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Radical prostatectomy for locally advanced prostate cancer: Results of a feasibility study (EORTC 30001)

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ABSTRACT

The aim of this open, non-randomised, 2-stage feasibility study was to determine whether radical prostatectomy (RP) was safe and could provide cure for good prognosis patients with clinical T3 prostate cancer, in a multicentre setting. Cure was defined as a 3 months post-operative of undetectable serum PSA in combination with the presence of pathologically negative margins in the surgical specimen. Forty patients were enrolled of whom 38 were eligible. Six patients (5 pN+ and 1 pNx) did not meet the inclusion criteria and were excluded leaving 32 evaluable pN0 patients of whom 19 (59.4%, SE = 4.26) achieved a complete response (CR) and in whom only two serious toxic events (STEs) were observed. The results of the first phase of the study passed the toxicity criteria (<3 STE's) but failed on the cure rate (>20 CRs). This resulted in discontinuation of the study after the first stage. The main reason for failure was the incidence of positive margins in the resected specimen. Although the study was stopped after the first phase, 28 of the 32 pN0 patients (87.5%) had undetectable serum PSA at 3 months. We continue to believe that RP with extensive resection can be beneficial as monotherapy for T3aN0M0 prostate cancer.

1. Introduction

Radical prostatectomy (RP) is often considered the standard treatment option for locally confined prostate cancer (T1–T2) but is traditionally discouraged for clinical T3 prostate cancer, mainly because of the increased risk of both lymph node metastases and local or distant relapse. Therefore, preference is given to a combination therapy of hormonal treatment (HT) and radiotherapy (RT).[1–4] However, this combination treatment has never been proven superior to surgical treatment either in monotherapy or in combination with RT or HT. Results of radical prostatectomy series suggest that RP remains a treatment option for good prognosis patients with locally advanced prostate cancer.[5–9] It has been reported that RP for cT3 locally advanced prostate cancer can be carried out with acceptable morbidity and mortality and is especially beneficial in patients who are clinically over-staged (17–30% of cT3 are pT2) and in those with moderately or

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well-differentiated disease and with a relatively low PSA. RP alone is clearly not useful in patients presenting with poorly differentiated disease or with prostate-specific antigen (PSA) values exceeding 20 μg/ml, with lymph node or seminal vesicle(s) invasion.[10] At present, the optimal treatment of cT3 prostate cancer remains unknown and the role of RP needs further clarification.

The main objective of the EORTC study (protocol 30001) presented here was to determine whether RP can provide cure for a subgroup of good prognosis patients with clinical stage T3 prostate cancer without excessive morbidity, in a multicentre setting. Cure is defined as a post-operative undetectable serum PSA at 3 months following the surgical procedure in combination with pathologically negative margins in the surgical specimen.

2. Patients and methods

2.1. Patients

Patients ⩽70 years were included in this trial if they met each of the following criteria: total serum PSA ⩽20 ng/ml (Hybritech equivalent); biopsy proven carcinoma of the prostate; well or moderately differentiated tumour (i.e. biopsy Gleason score ⩽7); WHO performance status 0–1; clinically unilateral extracapsular extension (unilateral cT3a) with negative seminal vesicles, negative nodes (cN0) and without distant metastases (M0). All patients had partial thromboplastin time and prothrombin time within normal limits; normal renal (creatinine ⩽135 μmol/L), liver (bilirubin ⩽1.5 times normal, ALAT or ASAT < 3.0 times normal) and bone marrow function (WBC > 3.0×10^9/L, PLT > 100×10^9/L, Hb > $5.6 \times$ mmol/L). Patients were not allowed to participate in the study if there had been previous surgery in the small pelvis that might interfere with prostatectomy, nor if they had received previous hormonal treatment or pelvic irradiation. Patients with pre-existing uncontrolled cardiac disease, signs of cardiac failure or rhythm disturbances requiring therapy, myocardial infarction within 6 months of registration, gross abnormalities on chest X-ray or any other disease increasing the surgical risk were excluded. Patients were also excluded if they had a second primary cancer or previous malignancy except adequately treated basal cell carcinoma of the skin. Before registration eligible patients provided written informed consent according to ICH/EUR GCP, and national/local regulations.

Patients were registered at the EORTC Data Centre within 2 weeks prior to RP and after verification of the eligibility criteria.

2.2. Statistical methods

2.2.1. Study design

This study was an open, non-randomised, multicentre, feasibility trial designed to assess the surgical treatment to patients with clinical stage T3N0M0 prostate cancer and negative seminal vesicles. The trial was planned to be conducted in two successive recruitment stages to avoid unsuccessful procedure in too many patients. The Bryant and Day 2-stage design was used to allow the simultaneous use of two primary endpoints: complete response (CR) rate to surgery, and the serious toxic events (STE) rate within 6 months of the surgical procedure.

2.2.2. Endpoints

CR after surgery was defined as a RP that led to negative margins and a 3-month post-prostatectomy PSA at or below the detection level (i.e. a PSA ⩽ 0.02 ng/ml). All patients not satisfying those criteria were classified as failures. A negative margin is a margin, which is at least 1 mm clear of any neoplastic invasion as assessed by the local pathologist and confirmed by the review pathologist.

A STE was defined as any of the following:

- Any serious adverse event (SAE) occurring within 30 days from the date of surgery.
- Post-operative death defined as death possibly, probably or definitely related to the surgical procedure.
- Post-operative complication leading to common toxicity criteria (CTC) grade ⩾ 3 possibly, probably or definitely related to the surgical procedure.
- Severe injury to the rectum, the ureter or the bladder (CTC grade ⩾ 3).
- Severe urinary stress incontinence (CTC grade ⩾ 3).
- (Note: Impotency was not considered a STE).

Secondary endpoints included the pN status of the sample registered in the study, the percentage of organ-confined tumours (pT2), surgical morbidity rates and the 2-year PSA free survival rate.

All patients deemed pN+ during the surgical procedure were classified as not evaluable for response but were evaluable for toxicity/morbidity. The statistical analysis was performed on the basis of the review pathology assessment of the surgical specimen.

2.2.3. Sample size

The trial was designed to have 95% power to demonstrate that the CR rate was >60% and the STE rate <10% under the assumption of a true CR rate of 80% and a true STE rate of 1%. The type I error rates were set to 10% for the CR rate and 5% for the STE rate.

With the 2-stage Bryant-and-Day design, the first stage sample size required 32 eligible pN0 patients. A further 29 eligible pN0 patients were to be included in a second stage, if the analysis of the first stage results showed there were <3 serious toxic events and >20 complete responses. At the end of the study, the success criteria required <4 STEs and >41 CR.

2.3. Selection of centres

To ensure consistent quality of surgical procedures, surgeons/urologists in eight centres were evaluated through a pre-study questionnaire on their most recent prostatectomies on cT3 patients. Based on the collected information and following the methods described by Van Poppel et al.,[11] the study coordinator selected surgeons/urologists for participation in this study. Five centres were selected each with one participating surgeon/urologist; two in Belgium, two in Italy and one in Slovakia.

2.4. Assessments

Clinical reassessment was planned at 3, 6, 9, 12, 16, 20 and 24 months after the surgical procedure. At each follow-up, the history of voiding, continence and potency during the previous period was registered. In addition digital rectal examination (DRE) was performed, serum PSA value and toxicity were assessed. The International common toxicity criteria version 2.0 were used for toxicity and adverse event reporting.

Clinical staging was performed using the 1997 TNM classification (UICC) based on the outcome of biopsies, DRE, transrectal ultrasonography (TRUS), bone scan and contrast-enhanced computerised tomography (CT). A CT scan of the pelvis with 8 mm-slices was performed to evaluate lymph nodes. When the CT scan showed suspicious metastatic lymph nodes ($\geqslant$6 mm) a puncture was performed under CT guidance with an 18 or 19.5 gauge needle. Measurements were done no more than 1 month prior to surgery.

The Gleason grading system was used for biopsies and resected prostate. Tumour extending to the inked surface of the prostatectomy specimen was interpreted as a positive margin. The pathology slides were examined by the local pathologist in each centre and were sent for assessment to a central review pathologist. Margin status and pathological review were assessed as early as possible after surgery.

PSA levels were determined with the Hybritech assay.

2.5. Surgery

Patients underwent a classical radical retropubic prostatectomy. This RP was performed as described by Walsh et al.[12] by the single selected surgeon/urologist of each centre. Radical retropubic prostatectomy consists of removal of the whole prostate en bloc within its capsule, together with the seminal vesicles. Prior to this prostatectomy a lymphadenectomy had to be carried out. A frozen section of the lymph nodes was mandatory even when the nodes were clinically normal. In case of a positive lymph node, further treatment was left to the surgeon's discretion. The main goal of the RP was to remove all cancer with acceptable morbidity (acceptable blood loss, and maintenance or recovering of continence). Because the primary objective of the procedure was removal of the entire tumour, preserving potency was of secondary concern. The final decision regarding nerve sparing was made intraoperatively based on the surgeon's assessment.

3. Central review pathology

A central pathologist reviewed the biopsies and resected specimens. The radical prostatectomy specimens are examined by the whole mount technique as described by Stamey and colleagues.[13]

The following parameters in the histological slides are evaluated: histological type of cancer, grade and staging of cancer, positive margins and volume of cancer.

Grade of cancer includes Gleason score with primary and secondary grades as well as WHO grade. Staging of cancer was determined according to the 1997 revision of the TNM system. The extraprostatic extension (EPE) is defined as focal or extensive. The amount of extraprostatic extension is considered as focal if the amount of EPE is equal to, or less than two high-power (40×) microscopic fields. Any amount in excess of two high-power fields is considered to be either non-focal or extensive. When cancer involves the anterior part of the prostate where the capsule is not present, EPE was defined according to Bostwick and Montironi.[14] For the evaluation of the positive surgical margins each positive margin was specifically categorised according to its extent, number and location. The margin extent is classified as focal, extensive or equivocal. A focal margin is defined as a margin present in only one section and equal to, or less than two high-power (40×) microscopic fields, and involvement greater than this was classified as an extensive positive margin. The locations of the positive surgical margins are classified and recorded as apical, anterior, prostate base, postero-lateral and posterior (for detail see Ref. [15]). The examining pathologist was aware of false positive margins due to the penetration of ink into cracks on the external surface. The volume of cancer was determined using the grid method as described by Humphrey and Vollmer.[16] The volume of cancer compared with the volume of the prostate give precise information on the amount of cancer in any individual RP specimen.

4. Results

4.1. Patients

A total of 40 patients were entered in the trial, of which 38 were eligible and evaluable. One person was deemed ineligible because of tumour stage (T3b; seminal vesicle invasion). Another patient was not evaluable, as he was not treated by the authorised surgeon/urologist of the treating centre. Five eligible patients were deemed pN+ and one was pNx. These six patients were not evaluable for the endpoint "complete response" thus leaving 32 eligible and evaluable T3pN0M0 patients.

The median age of the 32 T3pN0M0 patients at the time of RP was 63 years (range 42–69) and all patients had a WHO performance status 0. The median PSA value was 6.7 ng/ml (range 2.7–19.9) with the majority of the patients (75%) having a PSA > 4 and $\leqslant$10 ng/ml. Of all patients 14 patients had urinary problems at entry.

Table 1 shows the pathological staging of the tumours. Central pathological review data are reported for all patients. Based on pathological review data 14 of the 32 pN0 patients (43.8%) had organ-confined disease (pT2). Of these patients

Table 1 – Pathological staging

Pathological staging	Patient group			Total (N = 40)
	Ineligible (N = 2)	pN+/pNx (N = 6)	Eligible pN0 (N = 32)	
	N (%)	N (%)	N (%)	N (%)
pT2	1 (50.0)	1 (16.7)	14 (43.8)	16 (40.0)
pT2a	0	1	1	2
pT2b	1	0	13	14
pT3	1 (50.0)	5 (83.3)	18 (56.3)	24 (60.0)
pT3a	0	2	12	14
pT3b	1	3	6	10

one (7.1%) was classified in the subcategory pT2a (tumour involved one lobe) and 13 (92.9%) in pT2b (tumour involved both lobes). The remaining 18 patients (56.3%) had pT3 status with 12 patients in the subcategory pT3a and six in the subcategory pT3b. Extracapsular extension was considered unilateral in the 32 pN0 patients. The median diameter of the nodule was 1.8 cm. Review data show extraprostatic extension in 56.3% of all pN0 patients. According to the review pathologist six of the 32 pN0 patients (18.8%) showed invasion of the seminal vesicle(s) (pT3b). Bone scans were normal in the 31 patients for which bone scan was performed. The pelvis CT scan with 8 mm-slices performed to evaluate lymph nodes was considered normal in 31 and unknown in one pN0 patient. Several prostate puncture biopsies were taken with at least two biopsies at the target lesion. The Gleason scores of the 32 pN0 patients based on these biopsies at entry were 4 (1 pt), 5 (11 pts), 6 (9 pts) and 7 (11 pts). The Gleason scores of the pN0 patients based on the resected specimen (review data) were 6 (11 pts), 7 (20 pts) and 9 (1 pt). The WHO grade of differentiation of the RP specimen was "moderately differentiated" in 23 (71.9%) and "poorly differentiated" in 9 (28.1%) pN0 patients. Positive margins of resection occurred in 12 (37.5%) eligible pN0 patients and were mainly located at the apex and postero-lateral. Negative margins were obtained in 20 (62.5%) pN0 patients.

The median prostate volume was 39.5 cm^3 (12.9–101.3) and the median tumour volume was 2.2 ml (0.4–31.1). Both are review data. The median tumour contact length was 2.0 cm (0.5–6.5). Prostate capsular irregularities were seen in 33% of all patients.

4.2. *Surgery and complications*

Lymphadenectomy was carried out prior to RP. Frozen section of the lymph nodes was not performed in 13 of the 40 patients (32.5%). The majority of the prostatectomies were performed without any attempt to spare the neurovascular bundles. Five (12.5%) of all patients underwent a contra-lateral nerve sparing operation.

The median duration of RP (skin incision to skin closure excluding time of frozen section examination) was 90 min (range 43–180). The estimated blood loss during RP ranged from 150.0 to 1850.0 ml (median 555.0). During RP most patients (38) required 1–2 units blood except for two patients who received 3–4 units. The length of intensive care unit stay ranged from 0.0 to 24.0 h (median 4.5). After RP, patients stayed in hospital from 5.0 to 23.0 days (median 10 days).

Intraoperative complications occurred in four eligible patients and one ineligible. The acute side effects of surgery observed in these patients were haemorrhage (2), injury to the bladder (1), injury to colon/rectum (2). The toxicity of the events was not scored as severe except for blood loss CTC-grade 3 in two patients. Both patients required transfusion; one received 2 units, the other 4 units blood. All complications were repaired or uneventfully treated immediately.

No death related to surgery has been reported.

Two serious toxic events (STE with CTC grade 3) were observed in the 32 eligible evaluable pN0 patients; (1) haemorrhage requiring blood transfusion (2) perirenal urinary extravasation leading to nephrostomy (left side) and requiring hospitalisation. The third STE with CTC grade 3, a haemorrhage requiring blood transfusion was experienced by a patient who was not evaluable because he was not operated by the selected surgeon/urologist as indicated in the protocol. Serious toxic events are presented in Table 2.

4.3. *Follow-up*

The median follow-up of all patients in this study is 321 days (10.3 months). In none of the 40 patients there was evidence of local recurrence or distant metastases during follow-up. One patient died during follow-up because of a second primary malignancy in the lung without being related to the RP.

4.3.1. *Response to surgery*

The PSA values were determined at 3 months after surgery. Table 3 presents the number of patients with "3 months" post-operative undetectable and detectable PSA level and margin positivity. Twenty nine pN0 patients (90.6%) reached 3 months after surgery an undetectable serum PSA level. Three pN0 patients (9.4%) had a serum PSA above detection level (>0.02 ng/ml).

Table 4 presents the oncological response to surgery. A total of 19 (59.4%) of 32 eligible evaluable pN0 patients achieved CR to surgery i.e. a serum PSA at or below detection level and negative margins. The incomplete response to surgery (failure) in 13 pN0 patients (40.6%) was mainly due to positive margins of resection (10 patients or 76.9% of failures).

4.3.2. *Combination of response and serious toxic events*

In order to continue to the second phase of the study the protocol required <3 serious toxic events and >20 complete responses. Table 5 gives the combination of response to treatment and incidence of serious toxic events.

A total of 19 of 32 eligible evaluable pN0 patients achieved a CR to RP.

Two STE were observed in the 32 eligible evaluable pN0 patients; (1) haemorrhage requiring blood transfusion in a

Table 2 – Serious toxic events

Group	N status	Serious toxic event	Description
Eligible pN0	pN0	Post-operative complication leading to CTC $\geqslant$ 3 possibly, probably or definitively related to treatment	Haemorrhage grade 3 (4 units packed cells transfusion)
Eligible pN0	pN0	Post-operative complication leading to CTC $\geqslant$ 3 possibly, probably or definitively related to treatment	SAE: perineal urinary extravasation leading to nephrostomy (left)
Ineligible; not selected surgeon	pN0	Post-operative complication leading to CTC $\geqslant$ 3 possibly, probably or definitively related to treatment	Haemorrhage grade 3 (2 units packed cells transfusion)

Table 3 – Number of patients with "3 months" undetectable and detectable post-operative PSA level and margin positivity

	Patient group			Total (N = 40)
	Ineligible (N = 2)	pN+/pNx (N = 6)	Eligible pN0 (N = 32)	
	N (%)	N (%)	N (%)	N (%)
Undetectable PSA level	2 (100.0)	6 (100.0)	29 (90.6)	37 (92.5)
Negative margin			19	
Positive margin			10	
Detectable PSA level	0 (0.0)	0 (0.0)	3 (9.4)	3 (7.5)
Negative margin			1	
Positive margin			2	

Table 4 – Oncological response to surgery

Response to surgery	Patient group			Total (N = 40)
	Ineligible (N = 2)	pN+/pNx (N = 6)	Eligible pN0 (N = 32)	
	N (%)	N (%)	N (%)	N (%)
Complete response	1 (50.0)	3 (50.0)	19 (59.4)	23 (57.5)
Failed	1 (50.0)	3 (50.0)	13 (40.6)	17 (42.5)
Positive surgical margin	1	3	10	13
Elevated PSA		0	1	1
Elevated PSA and positive margins		0	2	2

Table 5 – Combination of response and serious toxic events in pN0 patients

Response to surgery	Serious toxic event		Total (N = 32)
	No (N = 30)	Yes (N = 2)	
	N (%)	N (%)	N (%)
Complete response	18 (60.0)	1 (50.0)	19 (59.4)
Failure	12 (40.0)	1 (50.0)	13 (40.6)

patient with CR, (2) perirenal urinary extravasation leading to nephrostomy (left side) and requiring hospitalisation in a patient without CR (failure). This last STE was a serious adverse event (SAE) grade 3 probably not related to treatment. The third STE as described in Table 2 was not taken in consideration as it presented in a non-evaluable pN0 patient.

In conclusion, the results passed the toxicity criterion set forward in the protocol (<3STEs) as only 2 STEs were observed in the 32 pN0 patients. Thus the risks associated with surgery appeared moderate. The results failed 2 units on the complete response criterion (>20 CRs) as only 19 (59.4%, SE = 4.26) eligible pN0 patients achieved a complete response. The main reason for failure was a high number of positive margins in resected specimen. Because the data did not support both protocol criteria for continuation of the recruitment, the study was closed after the first phase after advice of an Independent Data Monitoring Committee (IDMC).

5. Discussion

This present study has assessed the feasibility of RP as monotherapy for T3 prostate cancer in a multicentre setting. The results of the first phase of this EORTC study passed the toxicity criterion set forward in the protocol (<3 serious toxic events) but failed 2 units on the complete response criterion (>20 complete responses) resulting in an early closure of the study on advice of an Independent Data Monitoring Committee (IDMC).

The results of the full staging highlight the difficulty to correctly stage these patients at entry. Only about one third of the patients entered are those to which the study is really intended. Of the 32 evaluable patients for complete response on which RP is carried out, 14 are over-staged pT2 (1 pT2a and 13 pT2b), 12 are pT3a and 6 are under-staged pT3b patients. In seven of the 32 patients pN0 status based on the outcome of the CT scan was not confirmed by frozen section of the lymph nodes.

Although the study was stopped after the first phase because of the primary efficacy parameter set forward in the protocol, 29 patients of the 32 pN0 patients (90.4%) had a 3 months post-operative undetectable serum PSA level. So focusing on PSA, the outcome of the RP on the broad range of patients included in this study is encouraging.

The failures on the complete response criteria were mostly due to positive margins as these occurred in 12 of the 13 failures. The high incidence of positive margins could have resulted from (1) the type of tumour linked to the stage of the patients included, (2) not optimally performed surgery, and (3) difficulty in assessing positive margins. So the reason for early closure of the trial is more the result of failing a parameter evaluating surgery in the broad sense than the demonstration of lack of benefit of RP for the patient. The number of patients with a 3 months post-operative undetectable PSA level as single parameter was probably a better response criterion to evaluate the benefit of RP than the combination with "negative margins". Although many consider positive margins as an indicator for increased risk of disease progression, no evidence of local recurrence or distant metastases during follow-up with a median duration of 10.3 months was found in any of the 12 patients for which positive margins were identified. This is next to the positive evolution registered for PSA, another indication in this study that RP as monotherapy is a good initial treatment for patients with locally advanced prostate cancer.

In this perspective our data support the results that report survival rates of 85% and 72% at 5 and 10 years, respectively, after RP monotherapy for cT3 prostate cancer patients.[17] A recent large single-institution retrospective study reports, in line with the above findings, potential curative effect of monotherapy with RP in clinically over-staged T3 patients.[18]

Although positive margins in 12 patients (37.5%) is the main reason for not meeting the complete response criterion, the percentages of positive margins reported in this trial is lower than reported in other trials where effect of RP was evaluated (Van den Ouden 66%; Van Poppel 60%[9,17]). The

result in this study although not to the extent expected, was achieved by positive selection of the surgeon investigators participating in this trial. This confirms that surgery of T3 prostate cancer that needs to be extensive requires specialist expertise from the surgeon. It also indicates that more intensive implementation of the specific technical aspects of RP for T3 prostate cancer as described by Hsu et al.[19] and Van Poppel[20] leads to better oncological outcome.

The possible occurrence of complications is not a reason for not performing RP in locally advanced prostate cancer. The risks associated with RP for T3 prostate cancer appear moderate in our study as only two serious toxic events were observed. A recent study reports that the perioperative morbidity in patients with cT3 disease is similar to that previously reported for patients with cT2 disease undergoing RP.[18,21]

For patients who are not cured with RP as monotherapy, adjuvant treatment modalities offer a good alternative. Ward et al.[18] reported in this respect that based on retrospective data, RP as part of multimodal treatment strategy for patients with cT3 offered cancer control and survival rates similar to those reached with cT2 patients. Clinical trials comparing surgery or RT as part of a multimodal treatment regimen which includes HT and/or chemotherapy are needed. Until then, findings suggest that RP when combined with adjuvant HT compares favourably with current RT/HT strategies.[18]

In conclusion, although this feasibility study was stopped after the first phase, there are several aspects that support the belief that RP has a place in the treatment of good prognosis patients in locally advanced prostate cancer. In those where cure is not obtained by surgery alone, adjuvant treatment measures can be necessary and effective in prolonging disease free survival.

Conflict of interest statement

None declared.

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