Surgery alone for advanced prostate cancer?

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Introduction

Despite the successful efforts to diagnose prostate cancer at an increasingly early stage, there are still a significant number of men presenting with locally advanced disease. Locally advanced prostate cancer is defined as cancer that has extended clinically beyond the prostatic capsule with invasion of the pericapsular tissue, apex, bladder neck or seminal vesicles, but without lymph node involvement or distant metastases [1].

An important part of evaluating prostate cancer is determining the stage, or how far the cancer has spread. The most common staging system is the TNM (tumour, node, metastasis) system [2]. It includes the size of the tumour, the number of involved lymph nodes, and the presence of any other metastases. Locally advanced cancer is referred to as T3-T4 N0 M0 disease. T3 stage refers to palpable disease sufficient to indicate that the tumour has penetrated through the prostate capsule. T4 stage indicates local invasion of a structure adjacent to the prostate other than the seminal vesicle(s). N0 refers to no lymph node involvement and M0 to no distant metastasis. Local staging (T-staging) is based on the findings of digital rectal examination (DRE) and imaging modalities of which transrectal ultrasound (TRUS) is the most popular [3]. Prostate specific antigen (PSA) level and the extent of cancer in prostate biopsies and the Gleason score may provide additional information [4]. The gold standard for lymph node status (N-staging) is bilateral pelvic lymphadenectomy although computed tomography (CT) or MRI are used to show enlarged nodes. Skeletal metastasis (M-staging) is best assessed by bone scintigraphy [3]. Some methods are used to improve staging accuracy, for example endorectal coil MRI for better assessment of the seminal vesicles [5], or TRUS-guided biopsies of periprostatic tissue or seminal vesicles [6], but they are not routinely used. Correct staging of clinical T3 disease is difficult and both overstaged pathological T2 (pT2) tumours and understaged pT4 or node-positive (pN+) cases are common. Surgical series of clinical T3 cases have shown that 9–27% represent clinically overstaged pT2 disease [7–11]. In accordance with the European Association of Urology (EAU) guidelines on prostate cancer there are different treatment options available; watchful waiting, radiotherapy (RT), radical prostatectomy (RP), hormonal therapy (HT) and various combinations [3]. The objectives of treatment for T3 prostate cancer are to cure the disease, prolong survival or metastasis-free survival and improve quality of life.

There is currently no single standard of care for clinical T3 disease and there is an urgent need to determine which treatment options offer superior results in cT3 patients because if left untreated, a significant proportion of those patients will die of prostate cancer. In this manuscript we highlight the different treatment options and key studies that may provide interim answers while awaiting definitive results from randomised trials. We also aim to clarify the role of surgery as treatment option for locally advanced prostate cancer.

Different treatment options for locally advanced prostate cancer

Watchful waiting

In accordance with the EAU guidelines watchful waiting is an option for asymptomatic patients with well-differentiated and moderately differentiated T3 tumours and a life expectancy <10 years [3]. Watchful waiting can be considered as the treatment option of choice for certain patients. However, it is rarely advocated because of the high risk of metastasis and disease progression in patients with cT3 disease.

Radiation therapy as monotherapy

Until the early eighties, RT was the treatment of choice for locally advanced prostate cancer. After 10 years of follow-up, disease-free survival was 19–44% and overall survival (OS) varied between 21% and 54% [12–15]. In accordance with the EAU guidelines RT is an option for cT3 patients with a life expectancy

> 5–10 years. Randomised trials today clearly show that dose escalation is of benefit (> 70 Gy). If this is not available, a combination with HT could be recommended [3].

Outcome of cT3 disease has been improved by advances in external beam radiation therapy (EBRT) such as three-dimensional conformal RT with dose escalation and intensity-modulated radiation therapy (IMRT). High-dose rate brachytherapy is not considered effective for locally advanced prostatic disease when used alone. It must be combined with EBRT.

EBRT for T3 prostate cancer has complications such as urinary symptoms (retention, incontinence, haematuria, etc.), erectile dysfunction and rectal symptoms [16]. Thanks to the refinements in radiation techniques higher doses of radiation can be used with no increase in toxicity [17]. Outcomes for cT3 prostate cancer with these refined irradiation techniques however, are not yet available.

Hormonal therapy as monotherapy

When deprived of male hormones, the cancer cells of the prostate die and the size of the prostate shrinks. Androgen Deprivation Therapy (ADT) can be achieved by removing the testicles or by using gonadotrophin releasing hormone (GnRH) agonists that can be combined with an antiandrogen. Antiandrogens take over the cell receptors that usually respond to androgens and prevent the body from using its own androgens.

HT as monotherapy can be used for symptomatic unfit T3-T4 patients with high PSA level (> 25 ng/ml) [3]. Treatment most often consists of continuous gonadotrophin releasing hormone analogue (GnRHa) therapy, maximal androgen blockade (MAB) with a GnRHa in combination with an antiandrogen, or intermittent GnRHa treatment. However, debate continues concerning the optimal modality, timing and duration of treatment [1]. Although HT cannot cure, it will usually shrink the prostatic tumour, palliate the symptoms and delay the progression of the disease often for years [3].

Common side effects of HT are osteoporosis, anaemia, hot flushes, erectile dysfunction, muscle wasting, gynaecomastia, decline in cognitive function, depression, increase in body fat and metabolic changes [16,18].

Hormonal therapy in combination with radiation therapy

In current clinical practice, local RT (dose $\geqslant$ 72 Gy) with hormonal therapy HT is often the preferred treatment for locally advanced prostate cancer. A number of randomised phase III trials have compared RT versus RT combined with HT in patients with cT3 disease (Table 1).

A milestone study is the 22863 trial of the European Organisation for Research and Treatment of Cancer (EORTC) reported by Bolla and colleagues (2002). This study comparing RT versus RT combined with 3 years of long-term adjuvant HT (goserelin) showed a clear advantage for the combination treatment. After 5 years of follow-up, the overall survival (OS; 78% versus 62%, $P = 0.0002$), the disease-free survival (DFS; 74% versus 40%, $P = 0.0001$) and the cancer-specific survival (CSS; 94% versus 79%, $P = 0.0001$) were in favour of the combination treatment. It was the first study to report not only a 5-year disease-free survival benefit (34%) but also, more importantly, a 5-year OS advantage of 16% in favour of combined treatment of RT and HT [19]. Laverdière and colleagues (1997) and Pilepich and colleagues (2001) showed in randomised trials that the combination of RT and short-time adjuvant HT was favourable versus RT alone in locally advanced prostate cancer [20,21].

The Radiation Therapy Oncology Group (RTOG) 85–31 study showed that the combination of RT and adjuvant long-term HT (starting in the last week of RT) versus RT alone resulted in an improvement of all oncological parameters, although there was no significant OS benefit for the combined treatment group [22]. The long-term results of the RTOG 85–31 showed that at 10 years adjuvant HT after RT was associated with a reduction in disease progression and a significant improvement in absolute survival (49% versus 39%, $P = 0.002$). The adjuvant effect appeared preferentially in patients with a high Gleason score (7–10) [24]. Long-term hormones ($\geqslant$ 2 years) appeared to be more effective than short-term hormones ($\leqslant$ 6 months, typically 4 months) but the increase in 5-year OS was not significant. This was shown in the RTOG 92–02 trial [23].

In the RTOG 94–13 trial (2003) neoadjuvant HT appeared to be more effective than adjuvant HT and whole-pelvis RT appeared to be more effective than prostate-only RT [25]. Goserelin is the only LHRH agonist with a proven OS benefit when it is given as adjuvant to RT in patients with locally advanced prostate cancer [19,24]. After the publication of these trials, many considered the combination of RT and adjuvant HT the standard therapeutic choice in patients with T3 prostatic disease, although it was never shown to be superior to surgical treatment [26].

The Early Prostate Cancer (EPC) trial programme revealed that at a median follow-up of 7.4 years,

Table 1
Randomised studies of RT with or without HT (androgen ablation)

	No. of patients	Median follow-up in years	% survival	% Biochemical progression*
RTOG 85–31 [22]			8-years results	
RT/HT	477	5.6	49	
RT	468		47	
			p = 0.67	
EORTC 22863 [19]			5-years results	
RT + 3 years HT	207	5.5	78	24
RT	208		62	55
			p = 0.0002	p < 0.0001
RTOG 92–02 [23]		5.8	5-years results	
RT + 4 months HT	779		77	56
RT + 2 years HT	775		80	28
			p 0.62	p < 0.0001
RTOG 85–31 [24]		7.6	10-years results	
RT/immediate HT	488		49	19
RT/HT at relapse	489		39	
			p = 0.002	

RT: radiation therapy; HT: hormonal therapy; RTOG: Radiation Therapy Oncology Group.
*Three consecutive PSA increases, start of androgen deprivation and a PSA nadir after RT of greater than 4.0 ng/nl

bicalutamide 150 mg once daily significantly improved OS (HR 0.65; 95% CI 0.44–0.95; $P = 0.03$) in patients with locally advanced prostate cancer receiving RT. The survival benefit appears to be consistent with that seen in previous studies with goserelin [27].

It is still unsettled for how long adjuvant ADT should be given, whether it should be given before, during and or after RT, and in which dose it should be given to achieve the best possible survival benefits. Nevertheless it is clear that the ability of RT to eradicate cancer depends on the volume of the tumour at the time of treatment. One of the likely benefits of neoadjuvant ADT is tumour cytoreduction so that less mass remains to be eradicated with RT. Given the moderate results of ADT and RT, other treatment options have been explored more recently to destroy more cells, including increasing the radiation dose and adding chemotherapy. Thanks to the advances in surgical technique and the supposition that surgery might help a selected group of patients with locally advanced prostate cancer, there is also renewed interest in approaching cT3 disease with radical prostatectomy [17].

Chemotherapy

In recent years many small studies have been completed or are ongoing using neoadjuvant, concomitant or adjuvant chemotherapy with radiation for locally advanced prostate cancer. There is reason to believe that using the correct chemotherapeutics agents in this patient population may be able to improve the results of RT with or without ADT. Chemotherapeutic agents are also being considered in combination with surgery and tested in clinical trials [17].

Radical prostatectomy

The option of radical prostatectomy

The surgical treatment of prostate cancer consists of radical prostatectomy (RP), meaning the removal of the entire prostate gland between urethra and bladder, with resection of both seminal vesicles. Although laparascopic approaches are increasingly being used for management of early stage disease an open RP is preferred for locally advanced disease. The procedure is performed either using a transperineal or retropubic approach. The retropubic procedure in which the surgeon removes the prostate through an abdominal incision is more commonly performed and has the advantage that it permits sampling of the lymph nodes [3].

Until recently, surgery has been frequently discouraged for clinical T3 disease mainly because these patients have an increased risk of positive margins,

lymph node metastases or distant relapse [1]. Other reasons are the potential for incomplete excision of the tumour and the unknown morbidity of surgical therapy in these patients. Nevertheless, the EAU guidelines state that RP may be an appropriate option for selected patients with small T3 tumours, PSA < 20 ng/ml, Gleason score <8 and a life expectancy > 10 years [3]. We demonstrated in one of our series that RP is a valuable choice for T3 disease especially if the serum PSA value is <10 ng/ml [28].

T3a defined as capsular perforation and T3b defined as invasion of the seminal vesicles are extracapsular tumours. This implies that it could be more difficult to remove all the cancer. However, removal of all cancer is feasible in selected patients when performing an extensive resection of the prostate gland for which certain rules need to be applied. The operation of locally advanced T3 prostate cancer must focus on a more radical extirpation including an extensive lymph node dissection, clean apical dissection, neurovascular bundle resection at least at the tumour bearing site, complete resection of the seminal vesicles and mostly resection of the bladder neck [29,30]. With increased experience in surgery, positive surgical margin rates improved dramatically over time from 75% in 1987–1994 to 42% in 1995–1999 and 10.4% in 2000–2004 [31]. Pelvic lymphadenectomy in cT3 disease is indispensable, due to a higher risk of node-positive disease. In surgical series of cT3 disease the node-positive rate is between 27 and 41% [7,8,10]. Two of our series had a much lower rate of pN+ cases with only 11% and 8.5%, respectively, probably because of a more accurate and dedicated CT scanning of the pelvis [28,31]. We showed that CT scan and fine needle aspiration cytology increases the preoperative diagnostic accuracy of lymph node invasion [32].

Serious or life-threatening complications from RP are rare. The most common side effects are urinary incontinence and sexual dysfunction, which are highest directly after surgery and tend to improve over time. Nowadays, improvements in surgical techniques have reduced the incidence of these complications by sparing the nerves for urinary and sexual function. However in most men with locally advanced prostate cancer a non-nerve sparing RP needs to be performed [16]. Overall surgical experience in performing RP for cT3 disease is crucial and must contribute to a decreased operative morbidity and better functional results [33–35]. Furthermore it is possible to select those men who have the greatest chance of benefiting from RP. However, correct staging of cT3 disease is difficult and both overstaging pT2 and understaging pT4 or pN+ are common [36,37]. It has to be noted that misclassification is not limited to surgical patients. Not only overstaged patients (T2) are cured after surgery but also true unilateral pT3a patients benefit from RP [10,11,38]. Refusing RP as a treatment option for locally advanced prostate cancer would therefore be incorrect. Other pathologically more advanced tumours will also benefit from surgery but can often not be cured by RP alone and therefore combinations with HT and/or RT can be advocated.

Studies with radical prostatectomy as primary treatment

Although few authors have reported the treatment outcomes of surgery as a primary treatment of locally advanced prostate cancer, most of these studies support the belief that RP may be an acceptable treatment option for cT3 disease. After 5 and 10 years of follow-up the CSS after RP in cT3 disease is 85–100% and 57–91.6%, respectively [11]. The OS at 5 and 10 years is more than 75% and 60%, respectively (Table 2).

Gerber and colleagues (1997) performed a retrospective multi-institutional pooled analysis of the results of RP of 345 men with cT3 disease. The actuarial 10-year disease-specific survival for all patients treated with RP was only 57%. For men with well, moderately and poorly differentiated tumours, disease-specific survival rates at 10 years were 73%, 67% and 29%, respectively. These findings suggest that there may be a role for RP in men with cT3 disease with low to intermediate grade tumours [8].

Van den Ouden and colleagues (1998) analysed 83 patients with cT3 disease and negative lymph nodes on intraoperative frozen sections, who underwent RP monotherapy. They reported that RP alone could produce acceptable results in men with well or moderately differentiated tumours. The 5- and 10-year OS rates were 75% and 60%; the 5- and 10-year CSS were 85% and 72% [40,41]. According to our retrospective study in 158 patients, RP is a good choice for locally advanced prostate cancer, especially for men with a serum PSA value <10 ng/ml, uninvolved lymph nodes and seminal vesicles [28].

Martinez de la Riva and colleagues (2004) analysed 83 patients who underwent RP monotherapy for T3a prostate cancer and reported an OS and CSS of 97.6% and 100%, respectively at a mean follow-up of 68.7 months. The results confirm that RP as monotherapy is a curative treatment for selected locally advanced prostate cancer [9].

More recently our institution reported the results of a feasibility study (EORTC 30001) including 32 patients with locally advanced prostate cancer. The

Table 2
Schematic literature review on the outcome of surgery for locally advanced prostate cancer in different studies

Study	Survival rate by year of follow-up											
	BPFS			CPFS			CSS			OS		
	5	10	15	5	10	15	5	10	15	5	10	15
Yamada *et al.* [39] (median FU: 5.4 yr) (n = 57)	45.5 (PSA > 0.4)			81.4						91.2 (77.6 at 7.5 yr)		
Gerber *et al.* [8] (mean FU: 39 mo; median FU: 26 mo) (n = 242)				72 (meta free)	32 (meta free)		85	57				
Van den Ouden *et al.* [40] (median FU: 52 mo) (n = 83)	29 (PSA > 0.1)			59	31		85	72		75	60	
Martinez de la Riva *et al.* [9] (mean FU: 68.7 mo) (cT3 only) (n = 83)	59.8 (PSA > 0.3)						100			97.7	94.8	
Ward *et al.* [10] (median FU: 103 yr) (n = 841)	58 (PSA > 0.4)	43 (PSA > 0.4)	38 (PSA > 0.4)	85	73	67	95	90	79	90	76	53
Hsu *et al.* [11] (unilateral cT3 only) (n = 200)	59.5 (PSA > 0.2)	51.1 (PSA > 0.2)		95.9	85.4		98.7	91.6		95.9	77	

BPFS: biochemical progression-free survival; CPFS: clinical progression-free survival; CSS: cancer-specific survival; OS: overall survival; FU: follow-up; PSA: prostate-specific antigen

risks associated with RP in that study appeared moderate as only two serious toxic events were observed. The possible occurrence of complications is therefore not seen as a reason for not performing RP in locally advanced prostate cancer [42].

A few studies recently conducted in the US evaluated RP as monotherapy for locally advanced prostate cancer. Berglund and colleagues (2006) reported on the feasibility of RP as primary treatment modality for locally advanced prostate cancer, defined as clinical stage T2b or worse, PSA value > 15 ng/ml and/or a Gleason score ⩾8. A total of 281 RPs were reviewed. At a mean follow-up of 34 months 70% of the men had undetectable PSA level at the last follow-up examination. The authors reported that RP for cT2c-T3 is feasible with acute morbidity similar to that of RP for more localised disease and that short-term biochemical recurrence-free survival (BRFS) (70% at 3 years) is similar to that after combined RT and androgen ablation. They found that RP should be considered a feasible alternative to RT in healthy men with long life expectancy [43].

Secin and colleagues (2006) reported on the long-term PSA recurrence and CSS for patients with seminal vesicle invasion (SVI). Prospective data on 5377 RP were gathered. Among 4,441 eligible patients, 387 (9%) had SVI and 91 of those 387 pT3 patients had lymph node involvement (LNI) (24% N+). The authors suggested that SVI does not impact on PSA recurrence in patients who undergo RP and pelvic lymph node dissection. At 15 years approximately 33% of patients with SVI and negative lymph nodes (pT3N0) were PSA relapse-free. The 10 and 15-year CSS probabilities were 85% and 74% respectively for the entire cohort and 89% and 81%, respectively, for patients without lymph node involvement [44].

Masterson and colleagues (2005) reviewed the records of 941 men who underwent RP for clinically localised disease between 1984 and 2002. Of these men, 87 were identified with SVI. The authors reported that isolated SVI is associated with better biochemical survival rates compared with disease present at the surgical margin or involving regional lymph nodes. There is also a longer interval to biochemical failure in these patients [45].

Until now published data on treatment outcomes in patients with cT4 prostate cancer were non-existent. For the period of 1995 to 2001, data from the Surveillance Epidemiology and End Results (SEER) database were analysed for 1093 patients with cT4 M0 prostate cancer without distant lymph node involvement or a history of other cancer. It has to be noted that of the 72 patients who underwent RP for cT4 disease, only 31 patients (43%) had pT4 disease, 24 patients (33%) had pT3 or lower and the pathological stage remained unknown for 17 patients (24%). The SEER data revealed that patients who underwent RP for cT4 prostate cancer had a better survival then those who received HT alone or RT alone and a comparable survival as those who received combined RT and HT. Adjuvant treatment after RP did not appear to improve survival for cT4 patients. The benefit of RP was most pronounced in a relatively small group of patients (7%) who had limited regional lymph node invasion [46]. In another recent US study more than half (52%) of the 112 patients treated with RP monotherapy for cT3 disease remained free of disease recurrence. The authors reported that RP is an excellent treatment option for selected patients with cT3 disease with a disease specific survival at 10 years of 85% [47].

Can other treatment options improve the results of radical prostatectomy?

Some locally advanced prostate cancers will not be cured by RP alone and therefore combinations of RP with HT and RT have been used. Studies have tried to elucidate whether neoadjuvant (chemo)-HT, adjuvant/salvage (chemo)-HT and adjuvant/salvage RT can improve the results of RP.

Neoadjuvant hormonal therapy and prostatectomy

Neoadjuvant therapy is defined as therapy given prior to definitive local curative treatment (e.g. surgery or radiation therapy). The rationale of neoadjuvant therapy prior to RP is to shrink the tumour, reduce the number of positive margins and reduce both local recurrence and distant metastasis.

Several randomised phase III studies evaluating short-term neoadjuvant HT (6 weeks-4 months) prior to RP demonstrated a reduction in the rate of positive margins [48–53]. Follow-up of these randomised studies showed that this favourable finding did not translate into reduced PSA failure rates after 3–5 years of follow-up [54–57]. Since none of these trials studied OS, the impact of neoadjuvant HT on survival remains unclear.

The Southwest Oncology Group study SWOG-9109, a phase II feasibility study evaluating 4 months of neoadjuvant HT prior to RP for locally advanced prostate cancer showed optimistic results. The clinical stage distribution was T3 in 97% and T4 in 3% of the cases. Fifty-five (90%) of the 61 patients underwent RP after neoadjuvant HT. Before RP, there was a tumour size reduction in 98% and an undetectable PSA (<0.1 ng/ml) in 55% of the patients. 31% of

patients had SVI (pT3b) and 19% had lymph node metastasis (pN1). The positive margin rate of 30% was remarkably low. The 5-year progression-free survival and OS rates were 70% and 90%, respectively. The authors concluded that 4 months of neoadjuvant HT prior to RP is reasonable and appropriate for cT3 disease [58].

In a large retrospective study reported by Ward and colleagues (2005), neoadjuvant HT given to 21% of the study cohort had little effect on grade, stage or rates of margin positivity and did not influence progression-free survival or CSS. Both in the neoadjuvant HT group and the nontreated group, the positive margin rate was 56% ($P = 0.97$) [10].

Hsu and colleagues (2006) reported the results from 235 cT3 patients of whom 200 were not treated before surgery with neoadjuvant ADT and 35 were. They concluded that 6–12 weeks of neoadjuvant ADT can decrease tumour size but it does neither reduce the positive surgical margin rate nor the survival rate in unilateral cT3 disease [31].

Carver and colleagues (2006) reported the results from 176 cT3 patients of whom 64 (36%) had received neoadjuvant HT before RP. Positive surgical margins were present in 27 (24%) men in the RP monotherapy group and in 20 (31%) in the neoadjuvant HT group. Patients did not benefit from neoadjuvant HT with respect to disease recurrence [47].

With these results in mind, neoadjuvant ADT cannot be recommended in patients with cT3 disease for routine clinical use prior to RP. This does however not mean that a selected patient cannot benefit and the idea of ADT prior to RP for locally advanced prostate cancer needs to be studied further [59].

Adjuvant hormonal therapy or adjuvant/salvage radiation and prostatectomy

Adjuvant treatment is defined as either RT or HT given within 90 days after RP. Salvage treatment is defined as either RT or HT given postoperatively after 90 days [10].

Adjuvant hormonal therapy and prostatectomy

The administration of adjuvant HT after RP has shown since many years to be beneficial to the control of T3 disease, especially in poor prognosis pT3 patients [28]. Despite this there is no proof from randomised studies for a general benefit of ADT after RP. A delay in progression from adjuvant HT after RP may be seen for specific subgroups of patients; pN+; pT3–4pN0; pT1b-4, N0–1M0 [60].

RP with adjuvant HT resulted in excellent long-term survival rates and low treatment related morbidity in two studies in which approximately 30% of patients had node-positive disease [7,61]. Ward and colleagues (2003) reported that RP combined with early adjunctive HT for lymph node-positive cases is superior to all other forms of therapy and should be considered the standard of care [26].

A small randomised study with 98 patients with minimal lymph node disease and a median follow-up of 7 years, showed superiority of immediate adjuvant HT (goserelin or orchiectomy) versus deferred ADT after RP concerning disease-specific survival and OS. So far the results of this study have not been confirmed in other trials [62]. It has to be noted that this study included stage T1-T2 patients and that all patients were node positive [63]. Wirth and colleagues (2004) compared in a randomised multicentre study with median follow-up of 6 years, the outcome of the antiandrogen flutamide after RP versus no adjuvant HT after RP in 309 patients with locally advanced, lymph node-negative prostate cancer. Although having some effect on disease recurrence adjuvant flutamide did not improve OS after RP [64].

The Early Prostate Cancer (EPC) trial programme reported that in patients with locally advanced disease (T3–4, any N, or any T, N+, all M0) at a median follow-up of 7.4 years, adjuvant bicalutamide 150 mg daily after RP improved progression-free survival, but did not result in an OS benefit [27].

In conclusion, in lymph node-positive pT3 cases, adjuvant ADT seems to prolong survival, which it does not in lymph node-negative pT3 disease [60].

Adjuvant/salvage radiation therapy and prostatectomy

The larger the tumour the more difficult it is to eradicate the cancer by radiation. The benefit of RP is that the greatest bulk of the tumour is removed and only microscopic disease would remain that can be more easily eradicated by RT.

Early and late adjuvant RT has been used for years [65,66]. Postoperative RT gave a lower risk of local relapse when compared to surgery only. Two randomised studies from EORTC and SWOG showed a clear advantage of the combination of RP and RT above RP alone in high-risk patients [67,68].

In the large EORTC 22911 study Bolla and colleagues (2005) compared postoperative RT ($N = 502$) with RP alone ($N = 503$) for pN0M0 patients with one or more pathological risk factors: capsule perforation, positive margins and/or seminal vesicle invasion.

Postoperative RT consisted of 60 Gy conventional irradiation delivered over 6 weeks. Adjuvant immediate postoperative RT improved biochemical progression-free survival (74% versus 52.6%, $P < 0.0001$) within a follow-up period of 5 years. No difference in OS has been observed to date. The rate of 5-year grade 3 toxic effects was 2.6% in the no further treatment group and 4.2% in the postoperative RT group ($P = 0.0726$). No grade 4 toxic effects were reported [67].

In the SWOG 8794 study updated and published by Thompson and colleagues (2006) postoperative RT was compared with RP alone. In total 425 men with pathologically advanced prostate cancer were randomly assigned to receive 60–64 Gy of postoperative EBRT ($N = 214$) or usual RP plus observation ($N = 211$). Median follow-up was 10.6 years. Adjuvant postoperative RT significantly reduced risk of PSA relapse and disease recurrence but there were no significant between-group differences for overall survival [68].

Adjuvant radiotherapy after RP in pT3N0M0 patients improves biochemical and clinical progression-free survival [60]. Phase III trials comparing postoperative RT with or without 6 months total androgen blockade are underway.

Many clinicians choose to offer salvage RT rather than adjuvant RT for those patients who develop biochemical recurrences after RP. The Stephenson data delineate who may benefit from salvage RT for prostate cancer recurrence [69].

Adjuvant hormonal and adjuvant/salvage radiation therapy and prostatectomy

In a large single-institution retrospective study with a follow-up of 15 years reported by Ward and colleagues (2005), a substantial portion of the patients with pT3 disease (78%) received adjuvant or salvage treatment (HT, RT or both) at some point after RP. The study demonstrates the effectiveness of RP in a multi modal setting for cT3 prostate cancer in 842 patients, with 5-, 10- and 15-year progression-free survival rates of 85%, 73% and 67% respectively. The respective CSS rates were 95%, 90% and 79%. Clinical overstaging occurred in a significant portion of hormone-naïve patients (27%). For these patients monotherapy with RP was potentially curative. The combination of RP with adjuvant or salvage treatment achieved very good long-term survival rates. The authors reported that RP as part of a multimodality treatment strategy offers for cT3 patients' cancer control and survival rates similar to those reached with cT2 patients. Complications and incontinence rates in cT3 patients are also similar to those previously reported for patients with cT2 disease undergoing RP [10].

Recently our institution reported the outcome of RP in 200 patients with clinical unilateral T3a prostate cancer. Lymph node status was pN1 in 8.5% of the patients. Five and 10-year survival rates were: biochemical progression-free survival (BPFS), 59.5% and 51.1%; clinical progression-free survival (CPFS), 95.9% and 85.4%; cancer-specific survival (CSS), 98.7% and 91.6%, and overall survival (OS), 95.9% and 77.0%, respectively. These findings demonstrate that in a well-selected patient group with locally advanced prostate cancer, RP – with adjuvant or salvage treatment when needed – can yield very high long-term cancer control and survival rates. Margin status and cancer volume were significant independent predictors in BPFS and CPFS, respectively. Similar good long-term survival rates as in our trial were achieved in the study of Ward and colleagues (2005). In this study 78% of patients received adjuvant or salvage treatment, while this was 56% in our study. Both studies confirm the need of multimodality treatment in a considerable number of patients [11]. Gontero and colleagues (2006) reported that RP is technically feasible even in any clinical T extension up to M1a disease stage with an acceptable morbidity rate compared with organ-confined disease. RP has been conducted in 51 clinically advanced patients (any $T \geqslant 3$, N0–1, or any N1 or M1a disease according to the TNM 2002 classification system) and in 152 patients with clinically organ-confined disease. N1 refers to metastasis in regional lymph node(s) and M1a disease refers to metastasis in nonregional lymph nodes. The two groups did not differ significantly in surgical morbidity except for blood transfusion, operative time and lymphoceles, which showed a higher rate in the patients with advanced disease. The three patients with M1 disease were dead at median follow-up of 21 months. In the group with advanced patients the OS and CSS at 7 years were 77% and 90%, respectively. These rates seem comparable to the Bolla series of RT and 3 years of ADT. A limitation of the Gontero study is that the authors were not able to report the curative rate of RP alone because the majority of the patients (89.5%) received immediate adjuvant treatment after RP. The authors suggested the role of surgery as an essential part of the multimodal approach to treating advanced prostate cancer. The results support the belief that RP followed by adjuvant RT and/or HT for the treatment of advanced prostate cancer may provide a survival advantage over the frequently used combination of ADT and external RT,

Table 3
The outcome of radiotherapy for locally advanced prostate cancer [76]

Risk groups		Survival rate by year of follow-up					
		CSS			OS		
		5	10	15	5	10	15
1 (n = 363)	GS 2–6, T1–2 Nx	96	86	72	85	59	39
2 (n = 443)	GS 2–6, T3 Nx or N+ or GS 7, T1–2 Nx	94	75	61	82	59	24
3 (n = 338)	GS 7, T3 Nx or N+ or GS 8–10, T1–2 Nx	83	62	39	68	32	16
4 (n = 324)	GS 8–10, T3 Nx or N+	64	34	27	52	19	12

CSS: cancer-specific survival; OS: overall survival; GS: Gleason score

although randomised comparative trials are currently absent [38].

Neoadjuvant or adjuvant chemo- or chemohormonal therapy and prostatectomy

Neoadjuvant chemohormonal therapy followed by RP seems to be feasible in patients with locally advanced prostate cancer [70–73] and the short-time results seem acceptable [74]. However, the impact on long-term tumour recurrence and survival remain unknown. Additional well-designed studies are necessary.

Comparison of radical prostatectomy with other treatment options for locally advanced prostate cancer

Comparisons of different treatments are difficult due to many factors, from uncertainties in clinical staging to the questionable equivalence of PSA failure. To date, only one randomised trial was first published by Akakura in 1999 and was recently updated comparing RP+ADT and RT+ADT in 95 patients with locally advanced disease. At 10 years overall survival rates in the RP+ADT group were better than in the RT+ADT group (76.2% versus 71.1% for biochemical progression-free rates; $P = 0.25$, 83.5% versus 66.1% for clinical progression-free rates; $P = 0.14$, 85.7% versus 77.1% for cancer-specific survival rates; $P = 0.06$ and 67.9% versus 60.9% for overall survival rates; $P = 0.30$). However, the study was limited by a small sample size and the differences in survival analyses between the two groups were not statistically significant. Moreover, the radiation dose of 60–70 Gy might not be enough for the local treatment of locally advanced prostate cancer [75].

In the absence of data from prospective randomised trials comparing possible options for definitive therapy, we have made an attempt to compare the data of RP+ adjuvant or salvage treatment when needed with data of other treatment options for locally advanced prostate cancer. Direct comparison of these data [11] with the data of RT+ adjuvant HT and RT alone reported by Bolla and colleagues (2002) [19] may not be correct because the selection in favour of surgery may represent a more favourable subset of patients. In the study by Bolla and colleagues (2002) CSS and OS at 5 years were 79% and 62% in the RT group alone and 94% and 78% in the RT+ adjuvant HT group, respectively [19]. This is lower than in the series at our institution (CSS and OS at 5 years: 98.79% and 95.9%). The patients selected for RP in this series were patients with unilateral T3a prostate disease and a good performance score. Many of them had a PSA$\leqslant$ 10 (49%) and patients mostly fall within the limits of the EAU guidelines on prostate cancer [11]. This is in contrast with the Bolla series, in which some patients were N+ and only 16–19% of patients had PSA$\leqslant$ 10 [19].

For the comparison of RP outcomes with RT outcomes in patients with locally advanced prostate cancer we refer to the study of Roach and colleagues (2000). In this study 1557 patients from RTOG trials between 1975 and 1992 were analysed. Subgroups were identified based on their pretreatment Gleason score, T-stage and lymph node such that patients with similar risk of dying from prostate cancer were combined [76]. CSS and OS rates in all the subgroups that were treated with RT alone (Table 3) were lower than in the patient group of Hsu and colleagues (2007) that underwent RP at our institution and received adjuvant/salvage treatment when needed (Tables 2 and 3). It has to be noted that the total radiation dose to the prostate in the RTOG trials was 65–70 Gy, which is lower than the radiation doses administered these days.

In another analysis by Roach and colleagues (2000) the outcomes of combined RT and long-term ADT (generally $\geqslant$ 2 years) were reported for 364 patients from RTOG trials between 1975 and 1992

Table 4
The outcome of combined radiotherapy and long-term ADT for locally advanced prostate cancer [77]

Risk groups		Survival rate by year of follow-up			
		CSS		OS	
		5	8	5	8
2 (n = 144)	GS 2–6, T3 Nx or N+ or GS 7, T1–2 Nx	93	89	76	62
3 (n = 138)	GS, T3 Nx or N+ or GS 8–10, T1–2 Nx	93	88	79	61
4 (n = 103)	GS 8–10, T3 Nx or N+	81	69	63	44

CSS: cancer-specific survival; OS: overall survival; GS: Gleason score

(Table 4) [77]. Again the CSS and OS were lower than in the patient group of Hsu and colleagues (2007) that underwent RP at our institution and received adjuvant/salvage treatment when needed (Tables 2 and 4). Group 1 patients were excluded from this analysis because there were too few patients who received long-term HT in that group.

Future directions

The oncological outcome with RP can be improved by better preoperative staging modalities, by better patient selection and by increased surgical expertise in extensive local resection of locally advanced prostate cancer. The outcome in patients with locally advanced prostate cancer can be predicted by the use of appropriate nomograms such as the Partin tables and a nomogram recently developed by our institution [4,36]. Continued efforts have to be made to further optimise adjuvant treatments such as HT and RT: e.g. determine the optimal duration and dose of adjuvant HT, decide on the optimal radiation dose, improve the radiation therapy techniques and – maybe – explore new modalities of brachytherapy.

Nowadays systemic/chemotherapeutic agents in combination with surgery on one hand and in combination with RT and HT on the other hand are tested in small clinical trials. A novel approach for the management of locally advanced prostate cancer currently investigated is gene therapy [78] and targeted molecular therapy [79].

Conclusion

In conclusion, there is currently no consensus on the best approach for treating patients with locally advanced prostate cancer. A number of treatment options are available, including radiation therapy, hormonal therapy and radical prostatectomy. Locally advanced prostate cancer is a disease that will often warrant multimodal treatment. Radiation therapy in combination with hormones should no any longer be considered the treatment of choice for all T3 prostate cancers. Surgery should be considered in well-selected patients as it gives the chance for cure not only in pT2 but also in some pT3 patients. After radical prostatectomy the prostate specific antigen (PSA) level allows a follow-up that will indicate the need of appropriate adjuvant and salvage treatment for pathologically more advanced tumours. Urologists must use the pathological results to guide additional treatment after surgery in order to maximise patient outcomes.

The different treatment options for locally advanced prostate cancer are continuously evolving in an attempt to further improve the patient's outcome. Other systemic/chemotherapeutic agents are tested in clinical trials.

Although the optimal management for patients with locally advanced prostate cancer remains unclear, in well-selected patients, RP – with adjuvant or salvage treatment when needed – may result in better outcomes than RT alone and may even offer better outcomes than the combination of RT and HT therapy. These findings should be confirmed in well-designed, randomised, prospective studies. These trials should not only focus on the oncological outcome but have to take an objective comparison of the treatment related complications into account as well. Large randomised trials are required to define the precise patient groups suitable for surgery. In addition, the increased use of nomograms and the identification of prognostic factors could lead to a large number of well-selected patients, often with long life expectancy, who could benefit from surgical treatment.

Conflict of interest statement

None declared.

References

1 Boccon-Gibod L, Bertaccini A, Bono AV, *et al.* Management of locally advanced prostate cancer: a European consensus. *Int J Clin Pract* 2003, **57**(3), 187–194.

2 Sobin LH, Wittekind C, eds. *TNM Classification of prostate cancer* 6th ed. New York, Wiley. Liss, 2002, 184–187.

3 Aus G, Abbou CC, Bolla M, *et al.* European Association of Urology. EAU guidelines on prostate cancer. *Eur Urol* 2005, **48**(4), 546–551.

4 Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millenium. *Urology* 2001, **58**, 615–619.

5 Nakashima J, Tanimoto A, Imai Y, *et al.* Endorectal MRI for prediction of tumor site, tumor size, and local extension of prostate cancer. *Urology* 2004, **64**(1), 101–105.

6 Vallancien G, Bochereau G, Wetzel O, Bretheau D, Prapotnich D, Bougaran J. Influence of preoperative positive seminal vesicle biopsy on the staging of prostatic cancer. *J Urol* 1994, **152**(4), 1168–1169.

7 Amling CL, Leibovich BC, Lerner SE, *et al.* Primary surgical therapy for clinical stage T3 adenocarcinoma of the prostate. *Semin Urol Oncol* 1997, **15**(4), 215–221.

8 Gerber GS, Thisted RA, Chodak GW, *et al.* Results of Radical prostatectomy in men with locally advanced prostate cancer: multi-institution pooled analysis. *Eur Urol* 1997, **32**, 385–390.

9 Martinez de la Riva SI, Lopez-Tomasety JB, Dominguez RM, Cruz EA, Blanco PS. Radical prostatectomy as monotherapy for locally advanced prostate cancer (T3a): 12 years follow-up. *Arch Esp Urol* 2004, **57**(7), 679–692.

10 Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005, **95**(6), 751–756.

11 Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. *Eur Urol* 2007, **51**(1), 121–128; discussion 128–129.

12 Swanson GP, Riggs MW, Earle JD. Long-term follow-up of radiotherapy for prostate cancer. *Int J of Rad Onc Biol Phys* 2004, **59**(2), 406–411.

13 Hahn P, Baral E, Cheang M, Math MC, Kostyra J, Roelss R. Long-term outcome of radical radiation therapy for prostatic carcinoma: 1967–1987. *Int J Radiat Oncol Biol Phys* 1996, **34**(1), 41–47.

14 Ennis RD, Peschel RE. Radiation therapy for prostate cancer. Long-term results and implications for future advances. *Cancer* 1993, **72**(9), 2644–2650.

15 Zagars GK, Pollack A, Smith LG. Conventional external-beam radiation therapy alone or with androgen ablation for clinical stage III (T3, Nx/N0, M0) adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1999, **44**(4), 809–819.

16 O'Connor KM, Fitzpatrick JM. Side-effects of treatments for locally advanced prostate cancer. *BJU Int* 2006, **97**(1), 22–28.

17 Swanson GP. Management of locally advanced prostate cancer: past, present, future. *J Urol* 2006, **176**(6 Pt 2), S34–41.

18 Kumar RJ, Barqawi A, Crawford ED. Preventing and treating the complications of hormone therapy. *Curr Urol Rep* 2005, **6**(3), 217–223.

19 Bolla M, Collette L, Blank L, *et al.* Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002, **360**(9327), 103–106.

20 Laverdiere J, Gomez JL, Cusan L, *et al.* Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997, **37**(2), 247–252.

21 Pilepich MV, Winter K, John MJ, *et al.* Phase III radiation therapy oncology group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001, **50**(5), 1243–1252.

22 Lawton CA, Winter K, Murray K, *et al*. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85–31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001, **49**(4): 937–946.

23 Hanks GE, Pajak TF, Porter A, *et al.* Radiation Therapy Oncology Group. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92–02. *J Clin Oncol* 2003, **21**(21), 3972–3978. Erratum in: *J Clin Oncol* 2004, **22**(2), 386.

24 Pilepich MV, Winter K, Lawton CA, *et al.* Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma –long-term results of phase III RTOG 85–31. *Int J Radiat Oncol Biol Phys* 2005, **61**(5), 1285–1290.

25 Roach 3rd M, DeSilvio M, Lawton C, *et al.* Radiation Therapy Oncology Group 9413. 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**(10), 1904–1911.

26 Ward JF, Zincke H. Radical prostatectomy for the patient with locally advanced prostate cancer. *Curr Urol Rep* 2003, **4**(3), 196–204.

27 McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP; Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006, **97**(2), 247–254.

28 Van Poppel H, Goethuys H, Callewaert P, Vanuytsel L, Van de Voorde W, Baert L. Radical prostatectomy can provide a cure for well-selected clinical stage T3 prostate cancer. *Eur Urol* 2000, **38**, 372–379.

29 Hsu CY, Joniau S, Van Poppel H. Radical prostatectomy for locally advanced prostate cancer: technical aspects of radical prostatectomy. *EAU Update Series* 2005, **3**, 90–97.

30 Van Poppel H. Surgery for clinical T3 prostate cancer. *Eur Urol Suppl* 2005, **4**, 2–14.

31 Hsu CY, Joniau S, Roskams T, Oyen R, Van Poppel H. Comparing results after surgery in patients with clinical unilateral T3a, prostate cancer treated with or without neoadjuvant androgen-deprivation therapy. *BJU Int* 2006, **99**, 311–314.

32 Van Poppel H, Ameye F, Oyen R, Van de Voorde W, Baert L. Accuracy of combined computerized tomography and fine needle aspiration cytology in lymph node staging of localized prostatic carcinoma. *J Urol* 1994, **151**(5), 1310–1314.

33 Lepor H, Nieder AM, Ferrandino MN. Intraoperative and postoperative complications of radical retropubic prostatectomy in a consecutive series of 1,000 cases. *J Urol* 2001, **166**, 1729–1733.

34 Augustin H, Hammerer P, Graefen M, *et al.* Intraoperative and perioperative morbidity of contemporary radical retropubic

prostatectomy in a consecutive series of 1243 patients: results of a single centre between 1999 and 2002. *Eur Urol* 2003, **43**, 113–118.
35 Maffezzini M, Seveso M, Taverna G, Giusti G, Benetti A, Graziotti P. Evaluation of complications and results in a contemporary series of 300 consecutive radical retropubic prostatectomies with the anatomic approach at a single institution. *Urology* 2003, **61**, 982–986.
36 Joniau S, Hsu CY, Lerut E, *et al.* A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral t3a prostate cancer. *Eur Urol* 2007, **51**(2), 388–396.
37 Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Transrectal ultrasound in the staging of clinical T3a prostate cancer. *Eur J Surg Oncol* 2007, **33**(1), 79–82.
38 Gontero P, Marchioro G, Pisani R, *et al.* Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. *Eur Urol* 2006, [Epub ahead of print].
39 Yamada AH, Lieskovsky G, Petrovich Z, *et al.* Results of radical prostatectomy and adjuvant therapy in the management of locally advanced, clinical stage TC, prostate cancer. *Am J Clin Oncol* 1994, **17**, 277–285.
40 van den Ouden D, Hop WC, Schroder FH. Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. *J Urol* 1998, **160**(4), 1392–1397.
41 van den Ouden D, Schroder FH. Management of locally advanced prostate cancer. 1. Staging, natural history, and results of radical surgery. *World J Urol* 2000, **18**(3), 194–203.
42 Van Poppel H, Vekemans K, Da Pozzo L, *et al.* Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). *Eur J Cancer* 2006, **42**(8), 1062–1067.
43 Berglund RK, Jones JS, Ulchaker JC, *et al.* Radical prostatectomy as primary treatment modality for locally advanced prostate cancer: a prospective analysis. *Urology* 2006, **67**(6), 1253–1256.
44 Secin FP, Bianco FJ Jr, Vickers AJ, *et al.* Cancer-specific survival and predictors of prostate-specific antigen recurrence and survival in patients with seminal vesicle invasion after radical prostatectomy. *Cancer* 2006, **106**(11), 2369–2375.
45 Masterson TA, Pettus JA, Middleton RG, Stephenson RA. Isolated seminal vesicle invasion imparts better outcomes after radical retropubic prostatectomy for clinically localized prostate cancer: prognostic stratification of pt3b disease by nodal and margin status. *Urology* 2005, **66**(1), 152–155.
46 Johnstone PA, Ward KC, Goodman M, Assikis V, Petros JA. Radical prostatectomy for clinical T4 prostate cancer. *Cancer* 2006, **106**(12), 2603–2609.
47 Carver BS, Bianco Jr FJ, Scardino PT, Eastham JA. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol* 2006, **176**(2), 564–568.
48 Labrie F, Cusan L, Gomez J-L, *et al.* Down-staging of early stage prostate cancer before radical prostatectomy: the first randomised trial of neoadjuvant combination therapy with flutamide and a luteinizing hormone-releasing hormone agonist. *Urol Symp* 1994, **44**(6A), 29–37.
49 Van Poppel H, De Ridder D, Elgamal AA, *et al.* Neoadjuvant hormonal therapy before radical prostatectomy decreases the number of positive surgical margins in stage T2 prostate cancer: interim results of a prospective randomised trial. The Belgian Uro-Oncological Study Group. *J Urol* 1995, **154**, 429–434.
50 Soloway MS, Sharifi R, Wajsman Z, McLeod D, Wood Jr DP, Puras-Baez A. Randomised prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. The Lupron Depot Neoadjuvant Prostate Cancer Study Group. *J Urol* 1995, **154**, 424–428.
51 Hugosson J, Abrahamsson PA, Ahlgren G, *et al.* The risk of malignancy in the surgical margin at radical prostatectomy reduced almost three-fold in patients given neo-adjuvant hormone treatment. *Eur Urol* 1996, **29**, 413–419.
52 Goldenberg SL, Klotz LH, Srigley J, *et al.* Randomised, prospective, controlled study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. Canadian Urologic Oncology Group. *J Urol* 1996, **156**, 873–877.
53 Witjes WP, Schulman CC, Debruyne FM. Preliminary results of a prospective randomised study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2–3 N0 M0 prostatic carcinoma. The European Study Group on Neoadjuvant Treatment of Prostate Cancer. *Urology* 1997, **49**(Suppl. 3A), 65–69.
54 Aus G, Abrahamsson PA, Ahlgren G, *et al.* Three-month neoadjuvant hormonal therapy before radical prostatectomy; a 7-year follow-up of a randomised controlled trial. *BJU Int* 2002, **90**, 561–566.
55 Soloway MS, Pareek K, Sharifi R, *et al.* Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxM0 prostate cancer: 5-year results. The Lupron Depot Neoadjuvant Prostate Cancer Study Group. *J Urol* 2002, **167**, 112–116.
56 Schulman CC, Debruyne FM, Forster G, Selvaggi FP, Zlotta AR, Witjes WP. 4-year follow-up results of a European prospective randomised study on neoadjuvant hormonal therapy prior to radical prostatectomy in T2-T3N0M0 prostate cancer. European Study Group on Neoadjuvant Treatment of Prostate Cancer. *Eur Urol* 2000, **38**, 706–713.
57 Van Poppel H, Goethuys H, De Ridder D, *et al.* Neoadjuvant therapy before radical prostatectomy: impact on progression free survival. *Uro-Oncology* 2001, **1**, 302–307.
58 Powell IJ, Tangen CM, Miller GJ, *et al.* Neoadjuvant therapy before radical prostatectomy for clinical T3/T4 carcinoma of the prostate: 5-year follow-up, Phase II Southwest Oncology Group Study 9109. *J Urol* 2002, **168**(5), 2016–2019.
59 Van Poppel H. Neoadjuvant hormone therapy and radical prostatectomy: the jury is still out. *Eur Urol* 2001, **39**(Suppl. 1), 10–14.
60 Hakenberg OW, Frohner M, Wirth MP. Treatment of locally advanced prostate cancer–the case for radical prostatectomy. *Urol Int* 2006, **77**(3), 193–199.
61 Lerner SE, Blute ML, Zincke H. Extended experience with radical prostatectomy for clinical stage T3 prostate cancer: outcome and contemporary morbidity. *J Urol* 1995, **154**(4), 1447–1452.
62 Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999, **341**(24), 1781–1788.
63 Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. *Cochrane Database Syst Rev* 2006, **4**, CD006019.

64 Wirth MP, Weissbach L, Marx FJ, *et al.* Prospective randomised trial comparing flutamide as adjuvant treatment versus observation after radical prostatectomy for locally advanced, lymph node-negative prostate cancer. *Eur Urol* 2004, **45**(3), 267–720; discussion 270.

65 Jacobson GM, Smith JA Jr, Stewart JR. Postoperative radiation therapy for pathologic stage C prostate cancer. *Int J Radiat Oncol Biol Phys* 1987, **13**(7), 1021–1024.

66 Choo R, Hruby G, Hong J, *et al.* Positive resection margin and/or pathologic T3 adenocarcinoma of prostate with undetectable postoperative prostate-specific antigen after radical prostatectomy: to irradiate or not? *Int J Radiat Oncol Biol Phys* 2002, **52**(3), 674–680.

67 Bolla M, Van Poppel H, Collette L, *et al.* European Organization for Research and Treatment of Cancer. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005, 19, **366**(9485), 572–578.

68 Thompson Jr IM, Tangen CM, Paradelo J, *et al.* Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomised clinical trial. *JAMA* 2006, **296**(19), 2329–2335.

69 Stephenson AJ, Shariat SF, Zelefsky MJ, *et al.* Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004, **291**(11), 1325–1332.

70 Pettaway CA, Pisters LL, Troncoso P, *et al.* Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol* 2000, **18**(5), 1050–1057.

71 Hussain M, Smith DC, El-Rayes BF, *et al.* Neoadjuvant docetaxel and estramustine chemotherapy in high-risk/locallyadvanced prostate cancer. *Urology* 2003, **61**(4), 774–780.

72 Konety BR, Eastham JA, Reuter VE, *et al.* Feasibility of radical prostatectomy after neoadjuvant chemohormonal therapy for patients with high risk or locally advanced prostate cancer: results of a phase I/II study. *J Urol* 2004, **171**(2 Pt 1), 709–713.

73 Febbo PG, Richie JP, George DJ, *et al.* Neoadjuvant docetaxel before radical prostatectomy in patients with high-risk localized prostate cancer. *Clin Cancer Res* 2005, **11**(14), 5233–5240.

74 Dreicer R, Magi-Galluzzi C, Zhou M, *et al.* Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer. *Urology* 2004, **63**(6), 1138–1142.

75 Akakura K, Suzuki H, Ichikawa T, *et al.* A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: Results at median follow-up of 102 months. *Jpn J Clin Oncol* 2006, **36**(12), 789–793.

76 Roach M, Lu J, Pilepich MV, *et al.* Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. *Int J Radiat Oncol Biol Phys* 2000, **47**(3), 609–15. Erratum in: Mohuidden M [corrected to Mohiuddin M]. *Int J Radiat Oncol Biol Phys* 2000, **48**(1), 313.

77 Roach M, Lu J, Pilepich MV, *et al.* Predicting long-term survival, and the need for hormonal therapy: a meta-analysis of RTOG prostate cancer trials. *Int J Radiation Oncol Biol Phys* 2000, **47**, 617–627.

78 Jani AB. Management strategies for locally advanced prostate cancer. *Drugs Aging* 2006, **23**(2), 119–129.

79 Armstrong AJ, Carducci MA. New drugs in prostate cancer. *Curr Opin Urol* 2006, **16**(3), 138–145.