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Current Controversies in Cancer

Is Postoperative Irradiation after Radical Prostatectomy Necessary?

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INTRODUCTION

IN THE past two decades in the European Community and the U.S.A. there has been a sharp increase in the number of patients diagnosed with adenocarcinoma of the prostate (CaP) and an increase in the proportion of patients diagnosed with capsule confined tumours [1]. At the same time, major improvements in surgical techniques resulted in a higher probability of tumour control, improved survival and a better quality of life of treated patients [2–4]. The 5-year survival rates for caucasian CaP patients in U.S.A. in the early 1960s was 50% and it has increased to 73% in the early 1980s [1]. These factors helped to increase the acceptance of radical prostatectomy to become the most widely applied definitive therapy for patients with localised CaP. This increase in the incidence of the use of radical prostatectomy is apparent for all age groups and is particularly high (70%) in younger (< 55 years of age) patients [5].

Since the routine use of prostate specific antigen (PSA) after surgery, it has become obvious that complete tumour eradication is less commonly achieved than expected. Indeed, in spite of major advances in prostatic imaging modalities and the use of PSA, accurate preoperative staging remains an elusive goal [6]. In some published reports, over 50% of radical prostatectomy patients have pathological evidence of extracapsular tumour spread or the presence of positive surgical margins [7]. The presence of pT3 disease is of major importance since most of these patients eventually have a local recurrence or systemic disease manifested most frequently by PSA elevation [8].

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The most important factor responsible for treatment failure is the underestimation of the primary tumour, which although clinically locally confined, proves to be extraprostatic on pathological examination [9]. Local failure can lead to recurrent local tumour that can be responsible for progression and death. Distant spread can also be present at the time of surgery without being recognised. In both situations, one could find a rationale for adjuvant treatment, but the indication for adjuvant therapy after radical prostatectomy on the basis of the pathology of the resected specimen remains controversial. Whereas the presence of distant disease usually indicates the institution of systemic therapy, the presence of suspected localised persistent disease presents a therapeutic dilemma [10].

THE ROLE OF ADJUVANT RADIOTHERAPY AFTER RADICAL PROSTATECTOMY

The aim of giving early (within 3 months) radiotherapy after radical prostatectomy is the destruction of remaining malignant cells that will—if untreated—be a source of local recurrence which in turn can be the origin of systemic failure [11]. The presence of a local recurrence is a clinically relevant problem, since uncontrolled disease is frequently responsible for a sharp decrease in the patient's quality of life. In spite of the major clinical relevance of local recurrence following radical prostatectomy no randomised studies addressing the possible advantage of postoperative radiotherapy are available at this time. All available data on the efficacy of postoperative radiotherapy are based on multiple retrospective or prospective non-randomised studies [11, 12].

Adjuvant treatment after radical prostatectomy can be considered as elective if administered when there is a high

risk of recurrence i.e. positive surgical margins or the presence of extracapsular disease without biochemical or clinical evidence of tumour persistence or recurrence. Adjuvant treatment is considered as therapeutic if PSA failure occurs or if local recurrence is documented [12]. We would like to argue for a recommendation of planned adjuvant radiotherapy in the early postoperative period in selected patients who are at a high risk of local recurrence.

POSTOPERATIVE RADIOTHERAPY FOR PROSTATE CANCER WITH EXTRACAPSULAR EXTENSION (pT3)

Patients with pT3 prostate cancer have a higher risk of local relapse and cancer related death than those with pT2 tumours [13]. Retrospective, non-randomised studies, strongly suggest that early postoperative irradiation significantly decreases the local recurrence rate compared with the incidence of local recurrences in patients treated with surgery alone over the same time period [11, 14–18]. In studies, published in the 1990s the local relapse rate in patients with pT3-4N0-1 disease varies between 21 and 40% after surgery alone and between 0 and 8% after surgery followed by radiotherapy [19–23]. Although these differences were statistically significant, they did not translate into significantly different disease-free survival or overall survival rates, probably due to the small number of patients and the inclusion of patients with very high risk factors for micrometastatic disease at the time of diagnosis, i.e. positive seminal vesicles and positive lymph nodes [24]. The retrospective studies also showed that radiotherapy was less effective, in terms of local control, when the treatment was delayed till the appearance of a clinically evident recurrence [11, 14–18] while toxicity was increased, due to the higher doses necessary [25].

A recent single centre review on more than 200 unselected pT3 patients with a median follow-up of 5 years treated with a median dose of 48 Gy only, demonstrated excellent 5- and 10-year overall survival rates (93 and 83%), comparable with that of an age matched male population [18]. Adverse prognostic factors which were identified in pT3 patients include: high Gleason's score, seminal vesical invasion, and high (> 25 ng/ml) preoperative PSA. A recent update to the above study based on adjuvant radiotherapy in 311 patients helped to validate those data [26]. A non-randomised comparison of selected patients treated with radical prostatectomy with or without adjuvant pelvic irradiation is of some interest [27]. The selection process was based on the two study surgeon's impressions of the likelihood of local recurrence. Patients who did not receive a planned course of adjuvant radiotherapy, although presenting with significantly less advanced disease ($P = 0.001$) including a lower mean preoperative PSA ($P = 0.0001$), had twice the incidence of local recurrence when compared with those treated with adjuvant radiotherapy [27]. The conclusion that local radiotherapy only improves local control in stage pT3 cancer without an impact on overall and disease-free survival cannot be drawn until the results of prospective studies become available. Based on the published data and the authors' personal experience and in the absence of relevant prospective randomised trials it appears reasonable to offer postoperative radiotherapy to high risk pT3N0 patients.

POSTOPERATIVE RADIOTHERAPY FOR MARGIN-POSITIVE DISEASE

A broad radical excision of a malignant prostate is difficult because of its relationship to the surrounding vulnerable structures [28]. The occurrence of positive surgical margins is mostly due to the tumour extent outside the prostatic capsule and it is more frequently found in patients with poorly differentiated tumours [29]. Sometimes inadvertent incision of the prostate capsule or the performance of nerve sparing surgery can result in positive surgical margins [12, 30]. Positive surgical margins are not an uncommon feature of radical prostatectomy and in patients with clinical T2 cancer 10–40% of patients have tumour cells at the inked edge of the specimen [31]. Van den Ouden and associates showed that positive and negative margins are independent factors influencing the time to progression [32]. They also found that positive margins at the level of the prostatic apex did not influence the time to tumour progression, This could probably be due to the difficulties with the definition of the apical margins [32]. The impact of positive margins on survival is relevant since the 10-year recurrence rate is estimated at 80% while in patients with specimen confined disease a 90% 10-year survival is reported with only a 40% recurrence rate [33].

Until now, the usefulness of radiotherapy for patients that have positive surgical margins has not been evaluated in controlled randomised trials and most published reports on adjuvant radiotherapy are not providing PSA information and other important relevant data to evaluate the outcomes. When adjuvant radiotherapy is considered for patients with positive margins one should select a group of patients with a low risk of systemic micrometastasis and a high risk for local recurrence. A multivariate analysis of the factors predictive for local recurrence showed tumour grade and surgical margin involvement to be the most important prognosticators [34, 35]. It is clear that patients with positive surgical margins

Table 1. *Actuarial PSA-free survival after radical prostatectomy for clinically localised prostate cancer*

Author [Ref.]	Number of patients	Pathological status	Actuarial PSA-free survival (%)		
			4 year	5 year	10 year
Kupelian and colleagues [35]	228	Negative margins		78	
	195	Positive margins		37	
Paulson [36]	322	Organ confined		88	
	167	Specimen confined		68	
	124	Positive margins		52	
Epstein and colleagues [37]	259	Organ confined	98		85
	?	Negative margins	95		79
	142	Positive margins	74		55

have the highest rate of local recurrence. The probability of PSA failure after radical prostatectomy for clinically localised disease in three large series is shown in Table 1 [35–37]. A further detailed analysis of patients with Gleason sum 5–6 and Gleason sum 7 is shown in Table 2 [37]. The ratio of local recurrence to distant metastases after PSA failure is essentially unknown but it is estimated to be approximately one local for 3 on 4 distant recurrences [38]. This estimate is probably underscored as suggested by recent data from immunoscintigraphy [39]. This ratio will surely depend on the tumour characteristics (pre-operative PSA, Gleason's score and the surgical margin status). Assuming, however, a ratio of 1 to 3 on 4, and assuming that radiotherapy can improve a local control close to a 100%, then local pelvic irradiation would be expected to reduce the PSA failure rate by 20–25%. For patients with Gleason sum 7 and positive margins the PSA failure rate is approximately 60% at 10 years (Table 2). In this situation, adjuvant radiotherapy could improve the PSA progression-free survival rate from approximately 40 to 55%. For patients with Gleason score 5 to 6 and positive margins the rate of recurrence is nearly 30% at 10 years (Table 2). In this case the PSA-free survival rate could improve from approximately 70 to 77%.

TREATMENT RELATED TOXICITY

The dose of radiotherapy and the target volume used in the postoperative treatment remain controversial. In an adjuvant setting the total dose given to the prostate ranges between 55 and 65 Gy in 1.8–2 Gy fractions. With modern treatment techniques the side-effects of postoperative radiotherapy within this dose range are minimal [11, 18, 26, 27, 40–44]. There is, however, no need to use higher radiation doses nor to extend the target volume beyond the prostatic fossa. This was well demonstrated in large clinical studies reported from USC using even smaller doses [18, 26, 27, 40, 41] and in published experimental studies [45]. Recent publications contradict earlier statements that early adjuvant radiation therapy has significant side-effects when applied in the post-operative period and should expose treated patients to an increased risk of incontinence and strictures [40, 46]. In addition, in the authors' experience early postoperative radiotherapy is devoid of clinically important morbidity [18, 24, 26, 27, 40].

Table 2. Actuarial PSA-free survival after radical prostatectomy for localised prostate cancer without seminal vesicle and lymph node invasion [37]

Gleason score	Pathological status		Actuarial PSA-free survival (%) 5 year	10 year	
5–6	pT2	Negative margins	99	92	
					NS
	pT3	Negative margins	98	78	
					$P = 0.0009$
	pT3	Positive margins	85	72	
7	pT2	Negative margins	97	68	
					$P = 0.04$
	pT3	Negative margins	83	48	
					$P = 0.0005$
	pT3	Positive margins	50	42	

CONCLUSION

The goal of adjuvant radiotherapy after radical prostatectomy is the eradication of remaining cancer cells at the prostate bed, thereby improving legal control and more importantly preventing a secondary tumour dissemination. Retrospective series have strongly suggested that radiotherapy can improve local control in patients with high risk for local recurrence. This improvement in local control could translate into an improved disease-free and cause specific survival. This however still needs to be proven since the factors predicting local recurrence are also predictors of metastatic disease. Additionally, many metastases are known to develop concomitantly with local recurrence. Local adjuvant treatment is probably not likely to be of significant benefit in patients with evidence of seminal vesicles invasion or pelvic lymph node involvement. In patients with pT3N0 but specimen confined cancer without margin involvement adjuvant radiotherapy can be of a questionable value. However, in those with a Gleason score of 7 or less with negative nodes and negative seminal vesicles, the presence of positive surgical margins is a good indication for the early use of planned adjuvant local irradiation. The impact on cause-specific survival can be estimated to be at least 10%, depending on the subgroup of patients treated. It is well agreed that this has to be confirmed in well conducted randomised trials, which are currently underway, e.g. in the EORTC (European Organisation for Research and Treatment of Cancer) [47].

It is apparent that a gain in specific survival of 10% is worth pursuing: 10% improvement in cause-specific survival is considered to be significant by the oncological community. Moreover, properly selected patients who had a radical prostatectomy have a life expectancy of at least 10 years and reducing the psychological stress of being at risk for local recurrence is an important issue. In addition, the adjuvant radiation treatment is well tolerated in terms of acute and late toxicity, and finally is it economically sound as compared with medical and hormonal treatment for tumour recurrence.

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