediate- and high-risk prostate cancer the main options, radiotherapy and surgery, remain. One Swedish randomized trial (neoadjuvant endocrine therapy plus radical prostatectomy versus neoadjuvant endocrine therapy plus external beam radiotherapy with HDR brachytherapy boost) included 89 patients with HRQoL as main end-point. The data will be published in 2011. To our knowledge, no other prospective randomized trials comparing these modalities are being undertaken.

Discussion

There are very good reasons to expect that the role of radiation therapy will increase in coming years,

warranting further randomized studies in this area. Healthcare authorities have an important task in supporting and commissioning such trials to provide sufficient evidence to guide practice and improve patient outcomes. Strong growth is expected in the areas of dose escalation, both with external beam radiation therapy as monotherapy and combination treatment with external therapy and brachytherapy. In all dose escalation protocols, the need for minimizing the margins of surrounding normal tissue is imperative. The need for improved positioning is becoming increasingly important. The trend toward higher fractions per dose, hypofractionation, will remain, highlighting the need for adequate visualization of the prostate and its positioning with techniques such as IGRT. The need for IMRT will increase for treatment of regional lymph nodes in patients with high-risk disease.

The trend towards higher radiation doses to the prostate and the balance between efficacy and toxicity will place increasing demands on technical developments, their adequate use and understanding of their limitations.

Data from the early 1990s have clearly shown that radiotherapy doses of 70 Gy and below are in the majority of cases insufficient for eradication of the cancer [3–7,35], and four randomized trials comparing 64–70 Gy with 74–80 Gy have shown improved outcome with dose escalation [36–39]. Several studies have thereafter shown a correlation between residual cancer and the risk of local progression, metastatic disease and increased cancer-specific mortality [3,40–42]. This has also recently been shown in a biopsy study from the above mentioned SPCG-7 trial in which residual cancer was verified in 22% of patients after more than three years and that this presence was associated with the above negative factors including increased cancer-specific mortality [43]. Notable is that the residual cancer was poorly differentiated (Gleason sum 8) in all patients with recurrent disease [43]. Data from our own experience have shown that residual cancer is associated with poor overall survival (Ljung et al., unpublished).

The difficulties of implementing prospective randomized studies in radiation therapy as well as surgery are obvious, especially for the fact that at least 8–10 years of follow-up is needed to detect significant differences in overall survival. The difficulties in comparing outcome data from non-randomized studies, especially from different centers, are even more obvious, not only because of patient selection but also because different definitions have been used over the years to define biochemical free survival. The difficulties are compounded by the fact that PSA levels not only reflect residual disease within the prostate but also metastatic progression, particularly in patients with intermediate- and high-risk prostate cancer. An alternative endpoint would be to utilize transrectal ultrasound (TRUS)-guided biopsy mapping of the prostate two to three years after completion of radiotherapy, especially when comparing the outcome of different doses and dose fractionation schedules. Analysis of residual cancer is, by definition, a surrogate endpoint, but may have the potential of being more accurate than serum-PSA in assessing local radicality of a given radiation treatment.

The importance of randomized controlled trials comparing modern radiation therapy and radical prostatectomy cannot be stressed enough. The ProtecT trial in the UK will provide important information on the outcome and potential side-effects of these two modalities in comparison with active monitoring. However, it will take many years before mature data on overall survival become available. In the meantime it is important to continue the prospective evaluation of new radiation therapies and surgical treatment concepts in large and well conducted randomized controlled trials.

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References

[1] Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: A meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys 2009;74:1405–18.

[2] D'Amico AV, Whittington R, Malkowicz SB, Weinstein M, Tomaszewski JE, Schultz D, et al. Predicting prostate specific antigen outcome preoperatively in the prostate specific antigen era. J Urol 2001;166:2185–8.

[3] Crook JM, Malone S, Perry G, Eapen L, Owen J, Robertson S, et al. Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: Results from a Canadian randomized trial. Cancer 2009;115:673–9.

[4] Ljung G, Egevad L, Norberg M, Holmberg L, Nilsson S, Busch C. Expression of p21 and mutant p53 gene products in residual prostatic tumor cells after radical radiotherapy. Prostate 1997;32:99–105.

[5] Ljung G, Norberg M, Hansson H, de la Torre M, Egevad L, Holmberg L, et al. Transrectal ultrasonically-guided core biopsies in the assessment of local cure of prostatic cancer after radical external beam radiotherapy. Acta Oncol 1995; 34:945–52.

[6] Ljung G, Norberg M, Holmberg L, Busch C, Nilsson S. Characterization of residual tumor cells following radical radiation therapy for prostatic adenocarcinoma; immunohistochemical expression of prostate-specific antigen, prostatic acid phosphatase, and cytokeratin 8. Prostate 1997;31: 91–7.

[7] Almroth A, Ljung G, Eklund T, Nordgren H, Kalafatidis D, Ringqvist I, et al. Value of sextant biopsies in the assessment of local cure following external beam radiotherapy of prostatic adenocarcinoma. Scand J Urol Nephrol 1998;32:111–5.

[8] Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncol 2005; 44:265–76.
[9] Galalae RM, Kovacs G, Schultze J, Loch T, Rzehak P, Wilhelm R, et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2002;52:81–90.
[10] Vargas CE, Martinez AA, Boike TP, Spencer W, Goldstein N, Gustafson GS, et al. High-dose irradiation for prostate cancer via a high-dose-rate brachytherapy boost: Results of a phase I to II study. Int J Radiat Oncol Biol Phys 2006; 66:416–23.
[11] Deger S, Boehmer D, Roigas J, Schink T, Wernecke KD, Wiegel T, et al. High dose rate (HDR) brachytherapy with conformal radiation therapy for localized prostate cancer. Eur Urol 2005;47:441–8.
[12] Kalkner KM, Wahlgren T, Ryberg M, Cohn-Cedermark G, Castellanos E, Zimmerman R, et al. Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: A 6-year follow-up. Acta Oncol 2007;46:909–17.
[13] Guix B, Bartrina JM, Henriquez I. Dose escalation by combined treatment 3D-conformal radiotherapy plus HDR brachytherapy as treatment for intermediate- or high-risk cancer: Early toxicity and biochemical outcome of a prospective randomized trial. Radiother Oncol 2007;83:S39 [abstract 81].
[14] Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: Initial results of a randomised phase three trial. Radiother Oncol 2007;84:114–20.
[15] Pieters BR, de Back DZ, Koning CC, Zwinderman AH. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: A systematic review. Radiother Oncol 2009; 93:168–73.
[16] Gottschalk AR, Roach M, 3rd. The use of hormonal therapy with radiotherapy for prostate cancer: Analysis of prospective randomised trials. Br J Cancer 2004;90:950–4.
[17] Shelley MD, Kumar S, Wilt T, Staffurth J, Coles B, Mason MD. A systematic review and meta-analysis of randomised trials of neo-adjuvant hormone therapy for localised and locally advanced prostate carcinoma. Cancer Treat Rev 2009;35:9–17.
[18] Galalae RM, Martinez A, Nuernberg N, Edmundson G, Gustafson G, Gonzalez J, et al. Hypofractionated conformal HDR brachytherapy in hormone naive men with localized prostate cancer. Is escalation to very high biologically equivalent dose beneficial in all prognostic risk groups? Strahlenther Onkol 2006;182:135–41.
[19] Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term followup of a randomized clinical trial. J Urol 2009;181:956–62.
[20] Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: A randomised controlled trial (EORTC trial 22911). Lancet 2005;366(9485):572–8.
[21] Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Storkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27:2924–30.
[22] Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035–41.
[23] Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): An open randomised phase III trial. Lancet 2009;373(9660):301–8.
[24] Ordon M, Nam RK. Lymph node assessment and lymphadenectomy in prostate cancer. J Surg Oncol 2009;99: 215–24.
[25] Yu CX, Tang G. Intensity-modulated arc therapy: Principles, technologies and clinical implementation. Phys Med Biol 2011;56:R31–54.
[26] Nguyen PL, D'Amico AV. Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer despite two negative randomized trials. J Clin Oncol 2008;26:2055–6; author reply 2056–7.
[27] Roach M, 3rd. Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer, and confusion about the results of the randomized trials. J Clin Oncol 2008;26:3816–7; author reply 3817–8.
[28] Wang D, Lawton C. Pelvic lymph node irradiation for prostate cancer: Who, why, and when? Semin Radiat Oncol 2008;18:35–40.
[29] Kim BS, Lashkari A, Vongtama R, Lee SP, Parker RG. Effect of pelvic lymph node irradiation in salvage therapy for patients with prostate cancer with a biochemical relapse following radical prostatectomy. Clin Prostate Cancer 2004;3:93–7.
[30] Williams SG, Taylor JM, Liu N, Tra Y, Duchesne GM, Kestin LL, et al. Use of individual fraction size data from 3756 patients to directly determine the alpha/beta ratio of prostate cancer. Int J Radiat Oncol Biol Phys 2007;68: 24–33.
[31] Arcangeli G, Saracino B, Gomellini S, Petrongari MG, Arcangeli S, Sentinelli S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2010;78:11–8.
[32] Lennernas B, Nilsson S, Levitt SH. Hypofractionation for radiotherapy of prostate cancer using a low alpha/beta ratio – possible reasons for concerns? An example of five-dimensional radiotherapy. Acta Oncol 2011.
[33] Miles EF, Lee WR. Hypofractionation for prostate cancer: A critical review. Semin Radiat Oncol 2008;18:41–7.
[34] Lane JA, Hamdy FC, Martin RM, Turner EL, Neal DE, Donovan JL. Latest results from the UK trials evaluating prostate cancer screening and treatment: The CAP and ProtecT studies. Eur J Cancer 2010;46:3095–101.
[35] Ljung G, Egevad L, Norberg M, de la Torre M, Holmberg L, Busch C, et al. Assessment of proliferation indicators in residual prostatic adenocarcinoma cells after radical external beam radiotherapy. Prostate 1996;29:303–10.
[36] Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: Results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002;53:1097–105.
[37] Zietman AL, DeSilvio ML, Slater JD, Rossi CJ, Jr., Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA 2005;294:1233–9.
[38] Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007;8:475–87.

[39] Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006;24:1990–6.

[40] Vance W, Tucker SL, de Crevoisier R, Kuban DA, Cheung MR. The predictive value of 2-year posttreatment biopsy after prostate cancer radiotherapy for eventual biochemical outcome. Int J Radiat Oncol Biol Phys 2007;67: 828–33.

[41] Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. J Urol 2008;179:1368–73; discussion 1373.

[42] Coquard R. Re: Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer: Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A. J Urol 2008;179:1368–73. J Urol 2008;180:2258; author reply 2258.

[43] Solberg A, Haugen OA, Viset T, Bergh A, Tasdemir I, Ahlgren G, et al. Residual prostate cancer in patients treated with endocrine therapy with or without radical radiotherapy: A side study of the SPCG-7 randomized trial. Int J Radiat Oncol Biol Phys.