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PII: S0959-8049(99)00213-0

Arbiter:

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INTRODUCTION

RADICAL PROSTATECTOMY is the accepted standard treatment in the management of localised prostate cancer, clinically classified T1–2 (cT1–2), all the more as individual prostate specific antigen (PSA) screening is gaining in popularity [1]; this procedure was recommended by the National Cancer Institute (NCI) Conference Consensus meeting [2] in men under 75 years of age with a World Health Organisation (WHO) performance status lower than 2, provided pelvic lymphadenectomy made beforehand is negative on frozen sections. Nomograms taking into account clinical tumour stage, Gleason score, and baseline PSA, may assist physicians in predicting organ-confined disease [3]. Since three-dimensional conformal therapy with high-dose and high precision can provide results as good as those given by radical surgery [4] with regard to disease-free survival (biochemically defined) [5], concertation and a multidisciplinary approach between urological surgeons and radiation oncologists has to be reinforced to optimise the therapeutic choice. After radical prostatectomy, pathological analysis of resected tissue reveals that in 30–50%, the tumour has extended beyond the prostate, giving rise to pathological stage T3 (pT3) [6–8]. Capsule perforation, positive surgical margins, and invasion of seminal vesicles, represent criteria of high risk of local relapse either isolated or intercorrelated [9]: the definition of such criteria are linked to the quality assurance of the pathological assessment which improves the accuracy and validity of the pathological diagnosis [10]. pT3 patients have a risk of local relapse associated with significant morbidity and this risk may be the source of distant metastases: external irradiation, effective on infra-clinical disease, has been proposed to reduce this risk. There are two modalities of postoperative external irradiation: adjuvant in case of high risk of local failure or clinical evidence of tumour persistence, and therapeutic in case of documented local recurrence. In the present issue, two outstanding urological surgeons give their opinions on the role of postoperative external irradiation. Boccon-Gibod and colleagues advise irradiation only in the presence of a documented failure, but not immediately after surgery to avoid overtreatment and complications. Van Poppel and associates give updated data and recommend immediate postoperative irradiation as it increases local control. As radiation oncologists, we will try to give our point of

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Received 12 Apr. 1999; accepted 9 Aug. 1999.

view, limiting the discussion to stages cT1–2 N0, pT3 pN0 after surgery; we will not discuss stages pT3N1, which concern patients who have a more locally advanced disease, which requires either adjuvant hormonal treatment [11] or a combination of external irradiation and long-term hormonal adjuvant treatment [12].

PREDICTORS OF LOCAL FAILURE

Both authors have highlighted predictors of local relapse such as histological grade, positive margins (including apex) and baseline PSA. In a multivariate retrospective analysis including 273 cases, poorly differentiated histology ($P = 0.0007$), positive margins ($P = 0.0015$) and elevated acid phosphatase ($P = 0.02$) were significant predictors, while seminal vesicle involvement was the only predictor for distant metastases ($P = 0.0019$) [13]. In a more recent series of 423 cT1–2 cases, baseline PSA levels ($P = 0.005$), Gleason score from the surgical specimen ($P = 0.002$) and positive surgical margins ($P \leq 0.001$) independently predicted biochemical relapse [14]. Bruce and Lieberman [15] have identified two groups with significantly different risks of tumour progression ($P < 0.0001$): a low risk group including pT3a and pT3b with Gleason scores of 6 or less, baseline PSA levels of less than 10 ng/ml and no more than one positive margin: with a median follow-up of 45 months, the crude PSA recurrence rate was 9% (4/47) and there was no tumour progression; and a high risk group including all other pT3a and pT3b–c patients, which is associated with a PSA recurrence rate of 44% (30/68) and a tumour progression rate of 12% (8/68).

RESULTS, MODALITIES, ONGOING TRIALS OF POST-OPERATIVE EXTERNAL IRRADIATION

Updated results in favour of irradiation are mentioned by Van Poppel and associates [16]; we will only add pooled data published between 1985 and 1987 [17]: the overall local recurrence rate was 23% (166/716) when there was no irradiation after radical prostatectomy versus 3% in cases of postoperative irradiation (7/227). However, postprostatectomy radiation therapy after local recurrence required a higher dose, and had an increased risk of morbidity, for a higher relapse rate (30%).

Adjuvant irradiation with a high energy photon beam (6–25 MV) should be started once the patient has fully recovered his urinary function preferably 3 months and at the latest 4 months after surgery, to avoid neoplastic cell repopulation. The planning target volume, based on the preoperative imaging data computed tomography (CT) scan or magnetic resonance imaging (MRI) and the location of the surgical clips, is limited to the prostatic fossa and its immediate vicinity without encompassing the regional lymph nodes. Three or four fields can cover this volume with a security margin ranging between 1 and 2 cm, well visualised on a planning CT scan. Special care has to be taken to exclude normal structures not considered to be at high risk of tumour infiltration such as the small bowel, posterior rectal wall, and part of the bladder which for the last part of the treatment should be shielded with customised cerrobend blocks or by multileaf collimators [18, 19]; fields averaging 10×10 cm are sufficient to encompass the above-mentioned volume and particularly the apex in case of involvement. A dose of 46–50 Gy is delivered to this target volume, followed by a boost of 10–14 Gy on a reduced volume (8×8 cm) to bring the total dose up to 60 Gy, which is effective to control infraclinical disease [20]. Patients are treated in supine position without an immobilisation device, once a day, five fractions per week, 2 Gy per fraction, for 6 weeks.

Only a randomised trial can demonstrate a measurable benefit of this combination in cT1–2 N0, pT3 pN0 patients after radical retropubic prostatectomy, who present at least one of the following criteria on a well defined step section protocol: complete capsule invasion (perforation), positive surgical margins (microscopic or macroscopic), invasion of seminal vesicle(s), with an interval of no longer than 16 weeks between surgery and the onset of radiotherapy. In the EORTC trial 22911, a joint study between the Radiotherapy and the Genito-Urinary Cooperative Groups set up in 1992, the 'no further treatment arm' consists of a 'wait and see' policy—where radiotherapy will be delayed until the appearance of symptoms of local failure—and 'the treatment arm' consists of a postoperative irradiation as described above. Our aim is to detect an absolute difference of 7.5% in the 5-year disease-free survival rate from 60 to 67.5%. The sample size is 1000 patients and 440 patients would need to be observed to guarantee 80% power to the two-sided final test; more than 730 patients have been entered so far [21].

LATE TOXICITY

As usual, the likelihood of late toxicity depends on the expertise of the radiation team and its quality assurance; the radiation technique, the magnitude of the planning target volume, and the total dose are relevant parameters. Recent data from Van Cangh and associates [22] concerning 100 patients included in the randomised EORTC trial 22911 [21] shows no difference in complete urinary continence between 48 patients who received radiotherapy and 52 patients who did not, with a median follow-up of 24 months: 80 patients were dry with no difference between irradiated (77%) and non-irradiated (83%) patients ($P = 0.6$); besides there were no major complications, in particular anastomotic strictures. Small bowel toxicity, usually moderate, is seen in 5–10% of patients [23]; genital and lower extremity oedema is seen in patients who have full pelvic irradiation and do not comply with patients who have conservative fields [23].

CONCLUSION

For cT1–2 patients, pT3 pN0 after radical prostatectomy, postoperative radiation therapy can be delivered with acceptable long-term morbidity provided modest dose, high energy beams and conservative fields are used: it significantly improves local control, but a potential impact on disease-free survival remains to be proven through the EORTC randomised trial. Meanwhile, from a public health point of view the following indications may be recommended in daily practice: (1) patients with capsular penetration and negative margins should be followed clinically and biologically with PSA; should a documented local relapse occur, proven by biopsy of the urethro-vesical junction (biochemical relapse) or of a palpable nodule, irradiation has to be delivered up to 70 Gy. (2) patients with evidence of extracapsular extension and/or positive margin should receive postoperative radiation therapy; and (3) patients with seminal vesicle involvement can be considered candidates for postoperative radiation therapy, although they are at risk of systemic relapse; it is likely that the results of randomised trials will indicate the need for a systemic adjuvant treatment to eradicate infra-clinical disease outside the pelvis.

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