Adjuvant treatment to surgery

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INTRODUCTION

Despite the recent dramatic improvements in early diagnosis and staging, a significant proportion of patients with clinically localized prostate cancer who undergo radical surgery will ultimately experience a biochemical relapse, i.e. the reappearance of an increasing serum PSA level. This relapse can give rise to local or distant metastases, and eventually lead to death from prostate cancer. Adjuvant treatment to surgery is therefore of great importance; it can be given before or after surgery.

Adjuvant treatment given before surgery (i.e. neoadjuvant therapy) has two goals; to reduce the local tumour burden to allow more radical surgical excision, and to treat micrometastatic disease. There are two types of treatment; hormone therapy and cytotoxic chemotherapy. The main problems of neoadjuvant treatment are that patients who might not need the treatment are exposed to its side-effects, and patients given the treatment might suffer from the delay of the treatment might suffer from the delay of the treatment.

Adjuvant treatment given immediately after surgery (to be distinguished from salvage therapy given at relapse) involves radiotherapy (RT), hormone therapy, cytotoxic chemotherapy, or all three. Like neoadjuvant treatment, it might unnecessarily expose patients who do not require the therapy to side-effects.

NEOADJUVANT THERAPY BEFORE RADICAL PROSTATECTOMY (RP)

Two different approaches have been used, i.e. hormone therapy and, more recently, cytotoxic chemotherapy. Neoadjuvant hormone therapy in the form of androgen suppression by monotherapy with LHRH agonists or combined androgen blockade (CAB) became popular 10–15 years ago and has been the subject of several randomized clinical trials. Initial enthusiasm was based on spectacular reductions in the positive-margin rate and in the proportion of patients with positive lymph nodes after neoadjuvant hormone suppression compared with immediate RP. However, this approach fell into disuse because several randomized clinical trials were unable to detect a difference in the rate of ultimate PSA relapse. The apparent discrepancy between the improvement in pathological variables associated with poor prognosis and biological outcome was probably related to the difficulty of accurately evaluating pathological specimens after hormone therapy. These observations were made after 3 months of CAB neoadjuvant to surgery, and they were repeated with longer neoadjuvant CAB of 8 months [1–4]. Neoadjuvant hormone treatment before RP cannot as yet be considered a standard of care.

Neoadjuvant cytotoxic chemotherapy has been investigated with increasing interest since positive results were achieved with docetaxel in hormone-resistant prostate cancer. Two studies were published [5,6]; one investigated docetaxel and dexamethasone with or without estramustine neoadjuvant to RP, in five cycles of 3 weeks. None of the RP resections showed a pathological complete response, and the main side-effect was a risk of deep venous thrombosis probably related to the estramustine phosphate [5]. Another study using a combination of docetaxel and dexamethasone from 6 weeks to 6 months documented a reduction in PSA level (34% 2 months after treatment [6] and 50% after 3 weeks [5]) with a 25% median reduction in prostate volume. However, again no pathological complete response was documented [5,6]. Surgery does not appear to have been easier or more difficult than usual. Neoadjuvant CAB with or without docetaxel is being studied in phase II protocols. Until the results are available, neoadjuvant cytotoxic chemotherapy with or without hormone suppression must not be used outside carefully designed randomized clinical trials.

ADJUVANT THERAPY

Adjuvant therapy to RP has two goals; to treat local residual disease by RT, and to treat micrometastasic disease by hormone therapy, cytotoxic chemotherapy, or both. Adjuvant therapy is usually administered after surgery on the basis of pathological or biological risk factors, and should be distinguished from salvage therapy given at clinical or biochemical relapse. The main advantage of adjuvant over salvage therapy is that it represents an early intervention at a time when residual disease is presumably at its lowest volume. The disadvantage is the risk of ‘overkill’, a substantial proportion of patients who might not need any kind of adjuvant therapy are unnecessarily exposed to the potentially serious side-effects.

Many phase II studies of adjuvant and salvage RT have been published, but only three available randomized clinical trials compared observation with adjuvant RT after RP in patients considered to be at high risk of biochemical, clinical, local or distant relapse [7–9]. These three trials all showed that compared with patients who underwent observation, those who received adjuvant RT had a three-fold increase in PSA relapse-free survival (10.3 years for RT vs 3.1 years for observation; hazard ratio 0.43, P < 0.001). This benefit translated into a 39% increase in the time to local disease recurrence [13.8 years for RT vs 9.9 years for observation; hazard ratio 0.62, P = 0.001] but, unfortunately, did not translate into a significant increase in metastasis-free overall survival [9]. It is too early to know whether this improved biochemical relapse-free survival will translate into improved overall and cancer-specific survival. It should also be appreciated that adjuvant RT has some side-effects; these were considered minimal in the European Organization for Research and Treatment of Cancer study [7], but side-effects in randomized clinical trials, in which patients are treated under strict conditions, might differ from those seen in the community. Indeed, the CaPSURE study showed that the side-effects of adjuvant therapy are not negligible, particularly for bowel function, continence and bladder function [10].

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The aim of adjuvant intermittent androgen suppression after RP has proved or disproved the benefits of early androgen suppression in patients undergoing RP for high-risk disease. However, randomized clinical trial data indicate that early androgen suppression after RP can only be recommended when positive lymph nodes are present. One placebo-controlled trial (98 patients with node-positive disease who had RP) showed better overall survival with early androgen suppression than with delayed therapy at a median follow-up of 11.9 years (65% vs 45%) and better prostate cancer-specific survival (85% vs 51%) (Fig. 1) [11]. However, this study, with <100 patients, was small; as yet, no large randomized clinical trial has proved or disproved the benefits of early vs delayed androgen suppression after RP.

The aim of adjuvant intermittent androgen suppression is to reduce the side-effects of medical or surgical castration, such as anaemia, muscle loss, reduced bone mineral density, and, most importantly, metabolic syndrome. In preventing side-effects, intermittent androgen suppression is undoubtedly beneficial [12], but its equivalence to continuous therapy in terms of cancer control has yet to be confirmed.

Adjuvant hormone therapy with nonsteroidal androgens has been the subject of one of the largest ever double-blind randomized placebo-controlled clinical trials, which involved 8113 patients with localized or locally advanced nonmetastatic prostate cancer. The Early Prostate Cancer programme compared placebo with immediate treatment with bicalutamide, 150 mg/day, in addition to standard care including RP (4454 men). It comprised three parallel trials: one in North America, where most patients had RP as standard care; one in Europe, South Africa, Australia, Israel and Mexico, where patients had RP, RT or watchful waiting; and a specifically Scandinavian trial, associated with the second trial, in which most patients were observed. In the North American arm of the trial (3292 men, of whom 80% had RP and 20% RT) [13], there was no difference between bicalutamide and placebo in addition to standard care in terms of overall survival and clinical progression. However, the use of bicalutamide resulted in a 20% increase in the time to biochemical relapse at a median of 7.7 years of follow-up (P < 0.001). Whether this difference will result in improved overall and cancer-specific survival remains unknown, because PSA relapse per se is not considered a reliable surrogate endpoint. In the arm of the trial conducted in Europe, South Africa, Australia, Israel, and Mexico (3603 patients, 44% having RP) [14], again patients receiving bicalutamide adjuvant to standard care had a significantly better (P < 0.001) objective progression-free survival than did those receiving standard care alone at a median 5.1 years of follow-up. However, there was no difference (P = 0.746) in overall survival. This finding might be related to a slight shortfall in overall survival in the treatment arm, reflecting the trend observed in the Scandinavian trial, probably due to an increase in the non-cancer-related death rate that has yet to be explained [13]. In an overall analysis of the Early Prostate Cancer programme [15], there was no overall survival benefit to adjuvant bicalutamide at a median follow-up of 7.4 years in the subgroup having RP (Fig. 2). Although not considered a reliable surrogate endpoint, progression-free survival was significantly better in patients with locally advanced disease who received adjuvant bicalutamide than in those who received standard care alone. Although adjuvant hormone therapy might be considered the standard of care in node-positive disease, the same is not true in other settings.

Finally, adjuvant cytotoxic chemotherapy, which comprises mostly docetaxel-based regimens, must not be used outside well-designed randomized clinical trials, many of which are open or soon to be opened.

**FIG. 1. Kaplan–Meier curves for a, overall survival and b, prostate cancer-specific survival by intention-to-treat analysis. ADT, androgen-deprivation therapy. Reproduced from Messing et al. [11]. Copyright 2006, with permission from Elsevier.**

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<th>Patients (%)</th>
<th>Log-rank P</th>
<th>Hazard ratio</th>
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<tr>
<td>Immediate ADT</td>
<td>0.04</td>
<td>1.84 (95% CI 1.01–3.35)</td>
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<td>Observation</td>
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<td>&lt;0.001</td>
<td>6.09 (95% CI 3.17–11.73)</td>
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FIG. 2. Results from the Early Prostate Cancer programme [trials 23, 24 and 25]. Forest plot showing the hazard ratios and CIs for overall survival and objective progression-free survival in the subgroup of patients who had RP, comparing bicalutamide with placebo. From McLeod et al. [15] with permission, ©Blackwell Publishing.

but receive no tangible benefits [16]. It might be argued that treatment should not be decided before PSA relapse occurs, and when PSA relapse does occur, treatment could be withheld until the PSA kinetics are accurately determined. Thus, only patients with short PSA doubling times would be exposed to the benefits and risks of treatment [17].

In clinically localized prostate cancer, the real impact of adjuvant treatment to RP on overall survival remains to be determined. It is sobering that, in 10 years of experience of RP in the Cleveland clinic, the overall survival of patients who had RP was similar whether or not they had had biochemical relapse and whether or not the biochemical relapse was treated immediately or later. This was true in patients at low or high risk of recurrence [18].

CONCLUSIONS

The following can be concluded about adjuvant treatment to radical surgery.

- Neoadjuvant hormone treatment before radical surgery has not, as yet, been shown to improve clinical progression or overall survival.
- Neoadjuvant cytotoxic chemotherapy before RP should not be used outside randomized clinical trials.
- Adjuvant RT improves biochemical relapse-free survival after RP, but its impact on overall survival remains to be determined.
- The only evidence-based indication for adjuvant hormone therapy after RP is in patients with node-positive disease.
- The real impact of adjuvant treatment to radical surgery remains to be determined.

CONFLICTS OF INTERESTS

The author has declared no conflicts of interests.

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Abbreviations: CAB, combined androgen blockade; RP, radical prostatectomy; RT, radiotherapy.