LIMITS AND POSSIBILITIES OF SURGICAL TREATMENT OF LOCALLY ADVANCED PROSTATIC CARCINOMA.

(BEPERKINGEN EN MOGELIJKHEDEN VAN CHIRURGISCHE THERAPIE VOOR LOKAAL UITGEBREID PROSTAAT CARCINOOM).

PROEFSCHRIFT

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CONTENTS.

Introduction

INTRODUCTION.

TRENDS IN INCIDENCE AND MORTALITY IN PROSTATE CANCER

Prostatic carcinoma is the second most diagnosed malignant tumor in the Netherlands, only carcinoma of the lung is more frequent. In 1991 4343 men were diagnosed with prostate cancer, making up 14.1% of all diagnosed malignant tumors. In the age-group 60-74 years the incidence was second after pulmonary carcinoma, and in the age-group >75 years it is the most frequently diagnosed malignancy. In 1991 2108 patients died because of prostate cancer. The mortality/incidence ratio is 0,49; which means that about 50% of the patients will die because of their prostatic malignancy [1]. The incidence of prostatic cancer in developed countries is rising. Lu-Yao reported an increase in the incidence-rates of prostatic cancer in the United States of America of 6.4% per year between 1983 and 1989 [2]. This increase appeared to be due to the detection of early-stage disease, but there was no increase in the incidence-rate of metastatic cancer. There was no increase in mortality rates during this study-period. In the Netherlands 3% of all mortality among men was due to prostate cancer (1989) [3]. In 1994 van der Gulden reported on the trends in mortality-rates for patients with prostate cancer in the Netherlands [4]. The age-adjusted mortality-rates rose between 1950 and 1989 with an average increase of 1% per year. A continuous increase of mortality from prostate cancer was found in consecutive birth-cohorts (defined by combining age and calender-time periods on the basis of their central year of birth). There was a steep rise in the mortality from prostate cancer with age; for the age-category 55-59 years the prostate cancer mortality-rate was 11.2 per 100.000 man-years, but for the category >85 years this was 921.8. This rise in the incidence and mortality of prostate cancer points out that this disease will become more and more important in the years to come. Since more cancers tend to be localized, the role of radical prostatectomy in the treatment of prostatic carcinoma will become even more important than it is today.

HISTORY AND CONTEMPORARY DEVELOPMENTS IN RADICAL PROSTATECTOMY

The introduction of anaesthesiology in the nineteenth century made more extensive surgery possible. The first examples of prostatic surgery are found in the second half of this century: all used a perineal incision, since this was the best known procedure, because it was used in perineal lithotomy, which was in use since the times of the roman empire (Celsus described the curved perineal incision in 25 A.D.) [5].

In 1867 Billroth performed the first partial perineal prostatectomy [6]. After this initial step several surgeons practised partial perineal prostatectomy, however their patients rarely survived longer then one year after the operation. Küstner performed a total cystectomy and prostatectomy with anastomosis of the ureters to the bowel in 1891, using a combined suprapubic and perineal incision [7]. A radical suprapubic prostatectomy for prostatic cancer was described by Fuller in 1898, who also removed a part of the bladder wall [8]. The patient died of recurrence after 11 months. In 1905 Young described the first radical perineal prostatectomy with excision of the seminal vesicles, ampullae of the vasa, and the surrounding fascia [9,10]. This technique continued to be used with minor modifications suggested by Belt [11], Lowsley [12], and Vest [13]. In recent years the renewed interest in the perineal approach due to the developement of laparoscopic lymph node dissection , has resulted in applicating a nerve sparing technique. The retropubic approach was first described by Millin [14]. During the last 15 years the insights into the periprostatic anatomy have evolved. Reiner and Walsh described a technique for

2

control of the bleeding of the dorsal vein complex [15]. This enabled a more anatomic approach. After this the anatomy of the branches of the pelvic plexus which innervate the corpora cavernosa, was identified; this lead to modifications of the surgical technique allowing the saving of the neurovascular bundles [16,17]. These modifications and the excellent results for continence and potency reported (92% and 68%) [18,19], gave a strong impuls to the performance of radical prostatectomy, which is considered the first treatment of choice in patients with localized prostate cancer. In the last decade the number of radical prostatectomies performed has increased dramatically. Lu Yao even reported a nearly sixfold increase [2]. This increase may be due to the increased incidence of localized prostate cancer [20], caused by earlier detection because of increased public and doctors awareness and the induction of screening programs [21], enabled by the introduction of Prostate Specific Antigen (PSA) for routine use in 1986. Clinically organ-confined prostatic cancer is sometimes difficult to distinguish from locally advanced disease, in which the tumor extends outside the prostate, or invades the seminal vesicles. This explains the high percentage of understaging reported in series of patients undergoing radical prostatectomy for clinically organ-confined disease (43-75%) [22,23,24]. Many of these patients with pT3/pstage C disease do well after radical prostatectomy however, despite the fact that the tumor has crossed the limits of the prostate. This brings up the question whether radical prostatectomy can be a meaningful treatment in patients with clinical T3/C disease. Furthermore overstaging is known to occur in 17-30% in patients with T3 [25,26]; these patients may be denied a curative procedure because of staging errors. In the literature only a few studies performing radical prostatectomy for locally advanced tumors can be found, and in all studies all or a substantial percentage of the patients received adjuvant therapy (hormonal or radiotherapy).The results for T3-patients treated with radical prostatectomy as a monotherapy are therefore not known. Considering the fact that hormonal therapy is a palliative therapy, which will not prolong life, and that radiotherapy is only a local therapy, which has no effect on (occult) distant metastases already present at the time of surgery, and considering the fact that both therapies can give complications, the effect of radical prostatectomy alone should be known to make a deliberate treatment decision for patients with locally advanced disease.

GOALS OF THIS THESIS

The studies presented in this thesis were performed to define the place of radical surgery in the treatment of locally advanced prostatic carcinoma, and to determine prognostic factors for progression and survival, that can support the decision-making for the use of adjuvant therapy. To achieve this goal, the sub-goals of this thesis were:

1. To study the influence of pathological variables determined in the radical prostatectomy-specimen on progression and survival in patients undergoing radical prostatectomy for clinically localized prostate cancer (organ-confined and locally advanced).
2. To study the influence on progression of residual carcinoma after radical prostatectomy in patients with positive margins of resection; and the relation of the occurrence of positive margins of resection and other pathological variables.
3. To study the outcome of disease-control in patients with locally advanced prostate cancer treated by radical prostatectomy without adjuvant treatment, and to compare these results to those reported in the literature for clinical and pathological T3/C disease, treated with surgery or radiotherapy with or without adjuvant treatment.
4. To study which category of patients with locally advanced disease might benefit of adjuvant treatment after radical prostatectomy.

5. To study the mortality and morbidity associated with radical prostatectomy, and the influence of clinical stage on the complication-rate.

6. To study the disease outcome in patients with clinically localized and locally advanced prostate cancer, who were candidates for radical surgery, but didn't undergo the radical prostatectomy because of the detection of lymph node metastases on frozen sections during the pelvine lymph node dissection preceding the radical prostatectomy; and to evaluate the influence of early versus delayed endocrine therapy on tumor-control in these patient-group.

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PART 1

RADICAL PROSTATECTOMY FOR LOCALLY ADVANCED PROSTATIC CARCINOMA

Locally advanced disease: surgery: is there a rationale?

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LOCALLY ADVANCED DISEASE: SURGERY: IS THERE A RATIONALE?

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INCIDENCE

Locally advanced disease (clinical stage T3 or C) is present in 12 to 40% of all newly diagnosed prostate cancer patients.[1,2,3] In recent years the incidence of localized disease at the time of diagnosis has increased from 27,7% in 1985 to 48,5% in 1990.[4] The increasing public and doctors awareness and the induction of screening programs for prostate cancer, will probably result in earlier detection of prostate cancer, and a shift towards lower stage at diagnosis.[4,3]

DEFINITIONS

Locally advanced prostatic cancer is defined as tumor extending outside the prostate, with perforation of the prostatic capsule, and/or tumor invasion of the seminal vesicles. This situation is classified as stage III or C (C1 or 2) in the Whitmore classification[5], and stage T3 in the T.N.M. classification of 1992, according to the U.I.C.C. (Union International Contra Cancer). The latter has gained worldwide acceptance in recent years, and allows a subclassification in T3a: unilateral extracapsular extension, T3b: bilateral extra capsular extension, and T3c: invasion of the seminal vesicles.[6,7] This subclassification can identify subgroups with different outcome and has therefore prognostic value. Tumor extending into neighbouring organs is classified as T4. (C3 in the Whitmore classification).

STAGING

Over/understaging

Despite the development of new techniques (MRI, PSA) and the improvement of existing techniques (TRUS, Ct-scanning), it remains difficult to differentiate between locally confined and locally advanced disease. This is reflected not only in the understaging of T2 disease, which in 43-75% turns out to be histological pT3 disease[8,9,10], but also in the overstaging of T3 disease, which varies from 8-30%.[11,12,13,133] This means that in 8-30% of the clinical T3 patients, the disease is locally confined, and that they are candidates for radical surgery according to generally accepted standards. This treatment may be denied because of staging errors. Clinical overstaging was significantly associated with the preoperative tumor grade (p=0.04): in well and moderately differentiated tumors overstaging is more frequent than in poorly differentiated carcinoma.[133]
Understaging in clinical T3 disease occurs in 4%[12], which is pathologically pT4. These patients will suffer local recurrence and disease progression, despite surgery and are therefore not candidates for radical prostatectomy. In cases of doubt, T4 can be diagnosed performing a cystoscopy and bimanuel examination under anaesthesia.

Role of digital rectal examination (DRE), transrectal ultrasonography (TRUS), and magnetic resonance imaging (MRI) in detecting local extension of disease

Ohori[14] investigated 117 patients with clinically localized prostate cancer by DRE and TRUS. The sensitivity for detection of extracapsular extension(ECE) was 67% for DRE and 58% for TRUS. The positive and negative predictive values(PPV and NPV)for DRE and TRUS were 74% and 64%, and 82% and 63% respectively. When DRE and TRUS were combined, the PPV was 79% and the NPV 86%. There was however a big difference in sensitivity according to the localisation of the tumor: for anteriorly located tumors the sensitivity was 14%, compared to 60% for posterolateral and 86% for dorsally located tumors. Andriole[15] however, found

understaging of locally advanced disease by TRUS in 62%. McSherry found a PPV of 100% for DRE and 83% for TRUS. The NPV of DRE and TRUS however (i.e. the ability to exclude ECE) was 36% and 37% respectively[116]. These data indicate that there is a wide variation of the reliability of DRE and TRUS for determining ECE, probably because they are operator-dependent examinations, which depend on the personal skill of the investigator.

McSherry [116] reviewed the literature for the ability of MRI to identify ECE, and found PPV's varying from 66-82%, and NPV's from 30-90%, which again indicates a wide variation of reliability.

Role of prostate specific antigen (PSA) in detecting local extension of disease

PSA > 10 ng/ml has a sensitivity of 61% and a specificity of 88% for detection of ECE. The PPV is 88% and the NPV 62%[45]. Only 2% of the patients with a PSA > 15ng/ml have organ confined disease. Kabalin showed that the pre-operative PSA values correlate with cancer volume, grade, ECE, and the occurrence of lymph node metastases, and developed a PSA-based rating scale for use in treatment decisions. PSA did not significantly correlate with seminal vesicle involvement. A PSA > 10 ng/ml indicates a 40%, and a PSA > 25ng/ml a 50% chance of ECE[46]. Narayan et all investigated biopsy-based staging in combination with pre-operative PSA and biopsy Gleason score for detecting extraprostatic disease, and established probability plots for these variables, which give a prediction of the presence of ECE, seminal vesicle involvement and lymph node metastases[47].

Lymph node metastases in clinical T3 carcinoma.

Lymph node metastases (LNM) are frequently found in patients with clinical T3 carcinoma of the prostate; percentages of 33-56% are reported.[11,12,14,15] Once the pelvic lymph nodes are involved, the disease is no longer localized but systemic, and local radical therapy can not control the disease.[17]

Ct-scanning is of limited value in detecting LNM: Bosch described a sensitivity of only 35% for the detection of LNM, a PPV of 75% and a NPV of 59%.[18] MRI performs even worse, with a sensitivity for detecting LNM of 25%.[18] Wolf states that the probability of LNM should be 45% to make imaging beneficial. Partin developed nomograms which indicate a 50% risk for LNM when the Gleason score is 8-10 and the PSA is over 25 ng/ml.[19] Bluestein found LNM in 43% of patients with a PSA over 20 ng/ml and a primary Gleason grade 4 or 5.[20] If any doubt exists about the presence of LNM, a staging laparoscopic lymph node dissection should be performed, or frozen sections of the lymph nodes must be investigated intra operatively prior to the radical prostatectomy.

Influence of high grade disease on prognosis in T3 carcinoma

High grade disease (poorly differentiated carcinoma) is associated with high mortality due to prostate cancer (10 times higher than well or moderately differentiated carcinoma), and a high morbidity due to a high metastatic rate. (74% at 10 years post-diagnosis even in locally confined disease) in conservatively managed prostatic carcinoma.[21] Therefore effective therapy is urgently needed for this group of biologically agressive carcinomas. This aggressiveness is expressed in a high percentage of T3 disease (55-92%)[22,23], and a high percentage of aneuploidy, measured by DNA flowcytometry.[24] Nativ showed however that ploidy had no significant influence on progression once the tumor is poorly differentiated.[25]

Ohori found progression in 0% of the organ confined and in 80% of the non organ confined tumors with Gleason sum > 8.[22] Partin showed that 24% of the specimen confined tumors with Gleason > 8 progressed after 3 years, compared to 82% of the non-specimen confined tumors.[23] Both concluded that radical prostatectomy for high grade disease is to be limited to locally confined tumors.

Van den Ouden reported on a group of 100 patients with clinical T3 carcinoma, which contained 15 patients with T3pT3G3 carcinomas, treated by radical prostatectomy without adjuvant therapy. Of these patients 14 (93%) progressed within 2 years post surgery[12],

11

whereas patients with T3pT3G1 and 2 had similar progression rates as T2 disease.

Lerner performed radical prostatectomy in 501 patients with T3 Gleason > 7: 48% of the patients received adjuvant hormonal therapy. The actuarial cause specific survival rate at 5, 10 and 15 years was ± 80%, ± 70% and ± 50%[11], which may indicate a good response on the administration of adjuvant therapy in this high risk group, despite strong indications that adjuvant hormonal therapy probably does not influence survival.

In conclusion: patients with high grade tumors and stage T3 are not good candidates for radical prostatectomy. If radical prostatectomy is performed in selected cases (for example in young patients) for T3G3 carcinoma, adjuvant therapy is desirable.

NATURAL HISTORY

In recent years a number of studies is published on natural history of locally confined cancer, however the natural history of locally advanced prostate cancer is only rarely reported. This is probably due to the high risk for progression and death in these carcinomas, which appeals to the physician to start immediate treatment to prevent progression and to try to delay death due to cancer. Table 1 contains the studies concerning the natural history of locally advanced disease which were published in the last 30 years. Also some studies concerning locally confined carcinoma were summarized, since understaging is known to be a frequent event . For this reason especially the not very recent studies were selected, because staging in those days was less sophisticated than in the last decade, which added CT-scanning and transrectal ultrasonography to the diagnostic armamentarium (despite these further staging possibilities understaging still occurs in 43-75% in T2-disease). Since high stage-tumor is also known to correlate with a relatively high percentage of high grade and lymph node metastases, special attention was given to the composition of the reported groups in this matter. Therefore also a recent study concerning the natural history of lymph node positive patients was included [129].

The natural history of a disease may be defined as the clinical and pathological features characterizing the behaviour of the disease from its inception over time in the untreated patient. The important features are growth rate and metastatic potential. A simple form to describe growth rate is by relating tumor volume to a uniform and exponential increase in cells dependent only on the doubling time. A single cancer cell with a diameter of 10 micron takes 16 years to grow out to a tumor of 1 cm in diameter (30 doublings to produce 10^9 cells, with a doubling time of 6 months). Concerning the local progression rates listed in table 1, which vary between 22 and 84% in only 5 years, this means that all tumors were already long existing before they were diagnosed. This explanes the rapid local progression in some series [123]. Metastatic potential is the most important feature in prostate cancer, since most patients dying of prostate cancer do so because of metastases. Lymph nodes are often the first site of extraprostatic metastases. Once lymph node metastases occur, further dissemination of the tumor can be expected by the lymphatic chain, and its connection to the circulatory system. It is therefore not surprizing that the only series which has established lymph node metastases [129] , shows a higher metastatic rate at 5 years than the series where no lymph node metastases were expected: 39% versus 0-25%.

Fuks [124] is the only one who reports 10-year metastatic rates, in a group of patients who were treated by ^{125}I-implantation: this treatment is nowadays considered less effective for tumor-control, and may offer therefore an opportunity to study the natural history of prostate cancer. The metastatic rate increases with increasing grade, but there are to few patients in the G3-group, which may explain the lower percentage of metastases for these patients. The patient-groups reported by Aus [117], Adolfsson [121], Whitmore [122], Byar [128], and Graversen [127] contain no, or a very limited number of high-grade patients (<5%). Since high grade is more common in patients with locally advanced disease, these groups represent therefore a selection of patients with a relatively good prognosis , compared to the total population of patients with T3/C disease.

Overall survival is reported to vary from 10-92% at 5 years, 14-78% at 10 years, and 0-78% at 15 years. Whitmore [122] even reports a 20- and 25-year survival of 51 and 49%. These large differences indicate that these groups are hard to compare because of differences in: initial stage, grade, lymph node involvement, follow-up, and treatment when progression occurs. The

Table 1: Clinical progression, local progression, distant metastases, overall survival and cancer specific survival in patient with locally advanced untreated prostate cancer

Reference	N	Stage	CP 5yr(%)	LP 5yr(%)	DM 5yr(%)	DM 10yr(%)	OS 5yr(%)	OS 10yr(%)	OS 15yr(%)	CSS 5yr(%)	CSS 10yr(%)	CSS 15yr(%)
Aus (117)	88	T2b-T3M0G1-2	-	-	-	-	-	-	-	89	72[1]	-
Nesbit (118)	765	T3	-	-	-	-	10	-	-	-	-	-
Moskovitz (119)	17	T3[13]	-	-	-	-	42	42	-	-	-	-
Jones (120)	6	B2	-	-	-	-	83	17	0	-	-	-
	7	C[2]	-	-	-	-	71	14	0	-	-	-
Adolfsson (121)	50	T3NxM0G1-2[3]	-	64	24	37[4]	64	37[4]	-	88	70[4]	-
Whitmore (122)	37	B2	38	35	11	-	92	70	57[5]	86	78	78[6]
	9	B3	22	22	0	-	89	78	78[7]	100	100	100[8]
George (123)	120	T1-3M0	-	84	25	35[9]	-	-	-	60	-	-
Fuks (124)	33	B3-CN0G1[10]	-	-	-	27[11]	-	-	-	-	-	-
	62	B3-CN0G2[10]	-	-	-	56[11]	-	-	-	-	-	-
	10	B3-CN0G3[10]	-	-	-	50[11]	-	-	-	-	-	-
Vacurg (125)	248	III(placebo)	-	-	-	-	58	-	-	-	-	-
	251	III(orchidectomy)	-	-	-	-	56	-	-	-	-	-
	256	III(estrogen)	-	-	-	-	53	-	-	-	-	-
	237	III(orchidectomy + estrogen)	-	-	-	-	45	-	-	-	-	-
Byar (126)	20	II	35	-	-	-	84	-	-	-	-	-
Graversen (127)	18	II	-	-	-	-	-	-	39	-	-	-
Davidson (128)	36	T3-4N1-3M0	75[12]	36[12]	39[12]	-	-	-	-	-	-	-

[1] 9 year
[2] treated by [125] I-implant
[3] only 2 patients G3
[4] 9 year
[5] 20yr: 51%; 25yr: 49%
[6] 20yr: 78%; 25yr: 78%
[7] 20yr: 64%

[8] 20yr: 100%
[9] 7 year
[10] all pt. underwent ^{125}I-implantation
[11] after 4-9 years follow-up
[12] after a median follow-up of 41 months
[13] all patients underwent non-radical prostatectomy

VACURG-study is often referred to because it is the first study for untreated patients versus treatment patients in a randomized fashion. The articles by Byar [126] and Graversen [127] are follow-up studies of this report. Unfortunately several methodological flaws diminish the value of these observations: 22% of the patients had to be removed from the study because of protocol-violations, 75% of those had a second treatment; staging was inaccurate compared to modern standarts (no lymph node evaluation, no bone-scan); weak statistical power: Byar [126] indicated only a 33% chance of detecting a 50% difference in clinical progression, and Graversen [127] described a 47-90% chance to miss statistically significant differences in this material. So no definite conclusions can be drawn from these reports.

Cancer specific survival was only reported in 5 studies. After 5 years of follow-up the cancer specific survival varied between 60-100%, at 10 years from 70-100%, and at 15 years from 78-100%. In the study by George [123] several stages (T1-3) were reported together, but most patients must have had large tumors, considering the high local progression-rate and the fact that 90% was obstructed at the time of diagnosis. George does not describe the grade in his group. No patient had metastases at diagnosis. This, and the presence of large (and therefore probably many locally advanced) tumors leads to the suggestion that these patients represent a population with a selection for a non-metastatic phenotype. Despite this George reports the lowest percentage of cancer specific survival (60%). The other series reporting cancer specific survival, contain hardly any patients with high-grade disease, and are therefore selecting patients with a relatively favourable prognosis.

The fact that the patients described here did not receive curative treatment, did not mean that they had no treatment at all. Moskovitz [119] and Handley [120] performed non-radical prostatectomy in 100- and 95% of their patients. Whitmore [122] performed transurethral resection of the prostate in 31% of his patients, because of obstruction during follow-up, and hormonal therapy in 24%, Adolfsson [121] did TUR of the prostate in 22% to relieve obstruction; 58% received hormonal-, and 12% radio-therapy because of progression.

The natural history of locally advanced prostate cancer is not sufficiently understood. The articles reporting on this matter contain either patients who are not fit to undergo curative treatment, or they describe subgroups with a relatively good prognosis. In both ways a selection is made, so these results cannot be applied to the total population of patients with T3/C cancer.

RESULTS OF RADICAL SURGERY IN CLINICALLY LOCALLY ADVANCED DISEASE. (STAGE T3/C)

Overall Survival (O.S)

Table 2 shows the results for overall survival and cancer specific survival for patients with clinically advanced (stage T3/C) prostate cancer, treated by radical prostatectomy. There are many more reports in the literature concerning pathological stage T3/C, but this classification is only known after radical prostatectomy, when the major treatment decision has already been made; therefore these reports are summarized separately.

Overall survival depends, besides tumor control, on age (for all series the median age is about 65 years) and general health. This can make comparison with other treatments difficult, because patients fit to undergo radical surgery are generally in a better condition than their age-matched controls, who are treated with radiotherapy or conservative (hormonal) treatment. Overall survival ranged from 64-95% at 5 years, from 12,5-72% at 10 years and from 20-51% at 15 years post treatment. These differences can be explained by the difference in time (Jewett 1958 v.s. Lerner 1995): nowadays better postoperative care and better techniques of surgery are available. Many studies from early data do not evaluate LNM, since the prostatectomy is performed perineally. Therefore many patients with LNM may have early progression and death. Cancer specific survival is not reported in most studies before 1980. Zincke[31] reported 5 and 10 years survival of 80 and 65%, this was not significantly different from the survival in a group of men of the same age in the general population. This finding indicates excellent chances for patients with T3 carcinoma treated by radical prostatectomy, however these patients represent a selection of otherwise very healthy persons, because they

Table 2: Overall Survival and Cancer Specific Survival for patients with clinically diagnosed T3 or stage C prostate cancer.

Reference	N	Therapy	Adjuvant Therapy	Overall Survival (%)			Cancer specific survival (%)		
				5	10	15yr	5	10	15yr
Jewett (26)	48	RP	-	-	12,5	-	-	-	
Scott (27)	39	RP	HT (all)	74	61	29	83	79	68
Flocks (28)	69	RP	Au 198	74	67	28	-	-	-
Tomlinson (29)	24	RP	HT (43%)	82	-	-	-	-	-
Schroeder (30)	213	RP + PLND	HT (50%)	64	36	20	-	-	70*
Zincke (31)	49	RP + PLND	HT\RT(39%)	65	-	-	-	-	-
von Flamm (32)	20	RP	HT (90%)	46	-	-	-	-	-
Morgan (33)	232	RP + PLND	HT (54%)	84	72	-	89	82	-
Yamada (34)	25	RP + PLND	RT/HT	84	-	-	92	-	-
van den Ouden (12)	59	RP + PLND	-	83	-	-	90	-	-
Lerner (11)	812	RP + PLND	HT/RT (60%)	86	70	51	90	80	69
Gerber (133)	289	RP + PLND	RT/HT (?)	-	-	-	88	70	-

* during the observation period

RP = Radical prostatectomy
PLND = pelvine lymph node dissection
HT = hormonal therapy
RT = radiation therapy
Au 198 = interstitial radio active gold seeds implantation
- = not reported

are fit to undergo major surgery. Furthermore, many underwent hormonal therapy which has impact on short and intermediate term results.

Cancer specific survival (CSS)

CSS is the best parameter to evaluate the results of treatment for prostate cancer for survival, since intercurrent death by other diseases are excluded and the parameter relates more to the disease under study. CSS at 5, 10 and 15 years post treatment ranges from 85-92%; 70-82%; and 68-70% respectively. These ranges are remarkably narrow, considering the fact that a 25 years time difference lies between the first[27] and the last report.[11] Unfortunately this means also that little progress is made in the treatment of T3 carcinoma. Most studies administer either hormonal or adjuvant radiation treatment to a part of their patient populations. This however does not affect survival significantly.[11]

Clinical progression (CP)

Clinical progression, local recurrence and biochemical progression are listed in table 3. Clinical progression means (biopsy proven) local recurrence, and/or the occurrence of distant metastasis as detected by bone scans, ultrasonography or Ct-scans. Biochemical progression means a rise in PSA over a certain value; this value differs between the different reported series.
The clinical progression rates vary from 12-45% at 5 years, 39-49% at 10 years and 50-71% at 15 years post treatment. The progression rates for patients who did not have adjuvant treatment[12,15] were not very different from those who did.[27,31,33] The other studies contain too few patients to be reliable in this matter. This is surprising since adjuvant hormonal therapy is known to prolong the interval to progression[11,44]; this effect does not seem to last longer than 5 years.

Local recurrence (LR)

Local recurrence is expected when there is residual disease because of a positive margin of resection. The limited amount of periprostatic tissue and the presence of extra capsular extension (ECE) leads to a higher percentage of positive margins with increasing stage[37]. In T3 disease 47-81% have positive surgical margins.[37,38] Many surgeons hesitate therefore to save the neurovascular bundles in T3 disease. Partin showed positive margins after radical prostatectomy for ECE positive disease in 55% when the bundle was saved, versus 42% when it was sacrificed. Margin positive patients had a decreased time to disease recurrence (not significant), but after 3 years both groups showed biochemical progression in 70%. This may be due to occult metastasis in ECE patients at the time of surgery and suggests that fate is not determined by the margins but by the extent of the tumor.[39] Epstein investigated secondary resection of the bundle (during the same operation) after initially saving it in patients in whom a positive margin was expected. In 40% no tumor was found in the resected bundle[42]. This indicates the inefficiency of decision making intra operatively. Despite the high percentage of positive margins, the local recurrence rate is low indicating that radical prostatectomy for T3 disease leads to an excellent local control (table 3).

Biochemical progression (BP)

Data on biochemical progression are only available in 4 studies in this review. These were published after 1986, when PSA became available for routine-use. As can be seen in table 3 there are but little differences between the progression rates for the different groups, with exception of the group who received no adjuvant therapy, which showed a 5 year progression of 63%. All other groups administered hormonal and/or radiation adjuvant therapy in a considerable percentage of their patients (54-100%). The biochemical progression rates are higher than the clinical progression rates in all groups. The knowledge that biochemical progression preceeds clinical progression by 3-5 years[41], and that all biochemically progressed

16

Table 3: Clinical progression, local recurrence and biochemical progression in patients with clinically diagnosed T3 or stage C prostate cancer.

Reference	N	Clinical progression (%)			Local Recurrence (%)			Biochemical progression (%)	
		5	10	15yr	5	10	15yr	5	10yr
Scott (27)	39	38	49	7	–	–	–	–	–
Flocks (28)	69	–	–	–	–	4		–	–
Tomlinson (29)	24	–	–		–	9	–	–	–
Schroeder (30)	213	–	–	–	–	–	13*	–	–
Zincke (31)	49	45	–	–	18	–	–	–	–
Morgan (33)	232	31	44	–	10	18	–	49	62
Yamada (34)	25	12	–	–	–	–	–	48	–
van den Ouden (12)	59	36	–	–	–	–	–	63	–
Lerner (11)	812	–	39	50	–	20	29	42	59
Olsson (35)	7	14	–	–	–	–	–	–	–
Bosch (36)	15	36	–	–	–	–	–	–	–

* during the observation period

– = not reported

17

patients will suffer clinical progression, reveals a gloomy scenario for these patients.

COMPLICATIONS

The mortality rate of surgery in T3 disease is 0,4-1,5%.[11,42] The overall complication rate is 43%.[42] Stenosis of the anastomosis, requiring dilatation was present in 9-32%; incontinence in 14-23%, and impotence in 69%.[11,42] Davidson compared the complication rates of clinical stage T3 and T < 3, and found no significant differences.

RESULTS OF RADICAL SURGERY IN PATHOLOGICAL LOCALLY ADVANCED DISEASE (STAGE pT3/C)

Radical prostatectomy is a well established therapy for patients with clinically locally confined disease. However due to staging errors 43-75% of the patients with clinically confined disease turn out to have locally advanced disease (pT3/C)[8,9,10]. Based on local tumor extension these patients should have survival and progression rates, which are comparable to clinical stage T3 patients, since both have locally advanced disease. It is to be expected however, that in clinically T3 disease, the percentage of high grade tumors and LNM is higher, which leads to lower survival and higher progression rates.
In many patients with locally advanced disease adjuvant treatment is administered. Neo-adjuvant hormonal therapy is given pre-operatively, with the expectation that this may downstage the disease. Most patients however recieve postoperative adjuvant treatment, mostly radiotherapy(RT). To evaluate the effects on survival and progression, patient-groups with and without adjuvant treatment are reported separately here.

RESULTS OF RADICAL SURGERY IN PATHOLOGICAL LOCALLY ADVANCED DISEASE (STAGE pT3/C), IN PATIENTS TREATED WITH SURGERY ONLY

Overall survival

The results of overall survival in patients with pathological locally advanced prostate cancer in patients treated with surgery only are listed in table 4.The overall survival rates at 5,10, and 15 years range from 75-88%, 33-92%, and 13-21% respectively. Whereas the results of 5-year survival are quite comparable, there is a wide range in 10-year survival. This may be due to patient selection and treatment variables. The low percentage of survival noted by Elder(33%)[9] and Gibbons(39%)[50] may be the result of occult LNM at the time of surgery, since in both groups perineal prostatectomy was performed, without lymph node dissection.(in the group of Gibbons 5 out of 23 did undergo LND). On the other hand in the study with the highest percentage of survivors, which is also reported by Gibbons(92%)[49] , the lymph nodes were only evaluated by fine needle aspiration in selected patients with high risk for LNM,(tumor bulk>1,5 cm; bilateral tumor diagnosed by biopsy or high grade lesion). Patients with LNM which are not noted at the time of surgery may have the highest mortality in the period 5-10 years after operation. This explaines the large difference in survival at 5 and 10 years in the study by Elder[9]. Further evidence is found in the study by Hering[10], where cancer specific survival(CSS) drops from 83% at 5 year to 0% at 10 year(all patients died at 9 years postoperatively). In this group 55% of the patients had LNM at the time of surgery, which may explaine the drop in survival.

Cancer specific survival

CSS for patients with pathological stage pT3/C treated by surgery only is also listed in table 4. The CSS rates at 5,10, and 15 years range from 80-100%, 0-90%, and 25-89%. The considerations already made on behalf of the overall survival are also of concern for these numbers. The 0% CSS reported by Hering [10] is due to the high number of LNM(55%) in this

Table 4: Overall survival and cancer specific survival for patients with pathological stage pT3 or p-stage C prostate cancer, treated with surgery only.

Reference	N	Overall survival (%)			Cancer specific survival		
		5	10	15yr	5	10	15yr
Elder (9)	35	75	33	13	—	—	—
Gibbons (48)	49	—	92	—	—	—	—
Middleton (49) ECE	18	—	—	—	100	—	—
SV +	10	—	—	—	80	—	—
Gibbons (50)	23	—	39*	—	—	—	—
Anscher (51)	113	82	63	21	90	75	25
Fried (52)	6	83	67	—	100	83	—
Shevlin (53)	57	88	80	—	—	—	—
Gibbons (54)	9	—	—	—	—	—	89
Hering (10)	68	—	—	—	83	0**	—
Frohmuller (55)	22	—	55	—	—	68	—
Stein (56) SV -	82	—	—	—	—	90	—
SV +	33	—	—	—	—	63	—
Eisbruch (57)	43	—	55	—	—	—	—
Hawkins (58)	660	—	—	—	—	84	—

 * after average 9,2 year
** after 9 year
 - = not reported

Table 5: Clinical progression, local recurrence and biochemical progression in patients with pathological stage pT3 or C prostate cancer, treated with surgery only.

Reference		N	Clinical progression (%)			Local Recurrence (%)			Biochemical progression (%)	
			5	10	15yr	5	10	15yr	5	10yr
Elder (9)		35	25	66	87	-	-	-	-	-
Gibbons (48)		49	18	-	-	-	-	-	-	-
Middleton (49)	ECE	18	11*	-	-	0	-	-	-	-
	SV +	10	50	-	-	20	-	-	-	-
Gibbons (50)		23	-	39+	-	30××	-	-	-	-
Anscher(51)		113	-	-	-	25	51	68	-	-
Schellhammer (59)		16	-	-	-	31	-	31	-	-
Fried (52)		6	0	17	-	0	-	-	-	-
Catalona (60)		9	33	33	-	11	-	-	-	-
Shevlin (53)		57	-	-	-	20	28	-	-	-
Gibbons (54)		9	-	-	-	-	-	22	-	-
Mukamel (61)	ECE	48	25	50×	-	-	17×	-	-	-
	SV -	104	3	16×	-	-	-	-	-	-
	SV +	35	31	58×	-	-	-	-	-	-
Hering (10)		68	48	74'	-	-	-	-	-	-
Frohmuller (55)		22	-	45	-	-	-	-	-	-
Stein (56)	SV -	82	21	38	-	-	-	-	39•	59•
	SV +	33	42	-	-	-	-	-	-	-
Epstein (62)										
	focal ECE	93	-	-	-	-	-	-	18	-
	established ECE	103	-	-	-	-	-	-	35	-
Catalona (63)	ECE	227	-	-	-	-	-	-	26	-
	SV +	86	-	-	-	-	-	-	68	-
Eisbruch (57)		43	35	-	-	16	-	-	-	-
Zietman (38)		32	-	-	-	-	-	-	73'	-
Hawkins (58)										
	diploid	660	-	-	-	-	-	-	41	65
	non-diploid		-	-	-	-	-	-	50	72

* after 41,8 months
+ after average 9,2 years
× 8 years
' after 9 years

×× after average 51 months
• includes 115 organ-confined tumors
' after 4 years
ECE = extracapsular extension

- = not reported
SV = seminal vesicle invasion

group. After elimination of this study the range from 63-90% seems more reasonable. The 89% 15-year CSS reported by Gibbons[54] is remarkable, since none of these patients underwent LND. The group is however very small(only 9 patients), and a selection is made: the report considers only the patients who did not undergo adjuvant treatment after the finding of pathological stage T3 disease. It seems therefore logical that these patients represent a very favourable selection, and the excellent survival reported is not valid for the average pT3 patient.

Clinical progression
The results concerning the clinical progression (CP) in patients with pT3 treated by surgery only are listed in table 5. The CP-rates at 5 and 10 years range from 0-50%, 16-74% respectively. At 15 years only Elder[9] reports a 87% progression rate. The presence of LNM in 55% of the patients explanes the high progression rates reported by Hering[10]. Middleton[49] and Mukamel[51] reported the progression rates separately for patients with seminal vesicle involvement, which has a negative influence on progression.

Local recurrence

The results are also listed in table 5. Local recurrence(LR) is of special importance, since in many patients with locally advanced disease positive margins of resection occur, which point to local residual disease. This is the reason why adjuvant treatment is so frequently administered in this group of patients.
The local recurrence rates at 5, 10, and 15 years range from 0-31%, 17-51%, and 22-68% respectively. Mukamel found a significant difference between patients with only extracapsular extension and those with seminal vesicle involvement (0 versus 20%). The 0% LR reported by Fried[52] is in a very small group: only 6 patients. Schellhammer[69] found the same percentage (31%) LR at 5 and 15 years, indicating that LR occurs in the first 5 years postoperatively. There was a marked difference in LR between patients with extracapsular extension only and those with seminal vesicle involvement: 0 versus 44%. The study by Anscher[51] however shows an increasing percentage LR from 5 to 10 years. Considering that both groups are comparable for the percentage of high grade tumor and seminal vesicle involvement, this difference cannot be explained.

Biochemical progression

Biochemical progression for patients with pT3 treated by surgery only is listed in table 5, and ranges from 18-73% at 5 years and from 59-72% at 10 years. Since PSA only became a routine laboratory investigation in 1986, all 10 year progression rates are projections, and not observed values. For the same reason 15 year progression rates are not available. Since after a radical prostatectomy all prostatic tissue should be removed, the PSA should be 0, and therefore any elevation can be considered proof for residual prostatic tissue(and possibly cancer). The definition of BP varies among the different studies: Epstein[62] and Hawkins[54] use a limit of PSA>0,2 ng./ml; Stein[55] of PSA>0,4 ng./ml; Catalona[63] of PSA>0,6 ng./ml to define BP, whereas Zietman[36] only speaks of detectable PSA. These differences make the comparison between the different studies difficult. It is however clear that the BP rates exceed the CP rates, and given the fact that patients with BP will devellop CP in the line of time, the CP rates will rise with extended observation-time.

THE ROLE OF ADJUVANT TREATMENT IN THE MANAGEMENT OF LOCALLY ADVANCED PROSTATIC CANCER (STAGE pT3/C)

Neoadjuvant treatment

Neoadjuvant hormonal treatment is the administration of hormonal therapy before radical surgery, most often in locally advanced prostatic tumors, with the intent to downstage the tumor and make a radical resection possible. The rationale for neoadjuvant treatment is stated

Table 6: Downstaging by neo-adjuvant hormonal therapy prior to surgery for locally advanced prostate carcinoma.

Reference	N	Initial staging	Neo-adjuvant hormonal treatment	Down staged to pathologic stage T1/2 (A/B) (%)
Kennedy (67)	7	C stage C	LHRH-agonist 2-5 months	29
Labrie (68)	8	C stage C 1	LHRH-agonist + Flutamide	75
	7	C stage C 2	3 months	71
Pummer (69)	25	C stage B 2/C	LHRH-agonist 5 pt + Flutamine 4 months	4
Fair (64)	55	C stage B 2/3	DES 8-32 weeks	39
		C		26
		DO		40
Thompson (70)	24	C stage C	LHRH-agonist + Flutamide 3 months	13
Morgan (71)	36	C stage C	Megace + Estradiol cyclophosphamide (22pt) 3 months	11
Hellstrom (66)	35	C stage T3	LHRH-agonist (+ CPA) 3 months (CPA: 3 weeks)	50
Flamm (72)	21	C stage T3	LHRH-agonist + Flutamide 3 months	33
Schulman (130)	15	C stage T3	LHRH-agonist + Flutamide 2-12 months	27

LHRH = Luteinizing hormon releasing hormon
CPA = Cyproteron acetate

by Fair[64], and formulated in 5 points; 1:most prostatic tumors are significantly understaged; 2: hormonal therapy(HT) reduces the volume of the prostate gland and is standard therapy for metastatic prostate cancer; 3: animal studies with androgen sensitive tumors indicate that HT markedly depletes the tumor stam cell population; 4: the availability of PSA, TRUS, and improved biopty techniques allow earlier detection of disease progression, and therefore the impact of a given treatment can be evaluated earlier (we do not have to wait for survival data); 5: some data indicate that combined hormonal and surgical therapy is beneficial.

The initial enthousiasm for combined HT and surgery was raised by the study of Scott[27] in 1969, who administered HT to patients with locally advanced disease, who were therefore not candidates for surgery. In those patients who had a good respons to this treatment (i.e. a shrinkage of the tumor), radical perineal prostatectomy was performed. It is evident that this method of working contains a selection of patients: those who did not respond to HT did not undergo surgery. Scott reported excellent CSS of 68% at 15 years (see table 2). More recently Pilepich reported the results of a study in patients with bulky primairy lesions (clinical stage B or C); one group was treated with Gosereline and Flutamide 2 months prior to radiotherapy, the other group received only radiotherapy (65-70 Gy.). At 3 years there was a significant advantage in local control (84 versus 71%), survival free of clinical disease (61 versus 43%) and survival free of biochemical disease (46 versus 26%, BP is defined as PSA>4,0 ng./ml), and no significant advantage in the development of distant metastases (25 versus 30%)[65]. These early results seem encouraging, however since it is known that HT prolongs the time to progression, they are not surprizing. Long-term results, and especially CSS have to be awaited. In a recent thesis Hellström reports the results of 2 groups of patients, who underwent radical prostatectomy; group 1 had no neoadjuvant treatment, group 2 received a LHRH analoge 3 months before surgery. At 3 years the observed BP was only 16% in group 1 versus 43% in group 2. The latter contained however patients with more advanced disease, so these results have to be interpreted with caution[66]. Soloway reported on the results of a prospective randomized trial in which the patients with clinical stage T2b prostate cancerwere treated by radical prostatectomy alone, or in combination with neoadjuvant hormonal therapy (leuprolide and flutamide for 3 months). Despite the fact that the patients who recieved neoadjuvant androgen blockade showed a significant lower percentage of positive margins, the biochemical progression (PSA>0.4) at 12 months post surgery was not significantly different from the patient group that was treated with radical prostatectomy alone (BP: radical prostatectomy alone: 12%, radical prostatectomy and neoadjuvant hormonal therapy:16%; p=0.5). This finding was noted even after adjusting for preoperative PSA and Gleason score.[131] These findings are supported by a prospective multicentre randomized trial conducted by the Canadian Uro-Oncology Group, in which patients with stage A2, B1, or B2 were randomized for radical prostatectomy alone, or surgery after 12 weeks of Cyproterone acetate. No significant differences were found in post-treatment PSA at 6 and 12 months post-treatment between the two groups, despite the fact that the group who received neoadjuvant hormonal therapy showed a significantly lower percentage of positive margins of resection, lower prostatic weights, smaller tumor nodules, lower tumor volume, and higher Gleason scores.[132] Therefore long-term reports of progression and survival have to be awaited before neoadjuvant hormonal therapy can be considered beneficial.

Table 6 summarises some recent studies concerning the effect of downstaging by HT in locally advanced disease to organ confined disease. It is clear that there is a wide range in the results of downstaging by neoadjuvant HT. The high percentage of downstaging reported by Labrie[68] is remarkable, however: in the same study there was a control group of 7 patients with C1 and 5 patients with C2 disease who did not receive HT. Downstaging in these groups occurred in 57 and 20%. Especially the 57% downstaging in the stage C1-group raises questions about the accuracy of pre-treatment staging. In other studies concerning T3 patients downstaging without neoadjuvant HT occurs in 17-30%[11,12,13]. When these numbers are compared to the numbers in table 6, the downstaging by neoadjuvant therapy seems not very significant. Furthermore it has to be remembered that neoadjuvant HT causes histological changes. Hellström describes glandular atrophy, nuclear pyknosis, cytoplasmic vacuolisation, squamous metaplasia and an increase in the relative amount of stroma after the

administration of neoadjuvant hormonal therapy (LHRH agonist for 3 months and Cyproterone acetate for 3 weeks)[73]. These changes were not correlated to the pre-treatment tumor grade or volume of residual tumor. These changes make it more difficult to interpret the postoperative pathological histology, which may lead to postoperative staging errors, especially by pathologists who are not familiar with these changes. These staging errors may lead to a relatively high percentage of organ confined disease, since changed tumor cells outside the capsule are not recognized.

In conclusion: neoadjuvant HT is not recommended as standard treatment in locally advanced prostatic cancer. The results of downstaging are not impressive, and the results on survival are not yet known. Therefore it is advised to use neoadjuvant HT only in an experimental setting (preferably a randomized multi-center study).

<u>Postoperative adjuvant treatment</u>

Locally advanced disease treated by radical prostatectomy carries a relatively high risk of residual disease. Therefore many urologists tried to diminish the risk by the use of adjuvant treatment. Most studies reported are using radiotherapy, administered to the pelvis, and an extra boost for the prostatic bed. The total radiation-dose amounts to about 65 Gy., which is the same dose used in primairy RT for locally advanced prostate cancer. The ratio for this adjuvant radiotherapy(ART) is to eradicate all possible residual disease, to prevent local recurrence. Antagonists of this treatment argue that most patients with locally advanced prostate cancer die because of distant metastases and not of LR[77]. ART does not eradicate these micro-metastases, which are present, but unnoticed, at the time of surgery[74]. Lange treated 15 patients with persistent elavated PSA after RP with immediate ART(60 Gy.); the PSA level decreased to female levels in 53%, indicating that in 47% active prostatic tissue is left, which is not treated by local irradiation. Furthermore in 29 patients with BP, without evident CP, LR was found in 19 patients after biopty of the anastomosis. All patients received RT, but in no patient with LR the PSA level decreased to female levels, indicating that they had metastases elsewhere. Lange therefor advises adjuvant HT in patients with elevated PSA post-surgery[75].

Link reported on 12 patients with persistent elevated PSA immediately after surgery, who received immediately ART(6000-7000 rad). After 30 months only 1 out of 12 patients had a durable respons(PSA<0,3 ng./ml),all others had progressed, indicating that metastases were present at the time of RT[76].

As for local control: not all patients with positive margins of resection actually have local residual disease[40], and not all patients with positive margins experience progression. Paulson[77], in re-evaluating the patient-group reported by Anscher[51], failed to identify any benefit of postoperative ART in patients with p-stage C disease. McCarthy treated 2 patient-groups with either immediate or or delayed (after BP) RT post-surgery, and found no difference in survival with no evidence of disease (67 and 68% respectively)[78]. Since ART has also complications, and causes discomfort for the patient, it seems safe to wait with the administration until LR actually occurs.

Adjuvant hormonal therapy(AHT) is given in some patients with locally advanced tumors (see table 7-8). HT is however a palliative treatment, since only androgen-dependent cells respond to this treatment. Since the only established effect of AHT is the prolonged time to progression, only patients with a very high risk of early progression (like those with high-grade tumors) may benefit. An eventual survival-benefit is still a matter of debate.

<u>Overall survival</u>

The results of overall survival for patients with pT3 treated by surgery and adjuvant treatment are listed in table 7. OS at 5, 10, and 15 years ranges from 60-100%, 29-92%, and 17-90% respectively. Belt[79] also reports a 12% observed survival at 20 years. The survival reported in the early series, by Belt[79], Boxer[80],and Pilepich[81] is worse then in later series. This may be due to the fact that patients in this series had a perineal prostatectomy, without LND. Therefore those groups may contain many patients with lymph node positive disease, who are at risk for

Table 7: Overall survival and cancer specific survival for patients with pathological stage pT3 or C prostate cancer, treated with surgery and adjuvant treatment.

Reference	N	Adjuvant treatment	Overall survival (%)			Cancer specific survival (%)		
			5	10	15yr	5	10	15yr
Belt (79)	267	222 pt oral estrogens	63	37	17	-	-	-
Boxer (80)	74	most pt 1-5 mg estrogens	67	29	-	-	-	-
Pilepich (81)	18	RT: 6.000 - 7.000 RAD	60	-	-	-	-	-
Hanks (82)	11	RT: 60 GY	86	-	-	-	-	-
Lange (83)	24	RT: 6.000 RAD	79	-	-	-	-	-
Gibbons (50)	22	RT: 6.325 RAD	-	73*	-	-	-	-
Forman (84)	16	RT: 65 GY	100	-	-	-	-	-
Anscher (51)	46	RT: 45-65 GY Some pt hormonal therapy	96	90	90	96	91	90
Ami Sidi (85)	30	RT: 6.000 RAD	76	-	-	-	-	-
Fried (52)	6	RT: 50-65 GY	100	-	-	100	-	-
Carter (86)	31	RT: 45-55 GY	92[x]	92[x]	-	-	-	-
Shevlin (53)	16	RT: 45-72 GY	92	76	-	-	-	-
Terhorst (87)	51	RT in 9 pt (18%) and HT in 12 pt (24%)	-	-	-	98[+]	-	-
Cheng (88)	1035	HT only: 103 pt (10%) RT only: 131 pt (13%) all other pt: HT + RT	91	68	46	96	81	66
Freeman (89)	95	RT: ± 45 Gy,15 pt(DES)pré-OK	94	70	-	99	78	-
Eisbruch (57)	29	RT: 50-60 GY, 10 pt HT	-	46[x]	-	-	-	-
Hawkins (58)	131	RT: 60 GY	-	-	-	-	98	-
	103	Orchidectomy	-	-	-	-	95	-

[x] survival free of disease   RT = radiotherapy
[*] after average 9,2 years   HT = hormonal therapy
[+] after 4 years   DES = diëthylstilboestrol
- = not reported

Table 8: Clinical and biochemical progression in patients with pathological stage pT3 or C prostate cancer, treated with surgery and adjuvant treatment.

Reference	N	Adjuvant treatment	Clinical progression (%)			Biochemical progression (%)	
			5	10	15yr	5	10yr
Pilepich (81)	18	RT: 6.000 – 7.000 RAD	55	–	–	–	–
Hanks (82)	11	RT: 60 GY	14	–	–	–	–
Lange (83)	24	RT: 6.000 RAD	21	–	–	–	–
Gibbons (50)	22	RT: 6.325 RAD	–	27[x]	–	–	–
Forman (84)	16	RT: 65 GY	9	–	–	–	–
Anscher (51)	46	RT: 45-65 GY Some pt hormonal therapy	32	40	60	–	–
Ami Sidi (85)	30	RT: 6.000 RAD	24	–	–	–	–
Fried (52)	6	RT: 50-65 GY	0	0	–	–	–
Carter (86) ECE	31	RT: 45-55 GY	8	8	–	–	–
SV+	6		16	16	–	–	–
Shevlin (53)	16	RT: 45-72 GY	24	36	–	–	–
Terhorst (87)	51	RT in 9 pt (18%) and HT in 12 pt (24%)	4[•]	–	–	–	–
Kwon (90)	59	Radio-active gold seeds implantation	14	21	–	–	–
Cheng (88)	1035	HT only: (10%),RT only (13%) all other pt: HT + RT	22	44	52	36	54
Freeman (89)	95	RT: ± 45 Gy, 15 pt.DES pré-OK	6	13	–	34	46
Eisbruch (57)	29	RT: 50-60 GY, 10 pt HT	45	–	–	–	–
Hawkins (58)	131	RT: 60 GY	–	–	–	28-40	37-58
	103	Orchidectomy	–	–	–	15-19	19-35

[x] after average 9,2 years
[•] after 4 years
RT = radiotherapy
HT = hormonal therapy
– = not reported

Table 9: Local recurrence in patients with pathological stage pT3 or C prostate cancer, treated with surgery and adjuvant treatment.

Reference	N	Adjuvant treatment	Local recurrence (%) 5	10	15yr
Pilepich (81)	18	RT: 6.000 - 7.000 RAD	0	-	-
Hanks (82)	11	RT: 60 GY	0	-	-
Lange (83)	24	RT: 6.000 RAD	0	-	-
Gibbons (50)	22	RT: 6.325 RAD	-	5[x]	-
Anscher (51)	46	RT: 45-65 GY Some pt hormonal therapy	4	4	4
Ami Sidi (85)	30	RT: 6.000 RAD	0	3[*]	-
Fried (52)	6	RT: 50-65 GY	0	-	-
Carter (86)	31	RT: 45-55 GY	3	-	-
Shevlin (53)	16	RT: 45-72 GY	0	0	-
Terhorst (87)	51	RT in 9 pt (18%) and HT in 12 pt (24%)	0[*]	-	-
Kwon (90)	59	Radio-active gold seeds implantation	2	-	-
Eisbruch (57)	29	RT: 50-60 GY, 10 pt HT	14	-	-

[x] after average 107 months
[*] 101 months
[*] after 4 yr
RT = radiotherapy
HT = hormonal therapy
- = not reported

early progression and death.

Cancer specific survival

Table 7 contains the results of CSS for patients treated with surgery and adjuvant treatment. The CSS at 5, 10, and 15 years range from 96-100%, 78-98%, and from 66-90% respectively. CSS is reported only in series after 1987, so all patients underwent LND. This better selection may explain the excellent results. The series of Anscher[51] and Fried[52] show almost the same rates for OS and CSS, indicating that these are very healthy populations, and when a patient dies, it is of prostate cancer. The large study by Cheng[88](1035 patients), shows an increasing difference between OS and CSS over the years, indicating more intercurrent deaths with time.

Clinical and biochemical progression

Clinical and biochemical progression rates for patients treated with surgery and adjuvant treatment are listed in table 8. The CP rates at 5, 10, and 15 years range from 0-55%, 0-44%, and 52-60%. The high percentage of progression reported by Pilepich may be the result of unnoticed micro-metastases, since 10 out of 18 patients did not undergo a LND. Fried reports no progression after 10 years, however this is a very small serie (6 patients only). Only 3 studies report BP. The BP rates at 5, and 10 years range from 15-40% and from 19-58%. Freeman[89]uses a limit of PSA>0,4 ng./ml as indicator for BP; the other studies use PSA>0,2 ng./ml. In the serie by Hawkins[58] 2 progression rates are given; these are for diploid and non-diploid tumors respectively. It is evident that non-diploid tumors experience more progression, which confirmes the biological more agressive behaviour of these tumors. Furthermore, tumors treated by HT did better than those treated by RT, whether they were diploid or non-diploid. These differences may reflect the presence of micro-metastases at the time of surgery, which are not treated by (local) RT, but which are (palliatively) treated by HT.

Local recurrence

The results for LR after surgery and adjuvant treatment for pT3 patients are listed in table 9. The LR rates at 5 and 10 years range from 0-14%, and 0-5%; only Anscher[51] reports a 15 year LR rate of 4%. These rates are remarkably low. All patient-groups were treated with RT; these results confirm that excellent local control is achieved after ART. However when the LR rates are compared to the CP rates in table 8, large differences are evident. This means that when progression occurs in these patients, it is mostly the development of distant metastases, which cannot be prevented by local adjuvant treatment. Therefore delayed RT, which is administered only in those patients with proven LR, still remains a valid option; many patients will not develop LR and therefore do not need adjuvant RT.

LOCALLY ADVANCED PROSTATIC CANCER (pT3/C) TREATED BY RADIOTHERAPY

Since surgery for locally advanced carcinoma's has many difficulties, external beam radiotherapy has been the standard treatment for many years. Many patients however have a positive biopsy after RT, and it is known that this increases the chance of failing, with both local and distant recurrence[91,92,93]. Furthermore BP is less easy to interpret after RT, since the PSA nadir is only reached after 1 year. Stamey found that in only 8% of the patients treated by RT the PSA levels continued to decrease after one year post-treatment. Of 80 patients observed over 1 year post-RT, the PSA values increased in 51%, and remained stable in 41%, indicating that in 51% progression occurred after only one year. At 5 years only 11% of 183 patients had an undetectable PSA level[94]. Schellhammer reported on 45 patients with clinical stage C treated with external beam radiotherapy: only 13% reached a PSA level <0,5 ng./ml. There was no correlation between the PSA level and the finding of positive biopties post-treatment[95].
Porter described the role of RT in the management of locally advanced prostate cancer; in

Table 10: Overall survival and cancer specific survival for patients with clinically stage T3 or C prostate cancer, treated by radiotherapy.

Reference	N	Stage	Overall survival (%)			Cancer specific survival (%)		
			5	10	15yr	5	10	15yr
Holzman (97)	121	C stage C	75	31	16	83	43	25
Leibel (98)	324	T1,2,3: 102 pt T3	90	-	-	-	-	-
Fowler (99)	81	C stage C	47	22	-	67	30	-
Fellows (100)	88	T2-4; 50%, T3-4	44^x	-	-	-	-	-
Zagars (101)	602	C stage C	74	45	31	-	-	-
Rosen (102)	88	C stage C	61	35	-	-	-	-
Perez (103)	412	C stage C	65	42	-	-	-	-
Del Regato (104)	372	C stage C	66	38	17	-	-	-
Bagshaw (105)	385	C stage C	68	38	20	-	-	-
Hanks (106)	296	C stage C	56	32	23	-	-	-
Kaplan (107)	400	T3						
LR +			-	-	-	-	35	-
LR -			-	-	-	-	56	-

^{x} read from curves
- = not reported

Table 11: Clinical progression, local recurrence, distant metastases and biochemical progression in patients with clinical stage T3 or C prostate cancer, treated by radiotherapy.

Reference	N	Clinical progression (%)			Local Recurrence (%)			Distant metastases (%)			BP (%)	
		5	10	15yr	5	10	15yr	5	10	15yr	5	10yr
Holzman (97)	121	-	-	-	43	74	80	50	75	75	-	-
Leibel (98)	324	-	-	-	5^x	-	-	19^x	-	-	57^{xx}	-
Kaplan (107)	400	-	-	-	-	-	39	-	-	-		
Pilepich (65)												
HT+	227	39	-	-	16	-	-	25	-	-	54*	-
HT-	230	57	-	-	29	-	-	30	-	-	74*	-
Fowler (99)	81	61	91	-	-	-	-	50	68	-	66+	93+
Fellows (100)	88	-	-	-	65	-	-	75	-	-	-	-
Zagars (101)	602	41	56	70	14	24	41	34	45	54	-	-
Rosen (102)	88	47	65	-	-	30	-	-	-	-	-	-
Perez (103)	412	-	-	-	-	40	-	-	42	-	-	-
Bagshaw (105)	385	-	-	-	-	38	-	-	-	-	-	-
Hanks (106)	296	-	-	-	-	30	-	-	-	-	-	-

^{x} after median 18 months
^{xx}BP = 2x PSA > 4,0
* BP = PSA > 4,0 after one year
+ BP = PSA > 1,0
- = not reported

recent years 3 major radiotherapeutic modifications have been evaluated, which may lead to a better treatment of locally advanced prostate cancer[96]. 1: The relative integral dose can be increased using conformal external beam RT, photon therapy or brachytherapy; 2:The use of neoadjuvant HT to receive cyto-reduction; 3: Altering radiobiologic parameters by using altered fractionation and neutron radiotherapy. However, long-term results of these treatment alterations are not yet available.

<u>Overall survival</u>

The numbers for OS for patients with clinical locally advanced carcinoma treated by RT are listed in table 10. The OS percentages at 5, 10, and 15 years range from 44-90%, 22-45%, and 16-31% respectively. Only the patients reported by Holzman[97] underwent a staging LND; these patients were further treated by the implantation of AU[198]-seeds in the prostate, and external beam radiotherapy (6500-8000 rad). The patients reported by Leibel[98] underwent conformal RT with dose-escalation up to 81 Gy. All other groups used standard external beam RT (60-70 Gy.). The good results reported by Leibel[98] (90% OS at 5 years) are probably the result of the high radiation dose.

<u>Cancer specific survival</u>

Table 10 contains the results for patients with clinical T3/C disease treated by RT. There are unfortunately only a few studies that report this important parameter. Holzman[97] found CSS rates of 83, 43, and 25% at 5, 10 and 15 years respectively, whereas Fowler[99] reports 67% CSS at 5, and 30% CSS at 10 years. Kaplan[107] reports on CSS dependent on the presence or absence of LR. At 10 years the CSS rate for patients without LR is 56%, compared to only 35% for those with LR. The author states that these numbers prove the importance of local control for survival.

<u>Clinical progression</u>

The CP rates for patients with clinical T3/C treated by RT are listed in table 11. At 5 and 10 years, these rates range from 39-61%, and 56-91%; and at 15 years, only one study reports 70% CP. Pilepich[65] reports on 2 patients-groups, one treated with RT with neo-adjuvant HT (Goserelline and Flutamide for 2 months pre-treatment), and one group treated by RT only. He finds a clear difference in CP rates: 39 versus 57%. These numbers are however the results at 3 years post-treatment, and even the best result doesn't differ very much of the results reported by Zagars[101] and Rosen[102]. Holzman[97], Leibel[98], Fellows[100], and Perez[103] do not report CP separately, however these studies report metastatic rates, which give an indication for the presence of CP. These metastatic rates range from 19-75%, 42-75%, and 54-75%,at 5, 10, and 15 years.(table 11).

<u>Local recurrence</u>

The local recurrence rates for patients with clinical T3/C treated by RT are listed in table 11. At 5, 10, and 15 years these rates range from 5-65%, 24-74%, and 39-80%. The favourable 5% LR rate reported by Leibel[98] is after a median time of 18 months. The poor results for local control by RT alone are worrisome, considering the experiance of Kaplan[107], who finds that local control is important for survival. Furthermore LR leads to patient discomfort and the need for treatment; Holzman[97] reports that 36% of his patients needed a TUR of the prostate because of obstructing symptoms. He concludes that RT alone is not sufficient treatment for clinical stage C prostate cancer.

<u>Biochemical progression</u>

BP after RT for clinical stage T3/C disease is only reported in 3 studies (see table 10). BP after RT is a less sensitive parameter than after surgery, since there is always prostatic tissue

left and in most patients the PSA does not reach female levels. Furthermore the PSA nadir is reached at about 1 year, so the occurrence of BP cannot be determined very reliably in the first year, except when there is a rise of PSA after treatment, over the pre-treatment PSA value. Because of this limitations, the definition of BP after RT is less clear than after surgery. The 3 studies listed here are using 3 different definitions for BP. Leibel[98] defines BP as 2 consecutive PSA values >4,0 ng/ml, Pilepich as a PSA >4,0 ng/ml after one year post-treatment, and Fowler as a PSA>1,0 ng/ml. Despite these differences in definition, The BP rates are within a reasonable range of 54-74% at 5 years. The difference in BP in patient-groups treated with or without adjuvant HT , reported by Pilepich, is considerably (54 versus 74%), however since HT is known to prolong the time to progression, it is not spectacular.

Only Fowler reports a BP rate at 10 years, of 93%. Given the knowledge that all patients with BP will suffer CP in the end, this means that almost all patients in this group will suffer progression in the end.

SURGERY VERSUS RADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED PROSTATIC CARCINOMA

The comparison of surgery and radiotherapy in the treatment of prostate cancer is very difficult in the absence of randomized studies. In 1988 Hanks[108] reported on the obstacles for comparing RP and RT. These include the criteria for RP and RT (many patients who receive RT are not fit for RP because of a bad general condition), variations in endpoint reporting and method of data analysis (eliminating patients lost to follow-up from the calculated survival), the use of adjuvant HT, and differences in stage and grade between the different studies (in most patients treated by RT, the lymph nodes are not evaluated). Conant et all compared RP and RT for localized prostate cancer in a retrospective study of patients treated between 1950 and 1977, and found considerably better survival rates for patients treated by RP[109]. Lymph node status and grade are however not reported, which makes adeqate comparison difficult.

Olsson[33] compared RP, the implantation of ^{125}I seeds and external beam RT in a group of patients with stage A2, B, and C. All patients had negative lymph nodes. RP and ^{125}I treatment did not differ significantly for the time of first evidence of treatment failure, whereas patients treated by RT did significantly worse. Metastatic rates were 14% in patients treated by RP, versus 50% in patients treated by RT. Local control was considerably better in patients treated by RP than in those with[125]I implantation.

In 1995 Menon[110] compared the results of a study in patients treated by RP in the Mayo clinic[111] to a study of patients treated by RT[112] for clinically localized prostate cancer. The results were stratified by stage and grade; RP treated patients had a better overall, cancer specific, and progression-free survival then those treated by RT for all stages and grades.The marginal benefits in relative risks ranged from 1,10 to 1,79. In comparing patients treated by RP and RT with those treated by observation and delayed HT, they found better CSS in G1 and 2 patients for RP treated patients, whereas RT treated patients had no survival advantage. In G3 patients both RP and RT had better CSS compared to observation. They conclude that RP increases survival in patients with G1 and 2 prostate cancer under the age of 65 years, and in patients with G3 under the age of 75 years.

Paulson[113] compared RT to delayed HT in patients with clinical stage C carcinoma, in a randomized study and found no statistically significant difference in time to first evidence of treatment-failure. More recently Fellows compared patients with T2-4NxM0 prostate cancer treated with RT alone, orchiectomy alone, or a combination in a randomized study. He found no differences in local disease control or in overall survival, but only a significant delay in the detection of distant metastases in the patients treated by orchiectomy or the combined treatment[100].The results of these studies might be that RT alone is no better then HT for the treatment of localized prostate cancer; and that RP has a definite advantage in the treatment of localized prostate cancer. These studies comparing RP and RT are however done in localized cancer (stage<T3). Gibbons[114] reports on 2 studies of the National Prostate Cancer Projects: the multi-institutional protocols 900 and 1000. These protocols were conducted between 1978 and 1985, and contain respectively 55 patients treated by RT and 67 patients

Table 12. Average percentages for overall survival and cancer specific survival for patients treated by surgery or radiotherapy for clinical stage T3/c prostate cancer and patients with pathological pT3/c disease, treated by surgery with or without adjuvant therapy. The average numbers are calculated from table 1,3,6 and 9.

	clinical T3/c surgery	clinical T3/c radiotherapy	pathological pT3/c surgery only	pathological pT3/c surgery + adjuvant treatment
Overall survival (%)				
5yr	80,6	64,6	82	84,3
10yr	53,7	35,4	60,5	64,6
15yr	32	21,4	17	51
Cancer specific survival (%)				
5yr	89,2	75	90,6	97,8
10yr	80,3	41	66,1	88,6
15yr	69	25	57	78

Table 13. Average percentages for clinical progression, local recurrence and biochemical progression for patients treated by surgery or radiotherapy for clinical stage T3/c prostate cancer and patients with pathological pT3/c disease, treated by surgery with or without adjuvant therapy. The average numbers are calculated from table 2,4,7,8 and 10.

	clinical T3/c surgery	clinical T3/c radiotherapy	pathological pT3/c surgery only	pathological pT3/c surgery + adjuvant treatment
Clinical progression (%)				
5yr	30,3	49	26,3	19,6
10yr	44	70,6	43,6	22,8
15yr	60,5	70	87	56
Local recurrence (%)				
5yr	12,3	28,6	17	2,1
10yr	19	39,3	32	3
15yr	15,3	53,3	40,3	4
Biochemical progression (%)				
5yr	50,5	62,8	43,8	28,7
10yr	60,5	93	65,3	41,5

treated by RP for clinical stage T3 carcinoma. In each protocol comparable percentages of patients were treated with cyclophosphamide, estramustine, or no adjuvant treatment. There were no significant differences in overall survival and recurrence, regardless of the treatment. The results of studies that compare RP to RT for prostate cancer in the litterature are therefore not unanimous.

To estimate the outcome of RP versus RT in clinical T3 prostate cancer, we calculated the average percentages for survival and progression from the tables 1-4, and 6-10. The results are listed in table 12 and 13. It has to be stressed however that these numbers are only the average percentages of the studies reported in this chapter, and that they contain therefore a selection. The incorporation of other studies may alter these percentages. They have to be interpreted with caution.

It seems clear from the tables 12 and 13 that patients with locally advanced carcinoma treated by RP do better than those treated by RT, concerning overall and cancer specific survival, clinical and biochemical progression and in developping local recurrence, at all times during follow-up. It has however to be considered that patients who underwent surgery represent a subgroup with a better general health than those treated by RT, and that most patients in the surgery-groups also received adjuvant HT (see table 1 and 2). Furthermore the lymph nodes are only evaluated in one study concerning patients treated by RT, in contrast to patients treated by RP. A definite answer to the question which treatment is better for patients with locally advanced proatate cancer is therefore hard to give, altough there seems to be a trend that RP gives better results.

When the results of treatment-outcome are compared for patients with pathological stage pT3/C treated with surgery with or without adjuvant treatment, the first group seems to have an advantage in overall and cancer specific survival, at long-term follow-up (after 10-15 years), whereas the results at 5 years are comparable. Given the fact that RP is only offered to patients with a life-expectancy of at least 10 years, this may be of major importance in making a treatment decision: adjuvant therapy seems to offer an advantage.

The progression rates for clinical and biochemical progression are better for patients treated by adjuvant treatment; the difference is especially impressive for local recurrence. It has however to be remembered that patients who have not received adjuvant treatment can have this treatment at the actual time when progresssion occurs, whereas patients who already had got this treatment cannot. A better comparison would be to compare the time to second progression in patients who are initially not treated by adjuvant therapy, to the time of progression of those who received immediate adjuvant treatment. This has not been reported in the litterature.

Some studies have compared patients with pT3 treated with or without adjuvant treatment. Most studies confirm that progression rates are decreased after adjuvant treatment. A survival advantage is however only reported by Hawkins[59] who finds a trend that the CSS is better after adjuvant treatment. This trend however does not reach significance. Furthermore Anscher[61] reported a survival advantage after radiotherapy; this patient-group was however re-evaluated by Paulson[77], who excluded some patients who didn't have RP for prostate cancer. After this exclusion, the survival advantage was no longer existent. Lerner[11] did not find a survival advantage in patients treated by adjuvant HT.

Recently the EORTC started a protocol (EORTC 22911) to evaluate the treatment outcome in patients with pT3 disease treated with or without adjuvant radiotherapy.This is a randomized study, the results will have to be awaited.

In conclusion: patients with clinical locally advanced prostate cancer treated with RP do better than those treated by RT; and patients with pathological pT3/C do better after the administration of adjuvant therapy.

CONCLUSIONS

Radical prostatectomy for locally advanced (clinical stage T3 or C) disease is possible with acceptable mortality and morbidity, and is especially beneficial in patients who are down staged to pT2 (17-30%) and in those with well or moderately differentiated disease. Surgery for poorly differentiated disease seems only advisable in combination with adjuvant treatment.

Patients with lymph node metastasis should not undergo radical prostatectomy, but should be treated for systemic disease. For pathological T3-disease without adjuvant therapy, the survival- and progression rates are comparable to those for clinical T3-disease, some are even worse. The administration of adjuvant therapy (RT and/or HT) has some effect on CP and little effect on survival. The LR-rate is however significantly decreased after adjuvant radiotherapy.
Patients treated by radiotherapy for clinical T3-disease have the worst O.S. and CSS-rates. They also experience more progression and have a higher LR-rate, compared to patients treated by surgery. Especially the significant difference in CSS indicates that surgery (eventually combined with adjuvant therapy) is superior to radiotherapy alone for the treatment of locally advanced prostate cancer.
The results of pre-operative HT, given with the intention of downstaging the disease, are discouraging. Long-term results of survival and progression are not known; therefore this treatment cannot be advised as standard treatment.

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Radical prostatectomy as a monotherapy for locally advanced (stage T3) prostate cancer.

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RADICAL PROSTATECTOMY AS A MONOTHERAPY FOR LOCALLY ADVANCED (STAGE T3) PROSTATE CANCER

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ABSTRACT

Within a prospective protocol initiated in 1977, 100 patients with locally extensive prostate cancer (stage T3, 1982 tumor, nodes and metastasis classification) were treated by pelvic node dissection and radical prostatectomy as monotherapy. Adjuvant treatment was not given until disease progression. Radical prostatectomy, except for 3 young patients with a single micrometastasis, was not done if positive lymph nodes were found at frozen section. Six patients had positive lymph nodes at permanent sections but not at frozen section. Average followup was 43.9 months (range 1 to 155 months). Histological grade was determined according to the Mostofi system. Progression was determined biochemically (prostate specific antigen elevation) and clinically by evidence of metastatic disease, either histologically proved or evidenced as new hot spots on bone scan or chest x-rays.

Of the 100 patients 41 did not undergo radical prostatectomy: 39 because of positive lymph nodes and 2 because of evidence of a stage pT4 tumor at surgical exploration. Of those 59 patients who underwent radical prostatectomy 9 had positive lymph nodes, while 2 had stage pT4, 39 stage pT3 and 9 stage pT2 tumors. Only 1 of the 9 patients with lymph node metastases is free of biochemical or clinical progression. Disease also progressed in both stage pT4, 27 of 39 stage pT3 and none of the 9 stage pT2 cases. A total of 22 patients was free of clinical or biochemical progression. Clinical progression was evidenced in approximately half of the cases as distant and local progression. Data on stage T3 disease were compared to those of 129 patients with stages T0 to T2 disease. There was a significant difference in interval to clinical progression for these 2 groups (p = 0.001). However, if grade 3 cases were excluded from the stage T3 group, this difference disappeared.

Prognostic factors analyzed were pretreatment and posttreatment grade, pretreatment prostate specific antigen and prostatic acid phosphatase levels, positive margins, seminal vesicle invasion and nodal status. The analysis allows one to identify groups of patients who may benefit and others who certainly do not benefit from radical prostatectomy in this disease category. In the latter group effective adjuvant treatment is urgently indicated.

KEY WORDS: prostatic neoplasms, carcinoma, prostatectomy

The treatment of locally advanced stage T3 prostate carcinoma (stage C) remains controversial. Stage T3 prostate cancer has been treated by radical prostatectomy, radiotherapy, and hormonal and expectant treatment.[1] Several studies report the results of radical prostatectomy for pathological stage pT3 prostatic carcinoma, included as a result of clinical understaging.[2-4] Series reporting the results of radical prostatectomy in clinical stage T3 cases suffer from 2 problems: 1) the lymph node status is often not known[5] and 2) some form of postoperative adjuvant therapy is included.[6] The policy at our institution, within an ongoing prospective study, is to treat patients with stage T3N0M0 prostatic cancer by staging pelvic lymphadenectomy and, if lymph nodes are negative, radical prostatectomy. The early results were reported in 1987 by Bosch et al.[7] The updated results of the extended series are presented.

MATERIALS AND METHODS

Between 1977 and 1991, 100 patients with prostate cancer, clinically staged as T3N0M0 before treatment, were considered candidates for radical prostatectomy. These patients are included in a prospective study, with preoperative, perioperative and followup data being stored in a comprehensive database. Average age of all patients with stage T3 disease who presented for operation was 63.7 years (range 42 to 76). Average followup of patients who subsequently underwent radical prostatectomy was 43.9 months (range 1 to 155).

Clinical and pathological staging was done according to the

tumor, nodes and metastasis classification of 1982, in which a stage T3 tumor is one extending beyond the capsule, with or without involvement of the lateral sulci and/or seminal vesicles.[8] The stage pT3 classification follows the stage T3 classification and indicates carcinoma with invasion beyond the capsule and/or invasion of the seminal vesicles. Grading of these tumors was performed on the prostatic biopsy and on radical prostatectomy specimens according to the Mostofi system as either well (grade 1), moderately (grade 2) or poorly (grade 3) differentiated.[9] Cases in which the tumor extended microscopically into the surgical margin were positive. Cases of extension into 1 or both seminal vesicles were considered seminal vesicle positive. All patients judged to be free of lymph node metastases (N0) and distant metastases (M0) by physical examination, computerized tomography, lymphangiography (in the early part of the series), bone scan and chest x-ray were considered candidates for pelvic lymph node dissection and radical prostatectomy. In all patients either prostatic acid phosphatase (PAP) or prostate specific antigen (PSA) (Hybritech Tandem-R assay) levels were determined preoperatively but an elevated level of either did not influence the decision to operate.

All patients underwent staging pelvic lymphadenectomy and a frozen section examination of the lymph nodes was performed. In 6 patients nodal metastases were missed on frozen section but discovered on paraffin sections. Except for 3 patients in the latter part of the series who underwent radical prostatectomy and had a single microscopic focus of well differentiated tumor, patients with lymph node positive disease

48

did not undergo radical prostatectomy. Currently, a nerve sparing radical retropubic prostatectomy as described by Walsh et al[10,11] is performed. However, on the side(s) of the stage T3 tumor, a wide resection is performed and no attempt is made to spare the neurovascular bundles.

Patients were followed regularly with physical examination, PSA (PAP) levels, bone scans and, when indicated, other appropriate investigations. Clinical progression is defined as cytologically or histologically confirmed evidence of local recurrence and/or the presence of distant metastases, diagnosed by either bone scans or other radiological techniques. Biochemical progression was defined by a single PSA level of greater than 1.0 µg./l., or 2 consecutive PSA measurements of greater than 0.2 µg./l. (Hybritech assay). Patients with no evidence of clinical or biochemical progression at the time of the study were determined to have no evidence of disease. In this study no patient received any form of adjuvant treatment before clinical progression or preoperatively. Before 1987 PAP, determined according to the Abbott PAP sandwich solid phase enzyme immunassay using 2 different monoclonal antibodies, was used as a marker (normal value 2.2 µg./l. or less). The statistical techniques used are the Kaplan-Meier projection of interval to progression, the logrank test, the chi-square test and the Wilcoxon rank sum test.

RESULTS

Of the 100 patients 39 had positive lymph nodes on frozen section examination and did not undergo radical prostatectomy, as was the case with 2 patients who clearly had stage T4 disease at operation. Of the remaining 59 patients undergoing radical prostatectomy 3 were known to have positive nodes on frozen section, while 6 had positive nodes on definitive paraffin sectioning. Among the remaining 50 patients the disease was pathologically upstaged to pT4 in 2 (4%), pathologically downstaged to pT2 in 9 (18%) and remained at pT3 in 39 (78%, fig. 1). Of the 59 patients undergoing radical prostatectomy 1 was lost to followup, 6 died of prostate cancer, 4 died of intercurrent illness, and 48 remain alive and under followup. Furthermore, at the time of the evaluation 21 patients (36%) had clinical progression, 16 (27%) had evidence of biochemical (increased PSA level) progression only and 22 (37%) remained with no evidence of disease. The characteristics of the latter 22 patients are shown in table 1.

When compared with 129 stages T0 to T2 cases from our study database, patients with stage T3 disease had a significantly greater risk of clinical progression (fig. 2, A). Among the patients with stage T3 tumors the postoperative grade was found to affect the probability of progression, with grade 3 cancer patients having a significantly higher risk compared to those with grade 1 or 2 tumors (fig. 2, B). Figure 3 shows the probability of progression in stage T0 to T2 cases and in stage T3 cases divided into 2 groups according to preoperative grade (grades 1 plus 2 versus grade 3). There was no significant difference between patients with stage T0 to T2 (all grades) and stage T3 grade less than 3 disease but a significant difference did exist between these 2 groups and the stage T3 grade 3 group (p <0.01). The differences in the distribution of grade in figures 2, B and 3 are due to the use of preoperative versus postoperative grade in these figures. Table 2 shows the comparison between preoperative and postoperative grading. Under grading of pretreatment biopsies upgraded to grade 3 was noted in only 6 of 41 patients (14.6%). Curiously, in 3 patients with grade 3 tumor at biopsy, grade 2 tumors were diagnosed on definitive histology.

In stage T3pT3N0 cases positive surgical margins and seminal vesicle invasion did not significantly alter the risk of progression. This interesting finding was discussed in greater detail previously.[12] In figure 4 interval to progression in 71 patients from the data base who presented with less than stage T3 but stage PT3N0 tumor is compared to that of 39 patients with stage PT3N0 tumors. The difference is significant (p = 0.01). These data indicate that the clinical impression of capsular perforation is an important prognostic parameter despite all inaccuracy that has been associated with this finding.[7] However, this may not be an independent variable if it were compared to other adverse factors present in the stage T3pT3 group. Patients with a preoperative PSA level of greater than 20 µg./l. had a 58% chance of positive lymph nodes by clinical and biochemical means, and only a 5% chance of remaining with no evidence of disease at evaluation (fig. 5, A). Of those with a PAP level of greater than 2 µg./l. 62% had positive nodes and 7% remained with no evidence of disease (fig. 5, B). Of the patients with grade 3 cancer preoperatively 63% had positive nodes, while only 5% remained with no evidence of disease (fig. 5, C). There was a significantly greater risk of nodal disease with increasing grade (p = 0.04, table 3). Increasing PSA levels of greater than 20 µg./ml. or a PAP level of greater than 2 µg./ml. were not associated with a significantly elevated risk of positive nodes. Of those undergoing radical prostatectomy, patients with a preoperative PAP level of greater than 2 µg./l. had a significantly greater risk of progression (p = 0.02) than those with a PAP level of less than 2 µg./l. There was also a significant trend (p = 0.002) in risk of progression by increasing preoperative grade. Increasing preoperative PSA values (less than 10, 11 to 20 and greater than 20 µg./l.) did not significantly affect the risk of progression. Numbers of patients at risk are, however, few. The relationship between T categories and nodal metastases is shown in table 4.

Most patients with positive nodes were randomized to early versus delayed endocrine treatment within European Organization for Research and Treatment of Cancer protocol 30846, and the results are not yet known. All patients except 1 with negative frozen sections but positive paraffin sections who did undergo radical prostatectomy suffered progression. Of 15 patients 14 (93%) with stage T3pT3G3 tumors had progression.

DISCUSSION

Little is known about the natural course of stage T3 prostate cancer. However, recently Adolfsson reported on 50 patients with stage T3 disease followed expectantly for a median of 108 months.[13] The series included 29 patients (58%) with grade 1, 19 (38%) with grade 2 and only 2 (4%) with grade 3 tumors. For this and other reasons, the data cannot be compared to the results obtained in this study. Progression rates according to clinical and biochemical parameters are not indicated. The risk of progression to distant metastases was 24% at 5 years and 37% at 9 years. In our series the 5-year projected nonprogression rate was approximately 60%.
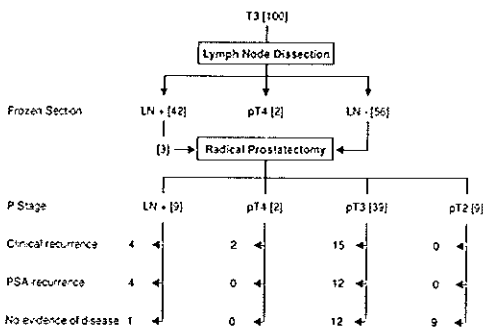

FIG. 1. Surgical staging and outcome in 100 patients with stage T3N0M0 prostate cancer. LN, lymph nodes.
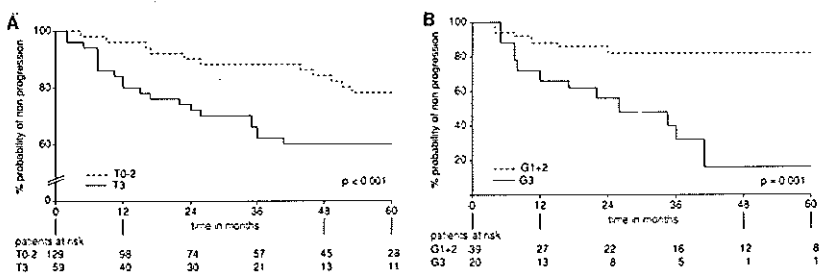
FIG. 2. *A*, probability of clinical progression is compared between patients who underwent radical prostatectomy for stage T3 (59) and stage T0-2pN0M0 (129) disease. *B*, probability of clinical nonprogression in 59 patients with stage T3 prostate cancer, and grades 1 plus 2 (39) and grade 3 (20) tumors. Grade is determined on radical prostatectomy specimens. Kaplan-Meier projection.
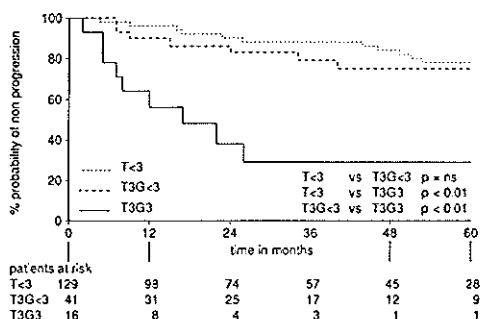

FIG. 3. Probability of clinical nonprogression is compared for 129 patients with less than stage T3 disease from data base to those with stage T3 grade less than 3 and stage T3 grade 3 disease (preoperative grading) from study population. No difference in probability of nonprogression is found for less than stage T3 versus stage T3 grade 3 groups. Kaplan-Meier projection.

TABLE 2. *Preoperative grading of core biopsies compared to grading of radical prostatectomy specimens*

Preop. Grade	No. Postop. Grade (%)			Total No. (%)
	1	2	3	
1	0 (0)	8 (80)	2 (20)	10 (18)
2	1 (3)	26 (84)	4 (13)	31 (54)
3	0 (0)	3 (19)	13 (81)	16 (28)
Totals	1 (2)	37 (65)	19 (33)	57 (100)
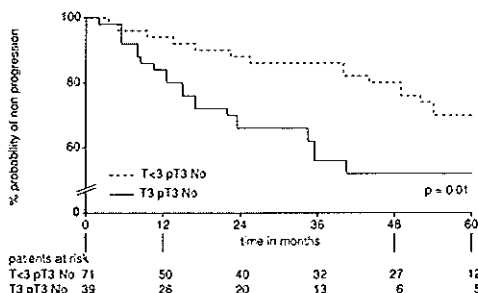
FIG. 4. Probability of clinical nonprogression is compared for 71 patients with less than stage T3pT3N0 tumors from data base to 39 with stage T3pT3 disease from study population. Significant difference indicates that impression of stage T3 disease on rectal examination is adverse prognostic factor compared with histological established penetration of prostatic capsule. Kaplan-Meier projection.

Little information exists about the use of radical prostatectomy as monotherapy for locally advanced (stage T3) prostatic carcinoma. The policy at our institution is to offer patients with stage T3 tumors of the prostate evaluation for potentially curative management within an ongoing study protocol. No adjuvant therapy is given until clinical progression occurs. The early results of this series were reported by Bosch et al.[7,14]

Staging pelvic lymphadenectomy always proceeded radical prostatectomy and in 48% of the stage T3 cases tumor-involved lymph nodes were found. This rate is similar to the 51% rate reported by Zincke et al in their cases of clinical stage C disease.[6] Six patients had positive lymph nodes on paraffin sectioning that were not detected by frozen section and all positive frozen sections were confirmed by paraffin section, for a sensitivity of 88% and a specificity of 100% for the frozen section, which compares favorably with other reported series.[15,16] Because positive lymph nodes predict a shorter interval

TABLE 1. *Pretreatment characteristics of progression-free patients*

Pt. No.	Grade		Seminal Vesicle Involvement	Margins	PSA	PAP	Followup (mos.)
	Preop.	Postop.					
Category T3pT2N0M0, 9 pts.							
1	1	2	Neg.	Neg.	6.5	0.9	12
2	2	2	Neg.	Neg.	—	0.9	105
3	2	2	Neg.	Neg.	44.0	1.2	36
4	1	2	Neg.	Neg.	—	6.3*	150
5	2	2	Neg.	Neg.	—	1.4	51
6	3	3	Neg.	Neg.	19.4	2.6	21
7	2	2	Neg.	Neg.	—	1.2	63
8	2	2	Neg.	Neg.	—	1.2	123
9	2	2	Neg.	Neg.	—	1.1	72
Category T3pT3N0M0, 12 pts.							
1	2	3	Pos.	Pos.	5.6	—	39
2	1	2	Neg.	Pos.	—	1.8	3
3	1	2	Neg.	Pos.	—	2.0	84
4	2	2	Pos.	Neg.	—	0.3*	123
5	2	2	Pos.	Neg.	—	8.0	21
6	1	2	Neg.	Neg.	7.4	—	6
7	1	2	Neg.	Neg.	—	5.0	45
8	2	1	Neg.	Neg.	13.9	—	12
9	3	2	Neg.	Neg.	5.7	—	9
10	2	2	Pos.	Neg.	7.7	1.2	36
11	2	2	Neg.	Neg.	—	2.4	45
12	2	2	Neg.	Neg.	—	1.1	33

* Acid phosphatase, King-Armstrong units.

A

% Patients

Legend: 0-10ug/L, 10-20ug/L, >20ug/L

OUTCOME [40 patients]

X-axis: LN+, CP, BP, NED

B

% Patients

Legend: 0-2ug/L, >2ug/L

OUTCOME [73 patients]

X-axis: LN+, CP, BP, NED

C

% Patients

Legend: G1, G2, G3

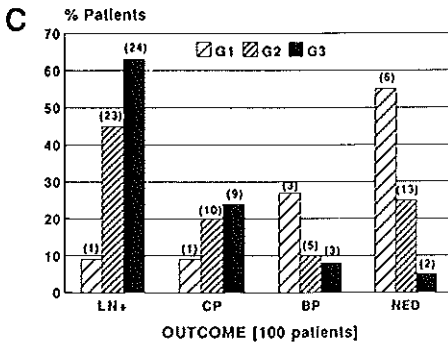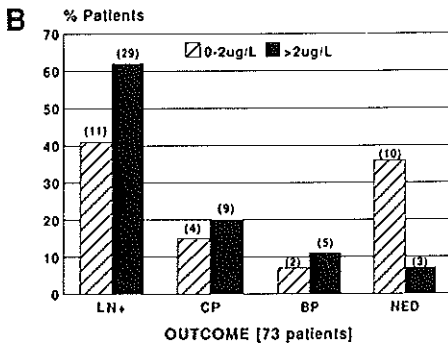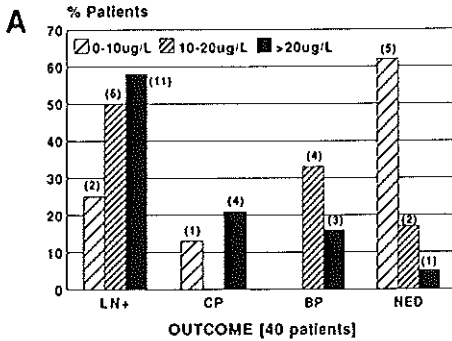OUTCOME [100 patients]

X-axis: LN+, CP, BP, NED

FIG. 5. Outcome for pN+ category, clinical progression (CP), biochemical progression (BP) and no evidence of disease (NED) status is correlated to preoperative levels of PSA (A) and PAP (B), and to preoperative grade of differentiation (C). While statistically significant correlation with presence of nodal metastases has been shown only for preoperative grade (table 3), all 3 parameters individually correlate significantly with presence or absence of progression. Patients with PSA of more than 20 ng./ml., PAP of more than 2 μg./l. or grade 3 tumors have only 5 to 10% chance of having no evidence of disease at 43 months. Numbers above bars indicate numbers of patients in given subgroups in whom this test result was available at entry into study. PSA was done since 1987. PAP was not always done later. Percentages on abscissa indicate for lymph node positive group (LN+) proportion of patients with positive modes. For lymph node negative patients who actually underwent radical prostatectomy proportions with clinical progression, biochemical progression and no evidence of disease are indicated separately.

TABLE 3. Relationship of preoperative grade, PSA and PAP to positive nodes and progression

Preop.	Node Pos.	Progression
Grade	p = 0.04	p = 0.002
PSA	Not significant	Not significant
PAP	Not significant	p = 0.02

TABLE 4. Tumor, nodes and metastasis classification, nodal metastases and progression in 100 patients with stage T3 prostate cancer

Classification	No.	No. Pos. Lymph Nodes	No. Radical Prostatectomy	No. Progression (%)
T3pTxG1	1	1	0	?
T3pTxG2	18	18	0	?
T3pTxG3	20	20	0	?
T3pT2G1-2	9	1	9	1 (7)
T3pT2G3	1	0	1	0 (0)
T3pT3G1-2	32	4	32	20 (63)
T3pT3G3	15	4	15	14 (93)
T3pT4G1-2	3	0	1	1 (33)
T3pT4G3	1	0	1	1 (100)

to progression[17] and a worse survival rate[18] radical prostatectomy is not performed in patients demonstrated to have lymph node positive disease by frozen section. Radical prostatectomy was done in 3 young patients, with a single microscopic focus of well differentiated tumor noted on frozen section. All 3 men had evidence of biochemical progression but have not yet demonstrated clinical progression. Only 1 of the 9 patients with positive nodes on paraffin section and who underwent radical prostatectomy remains without evidence of disease (grade 2 tumor with a 21-month followup), lending support to the concept that lymph node positive disease, even if limited to 1 microscopic focus, is a manifestation of systemic disease.

In this series 50 patients were free of lymph node disease and underwent radical prostatectomy. Of these men the disease was upstaged to stage pT4 in only 2. This low number is possibly due to the fact that in cases when there is any doubt urethrocystoscopy and bimanual examination with the patient under anesthesia were performed to exclude extension into either the external sphincter or bladder neck regions. Nine cases (18%) were pathologically downstaged to stage pT2, which is less than the 30% rate demonstrated by Boxer et al[2] and Rannikko and Salo,[19] the 26% rate reported by Zincke et al[6] and the 24% rate found in the earlier evaluation of this series by Bosch et al.[7] This relatively high incidence of downstaging should be considered when evaluating the results of phase 2 trials assessing androgen deprivation in stage T3 cases before radical prostatectomy. All 9 patients whose disease was downstaged to stage pT2 remained free of clinical and biochemical progression at the time of the study.

Of 39 patients in whom the histological stage (pT3pN0) matched the clinical staging (T3N0), 38% had evidence of clinical progression and 31% of biochemical progression at evaluation. Of those with clinical progression 11 had evidence of local progression and 12 of metastatic disease. This high incidence of metastatic disease and the short interval to progression support the concept that in many cases stage T3 prostate cancer is already a systemic disease.

Histopathological grade of the radical prostatectomy specimen has been shown previously to be an important prognostic factor in assessing the risk of progression.[20] In this series the patients with stage T3 disease treated by radical prostatectomy who had grade 3 tumors form a subgroup with a particularly high risk of progression. It is interesting to note that when this subgroup was eliminated, no significant difference in the risk of progression was shown between stages T3 and less than T3 tumors.

Involvement of the seminal vesicles and positive resection margins are believed by many to be important prognostic

51

factors in assessing the risk of progression. In this series neither of these factors had a significant, independent effect on the risk of progression in patients with stage T3pT3N0 tumors. Clearly, the presence of a stage T3 tumor is an overruling prognostic factor.

All patients were followed by regular PSA or PAP measurements postoperatively. At this institution the detectable limit of PSA is 0.1 μg./l. However, there were several patients with a single spurious result greater than 0.1 ng./ml. but this was never greater than 1.0 ng./ml. and always decreased to undetectable levels with subsequent measurement. Since no patient with a PSA level of greater than 0.2 ng./ml. on 2 consecutive tests or with a single PSA value of greater than 1.0 ng./ml. subsequently had an undetectable PSA value these were used as the indicators of an increased PSA level. Lange et al showed that all patients in their series with a PSA level of greater than 0.4 μg./l. subsequently had clinical progression[21] and Bentvelsen et al demonstrated that in those with a PSA level of greater than 1.0 μg./l. clinical progression was evident after a mean followup of 11 months.[22] Thus, it is reasonable to assume that all patients with an elevated PSA value will subsequently have clinical progression. Therefore, of these stage T3pT3 cancer patients only 12 (31%) remained without evidence of disease at the time of study. If these patients are combined with the 9 with stage pT2 cancer, then 38% of the 56 patients with negative frozen sections remained free of evident disease with an average followup of 43.9 months.

Preoperative PSA and PAP levels, and grade of the preoperative biopsy were assessed as predictors of risk of progression. There was no significant difference in the risk of progression between patients with PSA values of less than 10, 10 to 20 or greater than 20, which is probably due to the small number of patients with a preoperative PSA result available for analysis and the short followup. A preoperative PAP above the laboratory limit of 2.0 μg./l. was associated with a significantly increased risk of progression, which is in accordance with the findings of Byar and Corle, who showed an increasing risk of progression with increasing PAP levels.[23] The histopathological grade of the preoperative biopsy is a significant predictor of progression, even though it correlated with the grade of the surgical specimen in only 68% of the cases. Grade 3 tumors were correctly identified by biopsy in 16 of 22 cases (73%).

Although lymph node positive disease was found in the majority of patients with a PSA level of greater than 20 μg./l., PAP levels of greater than 2 μg./l. or grade 3 tumors, only grade was useful in predicting those with a greater likelihood of nodal disease. These findings are in agreement with those of Greskovich et al, who found no difference in the median PSA values between lymph node positive and negative disease in stage C cases[24] but contrary to those of Whitesel et al, who found a higher incidence of positive nodes when the PAP level was elevated.[25] This group was not directly comparable, however, since they were all patients with clinically localized disease (stages A1 to B2).

Because the mean followup in this series remains short, and because only 6 patients died of the disease, survival was not assessed in this study. We describe several subpopulations of patients who have a less than 10% chance of being free of biochemical or clinical progression at 43.9 months average followup. These are patients with stage T3 grade 3 tumors (grade 3 on biopsy), stage T3 tumor and either a PSA level of greater than 20 ng./ml. or a PAP level of greater than 2 μg./l., or stage T3N+ tumors. Of 9 patients with nodal micrometastases 8 showed progression. Patients with these prognostic factors probably should be excluded from radical surgery unless an effective adjuvant treatment is applied that still maintains a chance of cure.

In conclusion, radical prostatectomy for locally advanced prostatic carcinoma (stage T3) remains an option when the patient is treated with curative intent. The risk of progression

with the present limited followup in these patients is not significantly different when compared to those with locally confined (stages T0 to T2) tumors, if stage T3 grade 3 cases are excluded. Patients with poorly differentiated tumors (grade 3) represent a subgroup with an unfavorable prognosis within the stage T3 group. Whether radical prostatectomy offers advantages in local control, or whether adjuvant therapy can improve progression-free survival rates in these patients is unknown and will need to be the subject of further studies. Complications encountered during and after the operation were comparable in stages T3 and T2 cases. There was no increased requirement for blood transfusions and no increase of perioperative complications, incontinence or urethral stenosis. These data are subject to a separate report.[26]

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53

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Radical prostatectomy: prospective assessment of mortality and morbidity.

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Clinical Paper

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Radical Prostatectomy: Prospective Assessment of Mortality and Morbidity

Abstract
Objective: To prospectively analyse the morbidity of radical prostatectomy. Methods: Morbidity data from 188 consecutive radical prostatectomy patients were collected prospectively. Mortality, intraoperative, early postoperative and late postoperative complications were analysed. Results: 1.5% mortality. 3.7% suffered an intraoperative complication. Early postoperative problems were common (43%). Of those with greater than 1 year follow-up, 5.9% remained with some incontinence, and a further 11 patients had artificial sphincters implanted; 32% had narrowing of the anastomosis, requiring at least 1 dilation; 43% of patients retained their potency. Conclusion: It is concluded that radical prostatectomy can be performed with minimal mortality and acceptable morbidity.

Introduction

The combination of modifications to the operation of radical prostatectomy and the prostate- specific antigen driven upsurge in early detection of prostate cancer have led to both an increase in the popularity and numbers of radical prostatectomies performed. At the authors' institution, radical prostatectomy is being performed since 1977. The complications from these procedures are reviewed.

Patients and Methods

The patient population consists of 188 patients with prostate cancer. Five of the earlier patients had a radical perineal prostatectomy, and the rest were treated by radical retropubic prostatectomy. In 1986, the modifications described by Walsh [1] were adopted. The patients were included in a prospective study; preoperative, peri-

operative and follow-up data were stored in a comprehensive database. The average patient age was 63 years (range 45–76) and the operations were all performed between 1977 and April 1991.

Clinical and pathological staging is according to the TNM classification of 1982. At follow-up, each patient was asked specific questions about continence and the presence or absence of obstructive symptoms. From the beginning of 1987 onwards, questions on potency were included in the follow-up questionnaire.

Continence was defined as being completely dry and requiring no pads. Grade 1 incontinence was where a patient needed 1–2 pads per day and grade 2 required more than 2 pads per day. Further, pads were weighed in those who were incontinent after initial removal of the catheter. Anastomotic stenosis was defined as symptoms of outflow obstruction requiring a dilatation. A patient was considered potent if he could attain an erection sufficient for intercourse. Impotence was the inability to attain such an erection. All patients were asked preoperatively as to whether they were sexually active.

Late complications were analysed for risk factors. Age (older or younger than 70), previous transurethral resection of the prostate (TURP), T stage, pT stage, experience of the surgeon, presence or absence of extravasation on postoperative cystogram, and timing of the operation (before or after 1987) were all assessed. The cutoff of

56

1987 as a divider between an early and a late study group was chosen for two reasons: the first was that the number of radical prostatectomies performed each year rose to greater than 20 at that time. The second reason for this cutt-off date was that it was the first year where the technical modifications of the 'nerve-sparing' technique were universally adapted, having been introduced in 1986. The experience of the surgeon was assessed by comparing surgeon 1 (who had performed 58% of the operations) with the other surgeons collectively. Total number of units of blood transfused during hospital admission was chosen as a representation of operative blood loss. It was found that the recorded intraoperative blood loss was influenced by too many extraneous factors to be a reliable indicator.

The Fisher exact test was used to test the impact of the risk factors on late postoperative complications.

Results

There were 3 postoperative deaths in this series. One patient had an autopsy-confirmed pulmonary embolus on the 10th postoperative day. He had suffered a previous embolus at the time of vascular surgery 13 years before, and had both subcutaneous heparin and graduated compression stocking prophylaxis before his prostatectomy. The second patient collapsed at home on the 17th postoperative day. The cause of death was presumed to be a pulmonary embolus, although this was not confirmed by postmortem examination. He also had both heparin and stocking prophylaxis at the time of the operation. The last patient was one of the first in the series. He had considerable intraoperative blood loss and developed a hematoma postoperatively. Following this, he had prolonged drainage from his anastomotic site. He then became septic and died after a protracted intensive care. At postmortem examination he was found to have an aspiration pneumonia, myocardial infarction and peritonitis secondary to his drain perforating a loop of the ileum. All 3 of these deaths occurred in the early part of the series.

There were 7 intraoperative complications. Four of these were rectal injuries. Two of these were simply oversewn in two layers and 2 required colostomies. There were no sequelae from these injuries. Two external iliac vein injuries and 1 ureter injury were caused during lymph node dissection. All were immediately recognised and repaired without further consequences. The mean number of transfused units was 5.3, but this figure is skewed by 2 early cases requiring massive transfusions. The median number of transfused units was 4. Blood requirements decreased over the duration of the study.

The most common early postoperative complications are shown in table 1. The most common were wound infections, prolonged lymph drainage, lymphocele and

Table 1. The most common early postoperative complications seen in 81/188 consecutive patients after radical prostatectomy

	Patients, %
Lymph drainage >2 weeks	17
Lymphocele drained	7
Postoperative bleeding	6
Thromboembolic	5
Pneumonia	2
Fistula	1
Myocardial infarction	2
Ureteric obstruction	1
Other	16

107/188 (57%) were free from complications.

Table 2. Remaining postoperative complications of radical prostatectomy in 188 patients

UTI	9
Pyrexia unknown origin	4
Epididymitis	2
Superficial thrombophlebitis	2
Lymphedema	2
Ulnar nerve palsy	1
Femoral nerve palsy	1
Obturator nerve neuropraxia	1
Acute atrial fibrillation	1
Temporary unexplained jaundice	1
Urethritis	1
Acute psychosis	1
Urosepsis (ICU)	1
Burst balloon (OT)	1
Appendicitis (OT)	1
Wound dehiscence (OT)	1
Total	30

OT = Returned to operating theatre; ICU = required transfer to intensive care unit.

bleeding. The other early postoperative complications are listed in table 2. Of the 188 patients, 81 had one or more complications, leaving 107 (57%) with a completely uncomplicated postoperative course. The number of early postoperative complications per patient decreased over the course of the study (fig. 1).
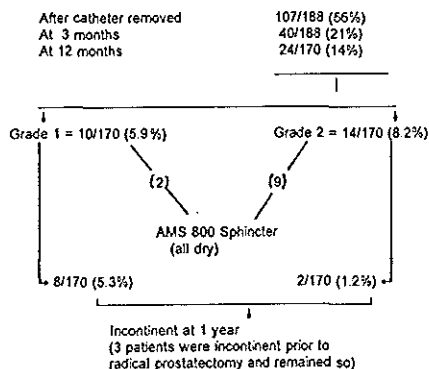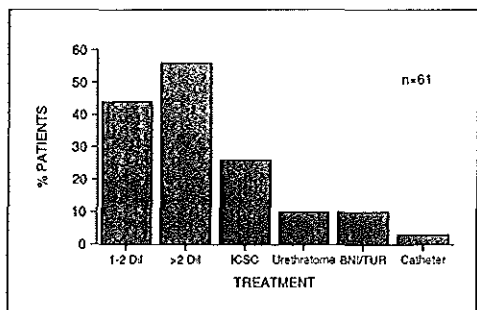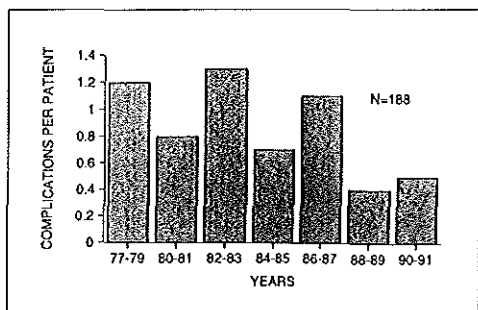
Incontinence was very common after removal of the catheter, with 107 (56%) requiring pads. The mean measured urinary loss in these patients over 24 h was 226 ml. The amount of this initial loss did not predict time to regaining continence. Hundred and eighty-eight patients had been followed for 3 months and 40 (21%) were still incontinent; 170 patients had been followed for more than 12 months, and of these, 10 (5.9%) had grade 1 and 14 (8.2%) grade 2 incontinence. At the time of study, 11 of these patients had been implanted with AMS artificial sphincters and were continent. Three of the patients with grade 2 incontinence were incontinent prior to surgery, and if these are excluded, then of those with >12 months follow-up at the time of study 8 patients (4.7%) remain with grade 1 and 2 (1.2%) with grade 2 incontinence (fig. 2).

Sixty-one patients required at least one dilatation of the anastomosis, and were therefore considered by definition to have a postoperative anastomotic stenosis. The majority of these were cured by simple dilatation (fig. 3). All of those requiring a bladder neck incision, TUR of the bladder neck or a permanent catheter were from the early part of the series, before the modifications described by Walsh [1].

Hundred and one patients had their potency status assessed on follow-up. Fifteen of these were impotent preoperatively and another 10 were potent but not sexually active. Intraoperative details of nerve sparing were not available in 3 of the earlier patients. Of the remaining 83 preoperatively potent patients, 42 had a bilateral nerve-sparing procedure; of these 18 (43%) were potent at the time of the study. Four of 17 patients undergoing a unilat-

58

Table 3. Risk factors for complications in 188 patients after radical prostatectomy

	Anastomotic leakage	Age (<70 vs. >70)	TURP	Experience (surgeon 1 vs. others) (<87 vs. >87)	Date (<87 vs. >87)	T stage ($<T_3$ vs. $>T_3$)	pT stage ($<pT_3$ vs. $>pT_3$)
Stenosis	NS	NS	NS	$p < 0.01$	NS	NS	NS
Incontinence	NS	$p = 0.02$	NS	NS	$p = 0.02$	NS	NS
Impotence	NS	NS	NS	NS	N/A	NS	NS

NS = $p > 0.05$; N/A = not applicable.

eral nerve-sparing procedure (24%) and 4 of 24 (17%) with no attempted nerve sparing were also potent at the time of the study. Of the 26 patients regaining their potency, 18 (69%) had done so by 15 months. There were also 8 patients who regained their potency between 18 and 30 months postoperatively.

The analysis of risk factors for the various complications is presented in table 3. The operator seemed only to have an influence on the risk of developing an anastomotic stenosis. The year of surgery influenced both the risk of anastomotic stricture and incontinence. Being older than 70 years of age increased the risk of incontinence. Previous transurethral resection, T stage, pT stage and leakage on cystogram influenced neither incontinence nor stenosis or impotence.

Discussion and Conclusions

In the interpretation of these data, several pertinent points must be made. The first is that this is a prospective study with data collection that is likely to be more complete than in studies based on chart reviews. The second point is that we are currently undertaking a parallel study on the effectiveness of radical prostatectomy in patients with T_3 prostate cancer. For this reason, we have 31 and 75% patients who are clinically and pathologically, respectively, judged to be extracapsular. This large cohort of bulky tumors may introduce unrecognised biases. Lastly, this is not the series of one person, but rather represents the workload of 4–6 surgeons sharing 25–40 cases per year.

The mortality in the study is low. Two of the postoperative deaths were sudden deaths despite prophylactic measures, while the other was as a direct result of the procedure itself.

The intraoperative complications included 4 rectal injuries. In the early part of the series these were treated with defunctioning colostomy. With the more recent injuries we have simply oversewn the rectum and performed an anal dilatation as proposed by Borland and Walsh [2]. These patients have had uncomplicated courses. The intraoperative blood loss has decreased in the more recent part of the series compared with the earlier cases. Hypotensive techniques are not employed in these patients and the use of temporary hypogastric artery occlusion is not routine. Perhaps with these modifications blood loss could be further reduced although the effect of hypogastric occlusion has been debated [3]. Previous TURP was the only other factor influencing blood loss.

The decrease in early postoperative complications over the course of the series is more likely due to improvements in anesthesia and postoperative care than surgical technique. The high incidence of wound infections was a surprise. The patients did not routinely receive prophylactic antibiotics. All but 4 positive cultures grew *Staphylococcus aureus*, and gram-negative organisms were seen in only 2. In the earlier part of the series, all patients received both subcutaneous heparin and graduated compression stockings. The heparin may have contributed to the high number of patients needing drainage of a lymphocele or having prolonged lymph drainage in the early part of the series. It is interesting to note that not only did these complications decrease after ceasing the use of heparin, but that there was also no increase in the number of thromboembolic events, with 7 out of 10 (including the fatal events) occurring before this time.

Incontinence must always be interpreted with the definition kept in mind. The criteria in this series were strict. Continent patients were completely dry without use of a pad. A number of our grade 1 incontinent patients wore their pad for 'security', even though they claimed to be 'dry with an occasional drip'. Any patient wearing more than 2 pads per day were categorized grade 2 incontinent, regardless of how much urine was on those pads. Just over half the patients were considered incontinent on removal

of their catheter and by 3 months the proportion requiring pads had fallen to 21%. Over the study period, the immediate incontinence rate did not change. Both the 3-month and 12-month incontinence rates decreased as the study progressed. Of the 11 artificial sphincters implanted, 9 were in patients who had their radical prostatectomy prior to the adaptation of the 'nerve-sparing' technique, many of whom had concurrent problems with anastomotic stenoses. This improvement in both the incidence and severity of incontinence may be due to increasing experience, but is more likely a result of the modifications to the operative technique. Recent adoption of the further adaptations suggested by Walsh [4] should reduce the risk of incontinence even further.

All 11 patients who were implanted with artificial sphincters received the AMS800 device. Continence was achieved in all patients. This high success rate with this device for incontinence after prostatectomy was confirmed by others [5]. In all these patients, urodynamic studies were performed and showed sphincter weakness. In this small number of patients we did not see additional significant bladder dysfunction in contrast to Leach et al. [6] who found such dysfunction in 60% of their patients. We have, however, found low compliance in patients referred secondarily to us with postprostatectomy incontinence, suggesting that technical nuances may play a role. Presti et al. [7] found detrusor instability in 25% of their incontinent patients, but this was similar to their continent group, whereas measures of sphincteric integrity were significantly different between the two groups.

5 patients with grade 2 incontinence (including 3 who were incontinent preoperatively) did not wish to have a sphincter placed. They could possibly have benefitted from the peri-urethral polytetrafluoroethylene injections as suggested by Stanisic et al. [8]. Our finding that the patients over the age of 70 years were more at risk of becoming incontinent is in contrast to the findings of others [9-11].

Thirty-two percent of the patients required at least one dilatation of the bladder neck. The definition required that anyone having a sound passed be recorded as requiring a dilatation. Many of these patients had minor symptoms and the sounds passed with ease. Although the incidence of stenosis did not change with time, the severity did. All of the severe strictures requiring bladder neck incision, resection of the anastomosis or long-term catheters were operated on prior to 1987 and prior to the adaptation of the 'nerve-sparing' technique. The surgeon's experience decreased the likelihood of stenosis. In contrast to the findings of Surya et al. [12], we did not find

that blood loss, extravasation of urine at the anastomotic site or prior contributed to the development of a stricture.

In patients where either a bilateral or a unilateral nerve-sparing procedure was attempted, the potency rates of 43 and 24%, respectively, are lower than others quoted in the literature [13-15]. This may in part be explained by the high incidence of pathological extracapsular extension (75%) in this series compared with those of Catalona and Bigg [13], Leandri et al. [14] and Quinlan et al. [15], which were 43, 55 and 42%, respectively. Extracapsular extension has been shown to decrease the likelihood of postoperative potency [13]. Although in the present series extracapsular extension was not statistically significantly different as concerns recovery of potency, this is almost certainly due to the small numbers, as a trend was indeed seen. It was interesting to note that, although all patients were offered impotence therapy, only 21% of patients accepted the offer of treatment, suggesting that for many this is not an important issue. Of those who were treated with papaverine, an average of 66 mg (range 25-100 mg) was required intracorporeally for an erection. Two patients were unable to achieve an erection on 100 mg. This suggests that the etiology of impotence in many patients is not entirely neurogenic, and that there is most likely an additional vasculogenic component, as proposed by Bahnson and Catalona [16]. In the current series, we did not find that patient age, previous TURP, surgeon, or presence of extravasation impacted on potency. Again the small numbers may have masked any such impact. Finally, we were surprised that almost a third of the patients who regained their potency did so more than 12 months after surgery.

In assessing the impact of radical prostatectomy on men 70 years and over, Middelton [9] found that the rates of both perioperative and postoperative complications were not different in those patients under 70 years when compared to those over 70. Our findings were similar in all aspects except incontinence. The impact of prior TURP has previously been addressed. We found that there was an increase in the median number of blood units transfused, but no change in risk for any of the complications assessed. This supports the concepts that TURP may make an operation more difficult, but does not make it more dangerous.

This series extended over a decade and a half. Over this period the operation has been performed more often. There have also been many modifications to the technique. These factors have decreased both the incidence and the severity of the complications. Although the expe-

60

rience gained with the larger number of patients operated on may be contributory, it is interesting to note that in all aspects except the risk of stenosis there was no difference between the most experienced surgeon (surgeon 1) and the other surgeons. This suggests that the decrease in morbidity should be ascribed to the improvements in the technique.

In summary, this prospective study shows that radical prostatectomy can be performed with minimal mortality and acceptable morbidity. Complications, if they occur, tend to be of limited duration or can be satisfactorily treated. Technical modifications have significantly decreased the morbidity of the procedure.

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PART 2

THE INFLUENCE OF PATHOLOGICAL VARIABLES DETERMINED IN THE RADICAL PROSTATECTOMY SPECIMENS ON PROGRESSION AND SURVIVAL IN PROSTATE CANCER

Tumor control according to pathological variables in patients treated by radical prostatectomy for clinically localized carcinoma of the prostate.

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SUMMARY.

Objective. Most studies reporting the results of radical prostatectomy for prostate cancer originate in centers with a very large experience, obtained by a few surgeons, where large numbers of patients are operated, and therefore much experience is at hand. The rise in detection-rate of locally confined prostate cancers in the last decade, and the associated rise in the number of radical prostatectomies, will lead to the performance of radical prostatectomies by urologists who are less experienced. This article reports the results from a clinic where 6 urologists shared about 50 radical prostatectomies a year, in the later years of the study-period (1977-1994). The radical prostatectomy-specimens were processed in a routine manner, no elaborate sampling was performed.

Material and methods. Radical prostatectomy was performed in 273 patients who were followed prospectively. The radical prostatectomy-specimens were evaluated for: pathological stage, histological grade, capsular perforation, positive lateral and apical margins of resection, seminal vesicle invasion, perineural invasion, vascular invasion, and the lymph node status was determined. The relation between these variables and the following outcome parameters was assessed: clinical progression, local recurrence, distant metastases, biochemical progression, overall survival, and cancer specific survival.

Results. All evaluated variables were significantly predictive for clinical and biochemical progression in the univariate analyses, and all but perineural invasion and lymph node status for cancer specific survival.Multivariate analysis showed vascular invasion to be the most important prognostic variable, followed by capsular perforation, positive margins of resection and poorly differentiated carcinoma. The overall results for the evaluated parameters were comparable to the results of the centers with a larger experience.

Conclusions. The treatment-outcome in a clinic where 6 urologists share 50 radical prostatectomies a year is similar to the results of more experienced clinics. The routine work-up of the radical prostatectomy specimens produces pathological variables which are important prognostic factors. Vascular invasion, capsular perforation, positive margins of resection, and poorly differentiated carcinoma are the most significant prognostic factors. Vascular invasion should be part of the routine evaluation of radical prostatectomy-specimens.

INTRODUCTION.

In recent years the incidence of locally confined prostatic carcinoma has increased from 27,5% in 1985 to 48,5% in 1990 of all prostate cancers identified in the US National Database (1). This trend is probably the result of increasing public and doctors awareness and the induction of screening programs for prostate cancer (2). Since more prostate cancer is locally confined at the time of diagnosis, the percentage of patients that is treated by radical prostatectomy has increased. Lu Yao reported a nearly six-fold increase in the rate of radical prostatectomy use in this same period (3).

Many studies reporting the results after radical prostatectomy for prostatic cancer , and especially those which contains large numbers of patients, originate from centers with a very large experience. However, with the recent increase in numbers of cases diagnosed, this operation will gain a more wide-spread use, and will become part of the standard armamentarium of urologists . Since it takes time and practice to build up a routine, the results in the beginning may be worse than those reported by centers of excellence, where more experience is at hand. We report the results of tumor control and survival after radical prostatectomy for clinically localized carcinoma of the prostate, from a clinic where 6 urologists share about 50 radical prostatectomies a year, during the last years of the study-period.

The role of pathological variables for progression and survival has also mostly been reported from centers with a large experience, where sometimes a very elaborate evaluation of the radical prostatectomy specimen was done. We report the influence of pathological variables on tumor control after a routine work-up of the radical prostatectomy specimen.

MATERIAL AND METHODS.

Between 1977 and 1994, 273 patients underwent a pelvine lymph node dissection and radical-retropubic prostatectomy for clinically localized or locally advanced carcinoma of the prostate. Originally, 375 patients were scheduled for surgery, but 102 patients appeared to have lymph node positive disease, detected by frozen sections, and therefore no radical prostatectomy was performed.

Preoperative evaluation. This included a digital rectal examination, histological biopsy of the prostate, determination of serum alkaline phosphatase and prostatic acid phosphatase,(from 1987 on replaced by prostate specific antigen:PSA), a bone scan, CT-scanning of the pelvis and abdomen, and a transrectal ultrasonography.

Patient-group characteristics. The median patient age was 63.8 years,(range 45-75 years). Staging was performed according to the TNM classification of 1992 (4):Twenty-seven patients were classified T1 (9.9%); 162 as T2 (59.3%); 83 as T3 (30.4%); and one as T4 (0.4%); however no subclassification in a,b or c was made, because of the small numbers in each group. The preoperative histological grading was done according to MD Anderson (5); 68 patients had well differentiated carcinoma (G1:25%); 161 moderately differentiated carcinoma (G2: 59%); and44 poorly differentiated carcinoma (G3: 16%). All patients were classified as M0. All patients underwent a pelvine lymph node dissection, before proceeding with the radical prostatectomy. In 9 patients a single microscopic metastasis was detected in the lymph nodes. The decision to proceed was made intra-operatively, because of the young age, and good health of these patients.In 18 patients, who had no evidence of tumor in the frozen sections, microscopic metastases were found on the paraffin sections; therefor 27 patients (10%) that

underwent surgery had lymph node metastases. All patients underwent a radical retropubic prostatectomy; the technique has been described before (6).In 143 patients an attempt was made to save the neurovascular bundles: in 84 patients bilaterally, and in 59 patients unilaterally. In 130 patients the bundles were sacrificed, because of suspicion of tumor growth in the area of the bundle. No patient received adjuvant treatment until progression occurred.

Pathological evaluation. The radical prostatectomy specimen was submitted in its entirety and cut in 5 mm thick slices, all of which were embedded in paraffine.Several 5 µm thick slices were taken of each slice and stained with haematoxylin/eosine for pathological review. The parameters studied were: histopathological grade (MD Andersen), capsular perforation, apical and lateral margins of resection, seminal vesicle invasion, perineural invasion,vascular invasion, and pT category. The pelvic lymph node specimens were embedded in paraffine and entirely sectioned and evaluated to detect micro metastases.

Follow-up. The median follow-up was 49 months (range 1-206 months).Patients were followed at regular intervals of 3 months during the first 2 years; of 6 months during year 3 till 5 and once a year during further follow-up.During each visit a digital rectal examination was performed, and serum PSA and alkaline phosphatasis was determined. Bone scanning, computer tomography and TRUS-guided biopsy were only performed when progressive disease was suspected. No additional treatment was started until clinical progression was proved.

All data were collected prospectively, and stored in a computer database which was especially designed for this study.

Study endpoints and definitions. The study endpoints were: clinical progression, local recurrence, distant metastases, biochemical progression, overall survival, and cancer specific survival.Clinical progression was defined as histologically confirmed evidence of local recurrence, and/or the presence of distant metastases diagnosed by bone scans, ultrasonography or CT-scanning.Local recurrence was defined as the presence of tumor cells around the bladder-urethra anastomosis, proved by biopsy. Distant metastases were considered by the presence of new hot spots on the bone scan, or by other imaging techniques (ultra sonography, chest X-rays, CT-scans). The presence of an elevated PSA alone was not considered clinical progression. Biochemical progression was defined as the first occurrence of two consecutive PSA values >0.1 ng/ml. To avoid biased selection of patients, only those were included who had regular PSA determinations during follow-up. Therefore only the patients who had their first PSA measurement within 12 months after the operation were evaluated for biochemical progression (n=173). Overall survival was defined as the percentage of patients who did not die of any cause at a certain time post surgery. In calculating cancer specific survival patients were considered withdrawn from study at the time when they died from causes not related to prostate cancer, post-operative deaths were counted as death due to prostate cancer.

Statistical analysis. Kaplan Meier projections of time to clinical progression(CP),local recurrence(LR),distant metastases(DM),biochemical progression(BP),overall survival(OS),and cancer specific survival(CSS) were used to calculate the actuarial progression and survival percentages at 5, 10, and 15 years.For the univariate analysis the statistical significance of differences was determined by the log-rank test. The Cox proportional hazards model was used to perform the multivariate analysis. P-values (two-tailed) ≤0.05 were considered significant.

RESULTS.

Under/over staging. Understaging occurred in 24/27 patients with T1 (89%); in 111/162 with T2 (69%); and in 4/83 with T3 (5%).Overstaging occurred in 3/27 patients with T1

68

(11%);in 3/162 with T2 (2%); in 15/83 with T3 (18%); and in the one patient in whom stage T4 was suspected: this turned out to be stage T3c. It is evident that clinical staging methods are not very reliable since the total percentage of understaged patients was 51%, and of overstaged patients 8%.Especially the 18% overstaging in clinical T3 disease is precarious; these patients may be denied a curative operation because of staging errors.

Under/over grading. Undergrading was found in 27%. In biopsy G1 patients 49/68 (72%) turned out to have Grade 2 (44 patients) or Grade 3 (5 patients). In 25/161 G2 patients the tumor was up-graded to G3 (15%). Overgrading by the biopsy specimen was determined in 15%; in 13/44 patients with G3 (29%), 24/161 with G2 (15%),and 3/68 with G1 (4%) the postoperative grade was lower then the biopsy grade.These differences are due to sampling errors.For the progression and survival percentages the postoperative grade was used.

*Observed progression and survival.*In this group of 273 patients, 75 experienced clinical progression (27%), at a median time of 110 months (range: 3-182 months).During the observation period 18 patients developped local recurrence (7%), 45 distant metastases (17%), and 12 patients had both (4%).Biochemical progression occurred in 66 of 173 patients (38%), at a median time of 58 months (range 2-84 months). During follow-up 53/273 patients died (19%); of those who died 19 patients died of prostate cancer (36%), 3 (6%) in the postoperative period due to postoperative complications (2 died of pulmonary embolism, one of sepsis),11 (21%) of a second malignancy, and 20 (37%) of intercurrent disease. The 6-week postoperative mortality-rate was 1%.

Actuarial 5,10, and 15 year cumulative percentages for clinical progression, local recurrence, distant metastases, biochemical progression, overall survival, and cancer specific survival, of 273[#] patients treated by radical prostatectomy for prostatic carcinoma.

Parameter	5 year(%)*	10 year(%)*	15 year(%)*
clinical progression	27 (89)	53 (15)	63 (4)
local recurrence	11 (106)	24 (20)	24 (5)
distant metastases	21 (96)	41 (16)	53 (4)
biochemical progression[#]	52 (14)	--- (0)	--- (0)
overall survival	82 (115)	63 (22)	55 (5)
cancer specific survival	92 (115)	82 (22)	82 (5)

*: numbers between parenthesis indicate patients at risk at indicated year.
[#]: values for biochemical progression based on 173 patients.
---: not evaluable.

Table 1.

Actuarial progression and survival. The actuarial percentages for progression and survival at 5, 10, and 15 years are listed in table 1. The median interval for the development of CP after the occurrence of BP was 56 months. Two patients had CP prior to BP, in all other patients in

this group who had both CP and BP, BP preceded CP.

There is a steady increase of LR until 10 years postoperatively, but between 10 and 15 years no more LR developped (at 10 years only 20 patients were at risk for LR).DM and CP also show a steady increase until 10 years, which slowes down in the period 10-15 years. However since the numbers at risk are smaller in the last period, these percentages are less reliable than those at 5 and 10 years. Given the median age of 63 years at the time of operation, the percentages of OS are relatively high (a 15 year survival of 55%), but it has to be considered that these patients had to be in good health to be candidates for surgery, which gave them an advantage over their age-matched controls. The CSS of 92%, 82% and 82% at 5, 10, and 15 years is excellent, especially when the patient-group is considered (30% of the patients had locally advanced carcinoma),and proves that radical prostatectomy is effective in many patients with locally confined carcinoma.

*Pathological variables.*The frequency and percentages of the pathological variables are listed in table 2. The relatively high percentages of pT3 (63%), and G3 (22%), indicate that this is a patient-group with a high risk for progression. Furthermore about 10% of the patients had lymph node metastases, and 29% seminal vesicle invasion.The presence of positive margins of resection in 34% of the patients is not surprising, considering that 64% had capsular perforati-on, and extension of the tumor into the peri-prostatic fat.The significant correlation between positive margins of resection and capsular perforation, seminal vesicle invasion, apical margins of resection and the pathological T-category has been studied in an earlier report.(7). There was also a significant correlation between perineural invasion and capsular perforation. Vascular invasion was present in 12%.

*Univariate analysis.*The results of the univariate statistical analysis for the different pathologi-cal variables are listed in table 2. The p-values indicate the significance of the log-rank test. Due to small numbers in the evaluation some categories were combined. For the pT-category the difference between pT1/2 and pT3/4 was tested; for the pN-category pN0 versus pN1/2; and for grade G0/1/2 versus G3. For all other variables the difference between presence and absence was evaluated.

For CP all variables showed a significant difference.The difference in BP rates was significant for all variables. For CSS rates all variables except the pN-category and the presence of perineural invasion were significant, despite the fact that only 22 patients died due to prostate cancer. With extended follow-up and more cancer-deaths more variables may become signifi-cant.

A sub-group analysis was performed for the patients with pT3-tumors, to evaluate the effect of seminal vesicle involvement on clinical progression. Patients with capsular perforation only (pT3a-b: 100 patients) were compared to those with seminal vesicle invasion (pT3c: 72 patients). A significant difference resulted: $p=0.006$, indicating that the invasion of tumor in the seminal vesicles determines a subgroup with a higher progression risk in the group of patients with locally advanced disease (pT3).

Multivariate analysis. Table 3 contains the final results of the multivariate analysis for CP, BP and CSS for the pathological variables, by the Cox proportional hazard model. For CP vascular invasion, capsular perforation, poorly differentiated carcinoma, and positive lateral margins of resection were significant, with relative risks varying from 1.6-2.5. All other variables were not of additional significant prognostic value. For BP only vascular invasion and capsular perforati-on were significant; for grade 3 and positive lateral margins of resection there was a trend,which did not reach significance.CSS was significantly influenced by the presence of vascular invasion and positive lateral margins of resection; the other variables did not reach

70

Univariate analysis for the influence of the different pathological variables on clinical and biochemical progression and cancer specific survival.						
Variable		N	%	CP p-value	BP p-value	CSS p-value
pT-category	pT0	6	2			
	pT1	0	0			
	pT2	80	29	p<0.001	p<0.001	p=0.01
	pT3	173	63			
	pT4	14	5			
pN-category	pN0	246	90			
	pN1	19	7	p=0.03	p<0.001	p=0.80
	pN2	8	3			
vascular invasion	present	33	12	p<0.001	p<0.001	p<0.001
	absent	240	88			
perineural invasion	present	207	76	p<0.001	p<0.001	p=0.13
	absent	66	24			
seminal vesicle invasion	present	78	29	p<0.001	p<0.001	p=0.01
	absent	195	72			
positive lateral margins of re-section	present	92	34	p<0.001	p<0.001	p=0.001
	absent	181	66			
positive apical margins of re-section	present	113	41	p=0.02	p<0.001	p=0.03
	absent	160	59			
capsular perforation	present	175	64	p<0.001	p<0.001	p=0.01
	absent	98	36			
grade	G0	6	2			
	G1	38	14	p<0.001	p<0.001	p=0.01
	G2	168	62			
	G3	61	22			
N= number of patients BP: biochemical progression CP: clinical progression. CSS: cancer specific survival P-value: log-rank test						

Table 2.

Multivariate analysis for the influence of the different pathological variables on clinical and biochemical progression and cancer specific survival.			
variable	relative risk	95% confidence interval	p-value
CLINICAL PROGRESSION			
vascular invasion	2.5	1.5 - 4.2	p=0.001
capsular perforation	2.5	1.2 - 5.2	p=0.01
grade 3	1.8	1.1 - 2.9	p=0.02
positive lateral margin	1.6	1.0 - 2.7	p=0.05
BIOCHEMICAL PROGRESSION			
vascular invasion	2.3	1.2 - 4.2	p=0.007
capsular perforation	2.6	1.2 - 5.5	p=0.01
grade 3	1.6	1.1 - 2.9	p=0.07
positive lateral margin	1.6	0.9 - 2.7	p=0.08
CANCER SPECIFIC SURVIVAL			
vascular invasion	2.7	1.1 - 6.7	p=0.03
capsular perforation	2.4	0.5 - 11.6	p=0.27
grade 3	1.9	0.8 - 4.5	p=0.17
positive lateral margin	2.5	1.0 - 6.2	p=0.05

Table 3.

significance The occurrence of more cancer-deaths at extended follow-up may alter these results.

*Actuarial percentages of 5 and 10 year progression and survival.*Table 4 shows the actuarial 5 and 10 year percentages of CP, LR, DM, BP, OS and CSS, according to the different pathological variables. BP was only evaluated at 5 years, since no patient had 10 years of follow-up after the introduction of PSA. No patient was classified pT1, and no patient with pT4 survived after 5 years. The 15 year progression and survival rates were not evaluated, since the numbers in the subgroups were too small to give reliable results.

DISCUSSION.

The patient-group reported is characterized by a high percentage of patients with clinical T3

Actuarial 5 and 10 year cumulative percentages of clinical progression, local recurrence, distant metastases, biochemical progression, overall survival, and cancer specific survival according to pathological variables.														
variable		N	CP(%)		LR(%)		DM(%)		BP(%)		OS(%)		CSS(%)	
			5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr
capsular perforation	present	175	37	77	13	39	29	58	69	---	80	57	89	73
	absent	98	9	18	5	8	6	13	21	---	88	74	97	97
lateral margins	positive	92	43	80	20	36	33	71	72	---	74	54	79	63
	negative	181	20	45	6	19	17	35	39	---	86	65	96	88
apical margins	positive	113	35	72	15	37	27	49	72	---	80	62	87	74
	negative	160	21	43	7	17	17	34	30	---	84	64	96	87
perineural invasion	present	207	34	63	12	26	27	46	64	---	81	57	90	77
	absent	66	7	29	5	19	5	22	14	---	88	78	96	96
seminal vesicle invasion	present	78	46	80	21	47	33	65	89	---	75	53	85	69
	absent	195	19	39	6	15	16	29	37	---	86	68	95	89
vascular invasion	present	33	68	81	36	36	39	68	83	---	64	40	77	48
	absent	240	21	49	7	23	19	37	47	---	85	66	94	87
grade	0/1/2	206	22	49	9	17	16	38	44	---	89	63	95	83
	3	61	46	75	16	53	42	57	100	---	62	59	77	73
pT	pT0	6	0	0	0	0	0	0	0	---	83	56	100	100
	pT1	0	---	---	---	---	---	---	---	---	---	---	---	---
	pT2	80	7	17	3	6	7	15	18	---	90	77	97	97
	pT3	173	34	75	14	39	26	55	67	---	81	59	90	75
	pT4	14	100	100	17*	---	100	100	100	---	0	0	0	0
pN	pN0	246	25	50	9	23	20	39	46	---	83	64	92	82
	pN1/2	27	48	79	23	34	30	66	94	---	79	50	90	82

N=number of patients
CP:clinical progression BP:biochemical progression   ---: not evaluable
LR:local recurrence   OS:overall survival   *: after 4 years
DM:distant metastases   CSS:cancer specific survival

Table 4.

(30%) and Grade 3 (22%) tumors. This indicates that a considerable amount of patients has a high risk for progression and death due to prostate cancer.These circumstances also explain the low percentage of patients with histologically organ-confined tumors (pT0-2):32%. The high percentage of locally advanced tumors created an opportunity to study the pathological variables associated with this condition.

Pathological stage. In 6 patients no residual tumor could be found in the radical prostatectomy-specimen; they were therefore classified pT0. All patients had a trans-urethral resection of the prostate prior to radical prostatectomy, and had probably only tumor in the transition-zone, which was resected during the TUR. Goldstein(8) reported on 13 patients with the "vanishing cancer phenomenon", who did not have a TUR before radical prostatectomy. After an elaborate work-up of the specimen cancer was found in 11 patients; the mean tumor volume was only 0.019 cc. No exhaustive sampling was performed in our patients, so some very small tumors may have been missed. The 0% progression rate and 100% CSS-rate after 10 years of follow-up indicate however that these tumors were probably not clinically significant.

The majority of the patients were classified pT3(63%). Some urologists and radiotherapists consider these patients candidates for adjuvant radiotherapy, because of an elevated risk for local tumor recurrence. Kaplan stated that clinical local control improved CSS (9). In his series T3-patients were treated with external beam radiotherapy; the 10 years CSS-rate for those with local control was 56%, and for those with local recurrence 35%.In the present series the LR-rate in pT3-patients was 14% at 5, and 39% at 10 years, the CSS-rates were 90% and 75% respectively. The progression rates were however 34% and 75% at 5 and 10 years, and it seems that many more patients experienced distant progression then local recurrence. Given these numbers, and considering the fact that adjuvant radiation therapy can cause complications and considerably patient discomfort, radiotherapy is not advised as standard treatment in pT3-patients. Currently the EORTC is running a protocol (EORTC 22911), which evaluates the results of tumor-control in pT3-patients with or without adjuvant radiotherapy. These results have to be awaited.

Grade. It is well established that the presence of poorly differentiated tumor leads to significantly higher rates of CP(10,11), BP(12) and CSS(13). Hawkins(14) performed a multivariate analysis in pT3-patients, and found a relative risk of 2.1 for systemic progression, 2.3 for BP, and 2.2 for CSS in patients with high grade tumors (Gleason $\geq$7) compared to those with low grade tumors.In the present series the multivariate analysis resulted in a relative risk of patients with poorly differentiated carcinoma's versus those with well or moderately carcinoma's of 1.8 for CP, 1.6 for BP, and 1.9 for CSS; however this was only significant for CP. For BP and CSS there was a trend which did not reach significance(p=0.07 and p=0.17). Longer follow-up and an extended patient-group may alter these results. Partin (15) studied a patient-group with high-grade carcinoma (Gleason$\geq$8) and found BP at 5 years in 24% of the patients with specimen confined disease, versus 82% in those with non-specimen confined disease (in the latter group lymph node positive disease was present in 40%).Ohori(16) reported a group of patients with Gleason$\geq$8, and found a 5-year BP of 72%. When this group was divided in those with organ-confined and non-organ-confined cancer, the percentages were 0% and80% respectively. Since the presence of high-grade tumor did not influence the progression in organ-confined cancer, it seems that the anatomical barrier of the prostatic capsule is very important.

*Capsular perforation.*Capsular perforation is one of the most extensively studied pathological variables of the last decade. The clinical importance lies in the fact that in most centers patients

74

with capsular perforation(T3) are not considered candidates for radical surgery. Unfortunately clinical staging is often insufficient to detect extracapsular disease. In the present series 69% of the patients with clinical stage T2 turned out to have pT3. Capsular perforation is significantly associated with perneural invasion; Villers(17) described that in patients with clinical stage B cancer 50% of the capsular perforation consisted exclusively of perineural invasion, and only 5% of the patients with capsular perforation had no perineural invasion. He concluded that the mechanism of capsular perforation may depend almost exclusively on perineural invasion. Perineural invasion was present in 76% of the patients in this series, and capsular perforation in 64%. The presence of perineural invasion only was not considered capsular perforation. Perineural invasion was a significant prognostic factor in the univariate analysis, but not in the multivariate analysis, probably because of the close relationship with capsular perforation. The latter was a significant prognostic factor for CP, BP, but not for CSS in the multivariate analysis, with a relative risk of 2.5; 2.6; and 2.4 respectively, when compared to those without capsular perforation. Epstein reported a significant difference between patients with focal (only a few tubules) and established capsular perforation; the 5-year BP-rates were 18% and 35% respectively (18). Stein calculated an actuarial survival rate free of clinical disease of 79% at 5- and 62% at 10 years (i.e. a CP-rate of 21% and 38%). These results compare favourable to the 37% and 77% found in the present series, however they also included patients with capsular invasion only (and no perforation). Initially we divided the capsular status in 4 categories, as described by Stamey (19): 1: no invasion, 2: invasion up to, but not into, 3: invasion, but no perforation, and 4: perforation of the capsule. The only significant prognostic category was perforation of the capsule; invasion into the capsule had no prognostic value, when compared to those without invasion. This must therefore be considered organ-confined disease.

A major concern in patients with capsular perforation is the occurrence of positive margins of resection and irradical tumor resection. McNeal found positive margins in 35 of 38 patients with extracapsular tumor-extension, but only 44% of these were due to capsular perforation, and 56% to incision of the capsule during the operation (20). The local recurrence-rates for patients with capsular perforation were 13% at 5-, and 39% at 10 years in this series. Morton (21) reports a LR-rate of 8% at 5 years, and Mukamel (11) a LR-rate of 17% at 8 years of follow-up.

Positive margins of resection. Rosen (22) described the relation between extracapsular tumor-extension and positive margins of resection. In clinical stage B-patients 63% had capsular perforation and 23% positive margins. Of the capsular perforation 87% occurred in the posterolateral area; 57% of the positive margins were found in this area. The high percentage of capsular perforation in this area is due to the location of the neurovascular bundle (17); however only 8 patients of 31 in which the neurovascular bundle was saved, had positive margins (22). In an earlier report we found no correlation between saving the neurovascular bundles and the occurrence of positive margins (7). Epstein found no residual tumor in the neurovascular bundle in 40% of the patients who had a positive margin at the site of the bundle (23). · Partin (24) found no difference in BP in patients with extracapsular tumor-extension, whether the bundle was resected or not: both groups had 70% BP after 3 years. He stated that radical prostatectomy cannot be advised in patients with extracapsular extension. In the present series 5-year BP occurred in 69% of the patients with capsular perforation and in 72% of those with positive margins. It has to be remembered however that a patient has no physical discomfort due to BP, and that CP follows BP at a distance of approximately 5 years. A 20% LR-rate at 5 years was reported by Morton (21) in patients with positive surgical margins; in our series this

was also 20%. Therefore radical prostatectomy can be beneficial in some patients, who would otherwise have early problems of local progression. Adjuvant therapy can best be started when local recurrence actually occurs, since the majority of the patients with positive margins will not experience LR during their life-time.

The apex is the site of frequent positive margins: 41% in this study. This high percentage was partly due to the method of evaluation of this margin (7). Stamey however also found 55% positive margins at the apex, and advised a wide resection of all tissues from the proximal membranous urethra to the levator muscles when an apical or near-apical node is present (25). We clearly visualize the apex and membranous urethra during operation, but carefully save the area of the external sphincter, since this is important for post-operative continence.

*Seminal vesicle invasion.*This occurred in 29% of the patients in this report. The results of the univariate analysis clearly indicate that the presence of seminal vesicle invasion significantly influences the progression and survival-rates in a negative way: the CP-rate was 46% at 5 years. Similar results were reported by Stein (26) and Mukamel (11): 42% and 31% CP at 5 years.The CSS-rate in this series matches that reported by Stein (26): at 10 years the percentages CSS were 69% and 63%.When the patients in the pT3-group were separated in those with capsular perforation only and those with seminal vesicle invasion, the latter had a significantly worse prognosis (p=0.006). It was therefore surprizing to find that seminal vesicle invasion was not significant in the multivariate analysis. The reason for this is probably the rather low number of deaths due to prostate cancer at this time in follow-up.

*Lymph node status.*In 27 patients of this study a radical prostatectomy was performed despite the fact that they had microscopic lymph node metastases. No patient received adjuvant treatment until progression occurred. The 5- and 10 years CP-rates of 48% and 79% are high, but comparable to those reported by Morton; 33% 5-year-CP (21), Hering; 35% CP at 3 years (27), and Frohmüller who found 100% CP at 10 years in patients with pT2-3pN1-2 (28). Hering performed an analysis for the influence of the amount of tumor in the lymph nodes on progression: in the pN1-category tumors<5cm did equally well as those >5cm; 35% CP at 3 years; but in the pN2-category all patients had progression after 3 year. The CSS-rates were respectively 80%, 100%, and 36%. In the present series the CSS-rates were 90% and 82% at 5- and 10 years. This, and the fact that the pN-category was not a prognostic factor in the multivariate analysis indicate that these 27 patients had a relatively good prognosis. It has to be emphasized that these patients are a small and strongly selected group, with very small lymph node metastases, a young age and an excellent general health. These results are therfore not valid for all patients with lymph node metastases.

*Vascular invasion.*Vascular invasion is an ominous sign in most tumors, indicating that they have already metastasized at the time of operation. However in prostatic cancer, with its relatively slow growth, this variable has attracted very little attention. Bahnson (29) reported an incidence of 51% vascular and/or lymphatic invasion in a group of 55 patients after radical prostatectomy. The presence of vascular or lymphatic invasion implied a fourfold increase of the risk for progression. Salomao described the correlations between vascular invasion and other pathological variables, however his study contained no follow-up and the prognostic significance was not reported (30). In the present series vascular invasion occurred in 33 patients (12%) and it was the most significant risk-factor in the multivariate analysis for both progression and survival, with a relative risk of 2.5 for CP, 2.3 for BP, and 2.7 for CSS. We advise to evaluate this variable in all patients undergoing radical prostatectomy.

CONCLUSIONS.

Radical prostatectomy is considered the treatment of first choice in patients with clinically locally confined prostate cancer. The reported results show that progression- and survival-rates are excellent, in a group which contained a relatively high percentage of patients with locally advanced carcinoma (T3), and in a clinic where 6 urologists share about 50 radical prostatectomies a year.
The pathological variables evaluated were all significant for clinical and biochemical progression in the univariate analysis, and all except perineural invasion and the pN-category were significant in the univariate analysis for cancer specific survival. The multivariate analysis showed vascular invasion to be the most significant factor for progression and cancer specific survival, followed by capsular perforation, positive margins of resection, and poorly differentiated carcinoma. The other evaluated variables did not reach significance. All variables were determined after a routine work-up of the radical prostatectomy-specimen, without elaborate sampling. The results show that in this way meaningfull prognostic information can be obtained.

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Positive margins after radical prostatectomy: correlation with local recurrence and distant progression.

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Positive Margins after Radical Prostatectomy: Correlation with Local Recurrence and Distant Progression

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Summary—The impact of positive and negative surgical margins of resection on the interval to and incidence of progression was analysed in 172 patients after radical retropubic prostatectomy combined with lymphadenectomy; 56 had positive margins. Lateral and apical positive margins were evaluated separately.

The status of surgical margins was correlated with other prognostic factors, such as the T category, the presence or absence of seminal vesicle invasion and the G category. This analysis showed that positive and negative margins significantly influenced time to progression independently of the other prognostic factors. Positive margins at the apex contrary to lateral margins did not significantly influence time to progression. This may be due to the definition of the status of apical margins used in this analysis. A total of 108 patients underwent a nerve-sparing radical prostatectomy, which did not lead to a higher incidence of positive margins than the standard procedure.

Prostate specific antigen accurately predicted tumour recurrence after radical prostatectomy. A rise of ≥ 1.0 ng/ml preceded other evidence of recurrence by a mean of 11 months.

Positive margins of resection are a frequent finding after radical prostatectomy. Their influence on progression has been insufficiently documented, since adjuvant therapy is usually administered immediately after the finding of positive margins.

This report presents a prospective analysis of 172 radical prostatectomies combined with pelvic lymph node dissection. The analysis examines the influence of positive margins of resection on time to progression and the correlation with other prognostic factors.

Special attention is given to the pT3 classification, which may need subdivision according to the status of surgical margins. The possible impact of the potency-preserving, nerve-sparing approach on surgical margins is analysed.

Patients and Methods

Radical retropubic prostatectomy combined with limited pelvic lymph node dissection was carried out in 172 patients; 166 had negative lymph nodes at frozen section and 6 had microscopic foci of lymph node metastases. On paraffin sections positive lymph nodes were found in an additional 10 patients. Eleven patients with lymph node positive disease had positive margins of resection and were included in this study.

Pre-operative investigations included digital rectal examination (DRE), histological and cytological biopsy, serum alkaline phosphatase (AP), prostatic acid phosphatase (PAP) (from 1987 on replaced by prostate specific antigen (PSA)), a bone scan, CT scanning of the pelvis and abdomen and a transrectal ultrasonographic examination (TRUS) (5 MHz probe).

This study was prospective. Patients were re-

cruited between 1977 and 1991. The average follow-up was 42.6 months (range 1-165). Patients were followed up every 3 months during the first 2 years, every 6 months for the next 3 years and then once a year. During each visit a digital rectal examination was performed and the PAP and AP were determined. After 1987 the PAP measurement was replaced by prostate specific antigen determination in serum (Hybritech Tandem R Assay). During the initial phase a lower limit of 1.0 ng/ml was used but this was then changed to 0.1 ng/ml. For the purpose of this report a PSA level > 1.0 ng/ml was considered elevated after radical prostatectomy. TRUS-guided biopsy, bone scanning and CT scans were performed only when progressive disease was suspected. The average age of the total population was 62.9 years (range 45-75). No additional treatment was given unless local recurrence or metastases occurred.

The 1978/1982 TNM classification has been used (UICC, 1978). The distribution of clinical T categories, lymph node positive disease and grade of differentiation (Mostofi, 1975) is listed according to positive and negative margins in Table 1.

There were 3 early deaths. One patient died 15 days post-operatively because of a septic complication resulting from penetration of a drain into the intraperitoneal space and subsequent perforation of a small bowel loop. Two other patients died 15 days post-operatively from an acute cardio-vascular complication and pulmonary embolus respectively.

The radical prostatectomy specimen was submitted in its entirety and cut into 5-mm slices, all of which were embedded in paraffin. Several 5-μm slices were taken from each slice and stained with haematoxylin and eosin. Differentiation was made between tumour not approaching or approaching the capsule up to 1 mm (organ-confined disease), invasion of the capsule (specimen-confined), penetration into the periprostatic fat and positive margins. These findings led to a sub-classification of the pT2 and pT3 categories which will be subject to a separate analysis. Differentiation was made between lateral and apical positive margins. Lateral positive margins were defined as tumour at the lateral cut surface of the specimen. No distinction was made between posterolateral and lateral margins.

The distal margin at the apex was defined as the presence of prostate cancer in the most distal 5 mm of the specimen.

Progression was defined as cytologically or histologically confirmed evidence of local recurr-ence and/or the presence of distant metastases diagnosed on bone and CT scans. Elevation of serum markers alone was not regarded as progression.

In 108 of the 172 patients nerve-sparing radical prostatectomy was done. In 24 of these only 1 neurovascular bundle was preserved. Many of the patients who were not operated upon in a potentially potency-preserving fashion were treated prior to the development of this technique by Walsh *et al.* (1983). In other more recent cases the decision to preserve one or both bundles was made intraoperatively.

Statistical analysis

The statistical techniques used were the Kaplan-Meier projection of time to progression, the Logrank test, the chi-squared test and Cox regression with time-dependent variables.

Results

The distribution of clinical T categories, grade of differentiation and the incidence of local recurrence and distant metastases are listed according to positive and negative margins in Table 1. In 4 patients in the T0 group no more tumour was found in the radical prostatectomy specimen. Local recurrence and progression to the M1 category occurred after an average period of 23.2 (range 1-109) and 32.9 (range 4-142) months respectively.

Figure 1 shows Kaplan-Meier projections of time to overall, local and distant progression. The overall progression and local recurrence rates were significantly different for the positive and negative margin groups. This significance persisted when a correction for the different pT categories had been done. The distant progression rate also showed a significant difference for positive and negative margins. However, no significant difference was found between the different margin groups when correction for the different pT categories had been done ($P=0.2$). Local recurrence usually occurred prior to distant progression. A strong correlation was found between local recurrence and (later in the follow-up) the incidence of distant metastases. The risk of developing distant metastases was 22 times higher in patients with local recurrence.

Table 2 shows the mean values of pre-operative PSA, PAP and prostatic volume by TRUS for the positive and negative margin groups.

Table 3 shows the correlation between the pT categories and surgical margins. When pT categories are compared with the clinical T category,

Table 1 Details of 172 Patients with Locally Confined Prostate Cancer

Parameter	Total no. of patients	Margins Positive No. (%)	Margins Negative No. (%)
T0	26	4 (15)	22 (85)
T1	10	2 (20)	8 (80)
T2	83	25 (30)	58 (70)
T3	53	25 (47)	28 (53)
N	156	45 (29)	111 (71)
N+	16	11 (69)	5 (31)
G1*	21	3 (14)	18 (86)
G2	104	33 (32)	71 (68)
G3	43	20 (47)	23 (53)
Local recurrence†			
present	19	9 (47)	10 (53)
absent	153	47 (31)	106 (69)
Distant metastases†			
M1	27	11 (41)	16 (59)
M0	145	45 (31)	100 (69)

* Four patients had no tumour in the radical prostatectomy specimen.
† Local recurrences and progression to M1 occurred after 23.2 (range 1–109) and 32.9 (range 4–142) months.

71% of the T2 tumours were upstaged to pT3. In Figure 2 the Kaplan-Meier curves for overall progression for pT3–4 with positive margins and for pT0–2 and pT3–4 with negative margins are shown. The difference between the positive and negative margin groups in category pT3–4 was statistically significant ($P = 0.05$), whereas the difference between pT0–2 and pT3–4 with negative margins was not. No positive margins occurred in the pT0–2 group.

The correlation between seminal vesicle invasion and the margin status is shown in Table 4.

Fig. 1 Kaplan-Meier projections of time to progression (distant, local, overall). Note the cut-off value at 50% of the y axis.

Table 2 PSA, PAP and Prostatic Volume Determined by TRUS in Pre-operative Staging, Related to Margins of Resection after Radical Prostatectomy

	Margins Positive No. (value)	Margins Negative No. (value)	Difference between mean values of groups
Mean value of pre-operative PSA level (n=62)	25 (29.0)	37 (16.6)	$P = 0.01$
Mean value of pre-operative PAP level (n=126)	45 (3.6)	81 (2.0)	$P = 0.006$
Mean value of pre-operative prostatic volume determined by TRUS (n=72)	32 (31.4)	40 (25.5)	$P = 0.053$

Table 3 Correlation of pT Categories and Surgical Margins

Margins	pT0-1 No. (%)	pT2 No. (%)	pT3 No. (%)	pT4 No. (%)
Positive	0 (0)	0 (0)	53 (45)	3 (100)
Negative	9 (100)	42 (100)	65 (55)	0 (0)
Total	9	42	118	3

Table 4 Correlation Between Seminal Vesicle Invasion and Surgical Margins

Seminal vesicle invasion	Margins		Total
	Positive No. (%)	Negative No. (%)	
Positive	30 (50)	30 (50)	60
Negative	26 (23)	86 (77)	112
Total	56	116	

$X^2 = 12.8; P < 0.001.$

The degree of capsular invasion increased with the occurrence of positive surgical margins (Table 5).

Table 6 shows the distribution of lateral and apical margins. There was a significant correlation between the lateral and apical margin status ($P < 0.001$) independent of the pT category.

In Figure 3 the Kaplan-Meier projections of the time to progression for the different locations of positive margins are shown. It is evident that lateral margins and both positive margins were associated with a shorter time to progression, whereas this was not the case for positive apical margins. A positive apical margin, defined as tumour in the most distal 5 mm of the prostate, contributed little to the progression rate.

The relation between nerve-sparing radical prostatectomy and the status of surgical margins is shown in Table 7. There was no significant difference in the incidence of positive margins between nerve-sparing (34%) and non nerve-sparing groups (30%).

After 1987, serum PSA was determined during every follow-up investigation. PSA values were available on 165 patients; 30 of these suffered disease recurrence. In 10 patients progression occurred before PSA determination became available. The remaining 20 patients all had PSA levels > 1.0 ng/ml at the time of progression. In a separate analysis in which 79 patients were followed up for
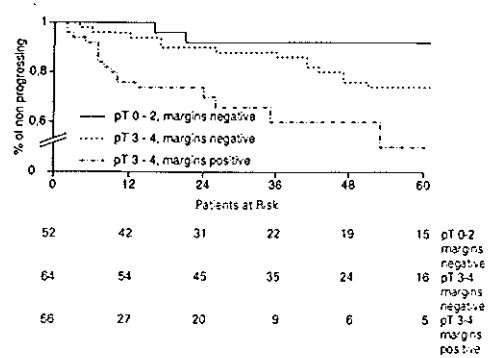
Fig. 2 Kaplan-Meier projections of time to overall progression for pT0-2 and pT3-4 with negative margins and for pT3-4 with positive margins of resection. Note the cut-off value at 50% of the y axis.

Table 5 Correlation between Degree of Capsular Invasion and Status of Surgical Margins

Capsular invasion	Total	Margins	
		Positive No. (%)	Negative No. (%)
None	21	0 (0)	21 (100)
Up to	14	0 (0)	14 (100)
Into	23	3* (13)	20 (87)
Fat/penetration	114	53 (47)	61 (53)
Total	172	56	116

* All apical positive margins.

Table 6 Correlation between Status of Lateral and Apical Margins

Apical margin	Lateral margin		Total
	Positive	Negative	
Positive	22	11	33
Negative	23	116	139
Total	45	127	172

$X^2 = 32.0; P < 0.001.$

1 to 4 years after radical prostatectomy, an elevated PSA serum level > 1.0 ng/ml was detected in 17 patients, 6 of whom showed recurrence (Table 8). In 62 patients with a serum PSA < 1.0 ng/ml no recurrence was evident. The difference between the groups was significant ($P < 0.005$). Positive margins
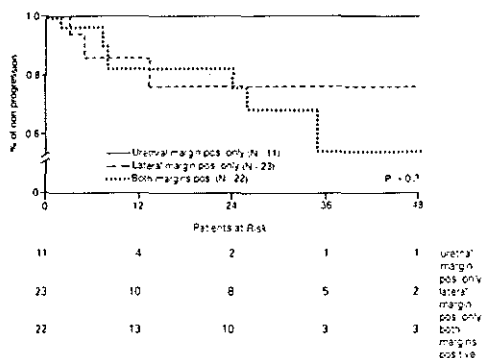
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Fig. 3 Kaplan-Meier projections of time to progression for different sites of positive margins of resection (n = 56). Note the cut-off value at 50% of the y axis.

Table 7 Nerve-sparing Radical Prostatectomy and Status of Surgical Margins

		Margins	
	Total	Positive No. (%)	Negative No. (%)
Nerve-sparing*	108	37 (34)	71 (66)
Bundle resection	64	19 (30)	45 (70)
Total		56	116

$X^2 = 0.5$; $P > 0.2$.
* Includes 24 unilateral cases.

of resection occurred in 10 patients in this elevated PSA group and in 10 in the normal PSA group.

In 6 patients with progressive disease, elevation of PSA predicted recurrence of prostate cancer at a mean period of 11 months before residual disease was evident. In the elevated PSA group the average follow-up was 24 months for patients with no evidence of disease and 32 months for patients with recurrence.

Discussion

The incidence of positive margins of resection described in the literature varies from 7% (Eggleston and Walsh, 1985) to 46% (Jones, 1990). These differences are the result of variations in surgical indications and techniques, differences in histological preparation and evaluation of radical prostatectomy specimens (Epstein, 1990).

Table 8 PSA Levels in 79 Patients 1–4 Years after Radical Prostatectomy

	PSA		
	PSA ≤ 1.0 ng/ml No. (%)	PSA ≥ 1.0 ng/ml No. (%)	Total
NED*	62 (85)	11 (15)	73
Recurrence	0 (0)	6 (100)	6
Total	62	17	79

* NED = no evidence of disease.

Positive margins of resection are likely to be seen in patients with extensive tumours, since the anatomy of the area allows only a limited resection of healthy tissue between the prostatic capsule and the margins of resection. The term "radical" therefore has a different meaning from the usual one in oncological surgery, when at least one or more centimetres of healthy surrounding tissue are resected. Furthermore, preservation of the delicate neurovascular bundles close to the lateral margins of resection may limit the resection of extraprostatic tissue in this area (Catalona and Bigg, 1990). Epstein (1990), however, found residual tumour in the neurovascular bundle in only 6 of 10 patients with positive margins when the bundle was removed (during the same session). In the present series the incidence of positive margins was similar with and without nerve-sparing surgery.

McNeal et al. (1990) described the apex as the most common site of positive margins of resection; 56% of these resulted from resection through the capsule into the tumour and 44% of capsular penetration by the tumour into the periprostatic fat. In this series the urethra was usually clearly seen distal to the apex prior to determining the dorsal plane of resection, and resection through the capsule was rare.

Jones (1990) described a significant correlation between the incidence of positive margins of resection and seminal vesicle invasion, capsular penetration, tumour volume and decreasing histological grade of differentiation. In our series the correlation between the occurrence of positive surgical margins was significant for seminal vesicle invasion, capsular penetration and increasing T, G and N categories, indicating that tumour extent and differentiation are of major importance for the occurrence of positive margins of resection. Furthermore, the mean PSA and PAP values were significantly different for groups with positive and negative margins, whereas tumour volume meas-

ured by ultrasonography approached significance ($P = 0.053$).

In the pT3 category 53 patients (45%) had positive margins. Penetration through the prostatic capsule and into the fat occurred in 53 of 56 patients with positive margins (95%), but in 3 patients (5%) there was only invasion of the capsule. All 3 patients had, however, only an apical positive margin. In 53% of the patients with capsular perforation no positive margins were found.

Nerve-sparing radical prostatectomy was performed in 108 patients, of whom 24 had only a unilateral bundle-sparing procedure. There were no significant differences in the occurrence of positive margins and progression between those who had a nerve-sparing operation and those who did not (Eggleston and Walsh, 1985).

Progression occurred significantly more frequently and earlier in patients with positive surgical margins than in those who appeared to have negative margins after surgery during a mean follow-up of 42.6 months. This indicates an increased risk of progression in patients with positive margins of resection.

In the present series, 79 patients were followed up for 1 to 4 years with PSA monitoring after radical prostatectomy. All patients with tumour recurrence had an elevated PSA level, while none of the patients with normal PSA showed recurrence. Elevation of serum PSA level preceded evidence of recurrence by a mean interval of 11 months. Lightner *et al.* (1990) showed that 40% of patients with an elevated PSA after radical prostatectomy had tumour recurrences in the urethrovesical anastomotic area, regardless of the finding at rectal examination. In the present series tumour recurrence was found in 6 of 17 patients with elevated PSA (35%).

Our data show that the TNM system differentiates only roughly between potentially curable disease (pT2 = carcinoma without penetration of the capsule) and non-curable disease (pT3 = carcinoma with invasion beyond the capsule and/or invasion of the seminal vesicles). Table 5 shows that 53% of patients with penetration through the capsule had negative margins of resection. Should the status of margins be used to differentiate between pT2 and pT3?

In conclusion, the occurrence of positive margins of resection after radical prostatectomy is associated with significantly more frequent and earlier progression, than in patients with negative margins. Longer follow-up is necessary to identify the true correlation and to establish whether adjuvant treatment is warranted in all patients with positive margins of resection.

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87

Microvascular invasion in prostate cancer: prognostic significance in patients treated by radical prostatectomy for clinically localized carcinoma.

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ABSTRACT.

Purpose: To investigate the clinical significance of vascular invasion in prostate cancer patients, treated by radical prostatectomy for clinically localized and locally advanced disease.
Materials and methods: Vascular invasion was determined during a routine work-up of radical prostatectomy specimens of 273 patients who underwent surgery for prostatic carcinoma. The correlation with other pathological variables was investigated. The prognostic influence for clinical progression, local recurrence, distant metastases, biochemical progression, overall survival and cancer specific survival was determined.
Results: Vascular invasion was present in 33 patients (12%). Vascular invasion correlated significantly with capsular perforation, seminal vesicle invasion, positive margins of resection, perineural invasion, high grade, and pathological stage. Vascular invasion was a significant prognostic factor for clinical progression ($p<0.001$), local recurrence ($p=0.007$), distant metastases ($p<0.001$), biochemical progression ($p<0.001$), overall survival ($p=0.02$), and cancer specific survival ($p<0.001$). The multivariate analysis, adjusting for capsular perforation, high grade, and positive margins of resection, showed that vascular invasion was associated with a 2.5 fold increased risk for clinical progression. This relative risk was 2.3 for biochemical progression, and 2.7 for cancer specific survival.
Conclusion: Vascular invasion is a very important pathological variable for progression and survival, and must be evaluated on a routine basis during the work-up of radical prostatectomy specimens.

90

INTRODUCTION

The invasion of tumor cells into blood- and lymphatic vessels is generally known to be the first step of the metastatic process, and is associated with progression of the malignant disease [1]. The effects of vascular invasion on progression have been studied for various tumors [2,3,4], indicating that it is an important prognostic factor. Only one study in the literature reports the effects of vascular invasion in prostatic carcinoma: Bahnson found a fourfold greater incidence of progression and death in patients with vascular invasion (VI) present in the radical prostatectomy specimen, compared to those without VI [5]. Despite this finding vascular invasion is rarely reported in prostatic carcinoma. In 1994 the Cancer Committee of the College of American Pathologists advised to report vascular invasion as a routine variable in the examination of the radical prostatectomy specimen in patients with prostatic carcinoma [6].
This study aims to determine the prognostic significance of vascular invasion in patients with clinically localized prostate cancer, and investigates the correlation between vascular invasion and the other established pathological variables.

MATERIAL AND METHODS.

Between 1977 and 1994, 273 patients underwent a pelvic lymph node dissection and radical-retropubic prostatectomy for clinically localized or locally advanced carcinoma of the prostate. Originally, 375 patients were scheduled for surgery, but 102 patients appeared to have lymph node positive disease, detected by frozen sections, and therefore no radical prostatectomy was performed.
Preoperative evaluation. This included a digital rectal examination, histological biopsy of the prostate, determination of serum alkaline phosphatase and prostatic acid phosphatase,(from 1987 on replaced by prostate specific antigen:PSA), a bone scan, CT-scanning of the pelvis and abdomen, and a transrectal ultrasonography.
Patient-group characteristics. The median patient age was 63.8 years,(range 45-75 years). Staging was performed according to the TNM classification of 1992 [7] ;twenty-seven patients were classified T1 (9,9%); 162 as T2 (59,3%); 83 as T3 (30,4%); and one as T4 (0.4%). No subclassification in a,b or c was made, because of the small numbers in each group. The preoperative histological grading was done according to the MD Anderson system [8] ; 68 patients had well differentiated carcinoma (G1:25%); 161 moderately differentiated carcinoma (G2: 59%); and 44 poorly differentiated carcinoma (G3: 16%). All patients were classified as M0. All patients underwent a pelvic lymph node dissection, before proceeding with the radical prostatectomy. In 9 treated patients a single microscopic metastasis had been detected in the lymph nodes. Because of the young age, and good health of these patients, it was decided intra-operatively to proceed with the radical prostatectomy. In 18 patients, who had no evidence of tumor in the frozen sections, microscopic metastases were found on the paraffin sections; therefore 27 patients (10%) that underwent surgery had lymph node metastases. All patients underwent a radical retropubic prostatectomy; the technique has been described before [9] .In 143 patients an attempt was made to save the neurovascular bundles: in 84 patients bilaterally, and in 59 patients unilaterally. In 130 patients the bundles were sacrificed, because of suspicion of tumor growth in the area of the bundle. No patient received adjuvant treatment.
Pathological evaluation. The radical prostatectomy specimen was submitted in its entirety and cut in 5 mm thick slices, all of which were embedded in paraffine. Several 5 μm thick slides

were taken of each slice and stained with haematoxylin/eosine for pathological review. The parameters studied were: vascular invasion, histopathological grade (MD Anderson), capsular perforation, apical and lateral margins of resection, seminal vesicle invasion, perineural invasion, and pT category. The pelvic lymph node specimens were embedded in paraffine and entirely sectioned and evaluated to detect micro metastases. All pathological information was obtained during routine evaluation of the radical prostatectomy specimen.

Vascular invasion was defined as unequivocal presence of tumor cells within endothelial-lined spaces. No attempt was made to differentiate between vascular and lymphatic channels, because of the difficulty and the lack of reproducibility of these observations by routine light microscopic examination [10].

Follow-up. The median follow-up was 49 months (range 1-206 months).Patients were followed at regular intervals of 3 months during the first 2 years; of 6 months during year 3 till 5 and once a year during further follow-up.During each visit a digital rectal examination was performed, and serum PSA and alkaline phosphatase was determined. Bone scanning, computer tomography and TRUS-guided biopsy were only performed when progressive disease was suspected. No additional treatment was started until clinical progression was proved.

All data were collected prospectively, and stored in a computer database which was especially designed for this study.

Study endpoints and definitions. Clinical progression, local recurrence, distant metastases, biochemical progression, overall survival, and cancer specific survival were studied. Clinical progression was defined as histologically confirmed evidence of local recurrence, and/or the presence of distant metastases diagnosed by bone scans, ultrasonography or CT-scanning.Local recurrence was defined as the presence of tumor cells around the bladder-urethra anastomosis, proved by biopsy. Distant metastases were considered by the presence of new hot spots on the bone scan, or by other imaging techniques (ultra sonography, chest X-rays, CT-scans). The presence of an elevated PSA alone was not considered clinical progression. Biochemical progression as a first sign of recurrent disease was defined as the first occurrence of two consecutive PSA values >0,1 ng/ml. To avoid biased selection of patients, only those were studied who had regular PSA determinations during follow-up. Therefore only the patients who had their first PSA measurement within 12 months after the operation were evaluated for biochemical progression (n=173). Overall survival was defined as the percentage of patients who did not die of any cause at a certain time post surgery. In calculating cancer specific survival patients were considered withdrawn from study at the time when they died from causes not related to prostate cancer, post-operative deaths were counted as death due to prostate cancer.

Statistical analysis. The difference between the preoperative PSA of patients with and without vascular invasion was tested by the Mann Whitney U-test. The relation between vascular invasion and the other pathological variables was determined by the chi-square test. Kaplan Meier projections of time to clinical progression(CP),local recurrence(LR),distant metastases(DM),biochemical progression(BP),overall survival(OS),and cancer specific survival(CSS) were used to calculate the actuarial progression and survival percentages at 5 and 10 years.For the univariate analyses the statistical significance of differences was determined by the log-rank test. The Cox proportional hazards model was used to perform multivariate analyses. P-values (two-tailed)≤0.05 were considered significant.

RESULTS

Incidence. Vascular invasion was present in 33 (12%), and absent in 240 patients (88%) in this group of 273 patients with clinically localized and locally advanced prostatic carcinoma.
Preoperative PSA. The preoperative PSA was known in 164 patients, who were diagnosed since 1987, when the determination of PSA became a routine laboratory investigation in our clinic. The relation between preoperative PSA and vascular invasion is shown in table 1. PSA-values tended to be higher in patients with VI as compared to those without. The difference is however not statistically significant (p=0.10). Considering the wide range of PSA-values, this finding has no practical value.

Correlation between pre-operative prostate specific antigen (PSA) and the occurrence of vascular invasion in 164 patients with prostate cancer.				
vascular invasion	N	PSA (ng/ml)		p-value*
		Median	range	
present	20	14.9	2.2-89.0	p=0.1
absent	144	11.1	0-181.4	
*: Mann Whitney U-test (two-tailed)				

Table 1.

Correlation to other pathological variables. The relation between vascular invasion and the other pathological variables is shown in table 2. It appears that there is a strong correlation between the presence of vascular invasion and the occurrence of capsular perforation, seminal vesicle invasion, positive margins of resection (lateral and apical), perineural invasion, high grade, and advanced stage. No significant correlation was found with pN-category..
Progression and survival. Clinical progression occurred in 75 patients (27%), local recurrence in 18 (7%), distant metastases in 45 (17%), and 12 patients had both (4%). In the group of 173 patients who had regular PSA determinations, 66 patients experienced biochemical progression (38%). During follow-up 53 patients died (19%). Of those who died 19 died of prostatic cancer, 3 died in the postoperative period due to complications (2 died of pulmonary embolisms, one of sepsis), and 31 died of other causes not related to prostate cancer. The 6-week postoperative mortality was 1%.
Actuarial progression and survival. The actuarial cumulative percentages for progression and survival are listed in table 3. The 10-year BP-rate is not evaluable, since the number of patients at that time in follow-up is too low to produce reliable results. It is evident that the presence of vascular invasion has a negative influence on prognosis for all parameters. The Kaplan Meier curves for the different outcome-parameters are shown in figure 1-6. It is clear that the presence of vascular invasion is a significantly unfavourable prognostic factor in all aspects studied.
Multivariate analyses. Multivariate analysis of the various pathological variables regarding their relation with clinical progression showed that the factors most strongly related to CP were: the presence of VI: relative risk (RR)= 2.5 (p=0.001), capsular perforation: RR=2.5 (p=0.01), grade 3:RR=1.8 (p=0.02), and positive margins of resection: RR=1.6 (p=0.05). In

Correlation of vascular invasion and pathological variables in 273 radical prostatectomy specimens of patients with prostate cancer.					
pathological variable		N (%)*	vascular invasion		p-value (χ^2)
			absent N (%)#	present N (%)#	
capsular perforation	present	175 (64)	145 (83)	30 (17)	p=0.001
	absent	98 (36)	95 (97)	3 (3)	
seminal vesicle invasion	present	78 (29)	57 (73)	21 (27)	p<0.001
	absent	195 (71)	183 (94)	12 (6)	
positive margin of resection	present	92 (34)	75 (82)	17 (18)	p=0.02
	absent	181 (66)	165 (91)	16 (9)	
positive apex resection margin	present	113 (41)	92 (81)	21 (19)	p=0.006
	absent	160 (59)	148 (93)	12 (7)	
perineural invasion	present	207 (76)	175 (85)	32 (15)	p=0.002
	absent	66 (24)	65 (98)	1 (2)	
pT	0/1/2	86 (32)	85 (99)	1 (1)	p<0.001
	3/4	187 (68)	155 (83)	32 (17)	
pN	0	246 (90)	218 (89)	28 (11)	p=0.28
	1/2	27 (10)	22 (82)	5 (18)	
grade	0§	6 (2)	6 (100)	0 (0)	p<0.001
	1	38 (14)	38 (100)	0 (0)	
	2	168 (62)	151 (90)	17 (10)	
	3	61 (22)	45 (74)	16 (26)	

N=number of patients
*=column percentage
#=row percentage
§: in 6 patients no tumor was found in the prostatectomy specimen

Table 2.

addition to VI (RR=2.3; p=0.007), the only variable significantly related to BP was capsular perforation (RR=2.6; p=0.01). For cancer specific survival the only other predictive factor in addition to VI (RR=2.7; p=0.03) was positive margins of resection (RR=2.5; p=0.05). None of

the other pathological variables added significant information for the occurrence of either CP, BP, and CSS.

		N	CP(%)		LR(%)		DM(%)		BP(%)		OS(%)		CSS(%)	
			5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr
vascular invasion	present	33	68	81	36	36	39	68	83	---	64	40	77	48
	absent	240	21	49	7	23	19	37	47	---	85	66	94	87

Actuarial 5 and 10 year cumulative percentages of clinical progression, local recurrence, distant metastases, biochemical progression, overall survival, and cancer specific survival according to the presence or absence of vascular invasion.

N=number of patients
CP=clinical progression   BP=biochemical progression
LR=local recurrence   OS=overall survival
DM=distant metastases   CSS=cancer specific survival

Table 3.
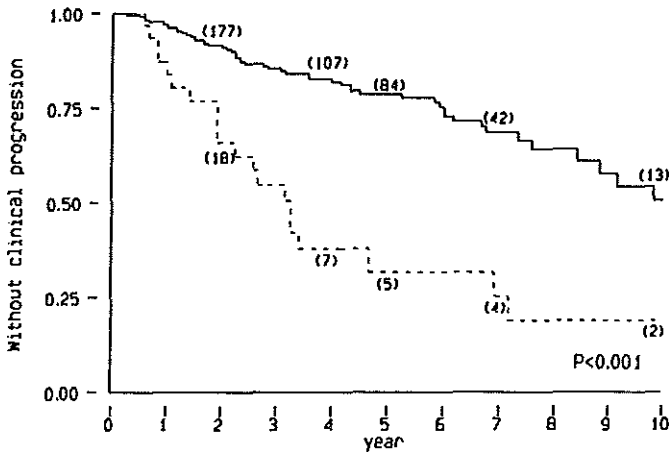
Figure 1: Kaplan Meier projections of time to clinical progression in 240 patients without (____), and 33 patients with (-----) vascular invasion. The numbers between parenthesis indicate the patients at risk at that time, the p-value indicates the significance of the difference between the curves, determined by the logrank-test.
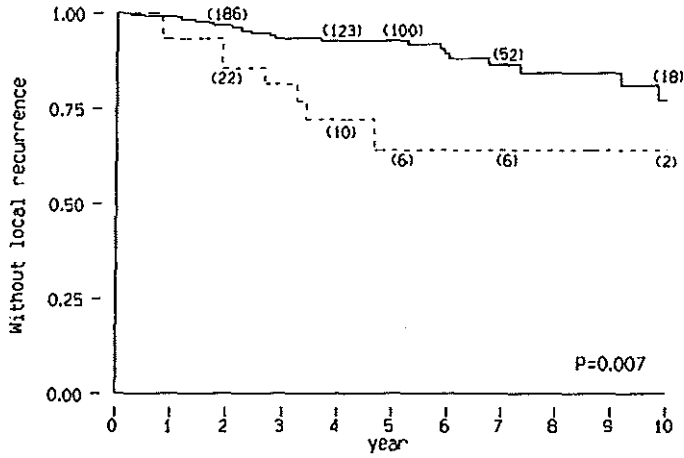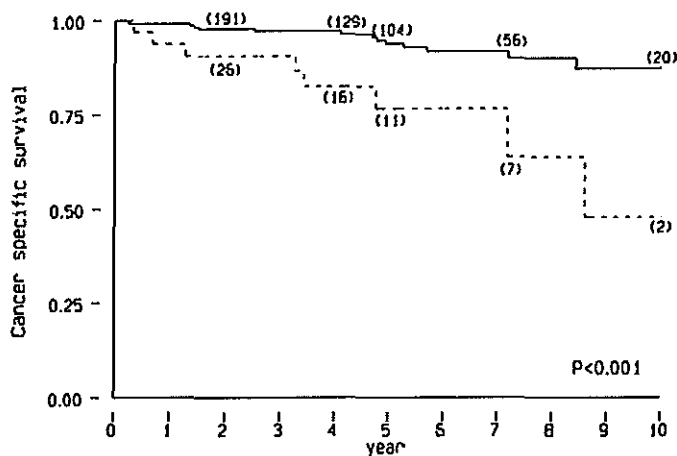
Figure 2: Kaplan Meier projections of time to local recurrence in 240 patients without (_____), and 33 patients with (-----) vascular invasion. The numbers between parenthesis indicate the patients at risk at that time, the p-value indicates the significance of the difference between the curves, determined by the logrank-test.
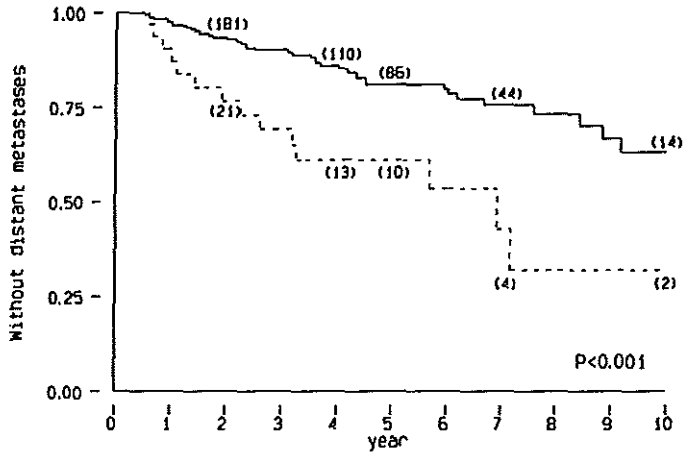
Figure 3: Kaplan Meier projections of time to distant metastases in 240 patients without (_____), and 33 patients with (-----) vascular invasion. The numbers between parenthesis indicate the patients at risk at that time, the p-value indicates the significance of the difference between the curves, determined by the logrank-test.
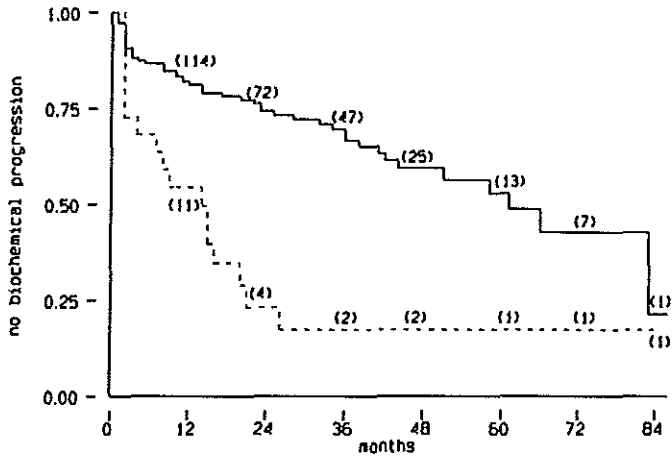
Figure 4: Kaplan Meier projections of time to biochemical progression in 151 patients without (_____), and 22 patients with (-----) vascular invasion. The numbers between parenthesis indicate the patients at risk at that time, the p-value indicates the significance of the difference between the curves, determined by the logrank-test.
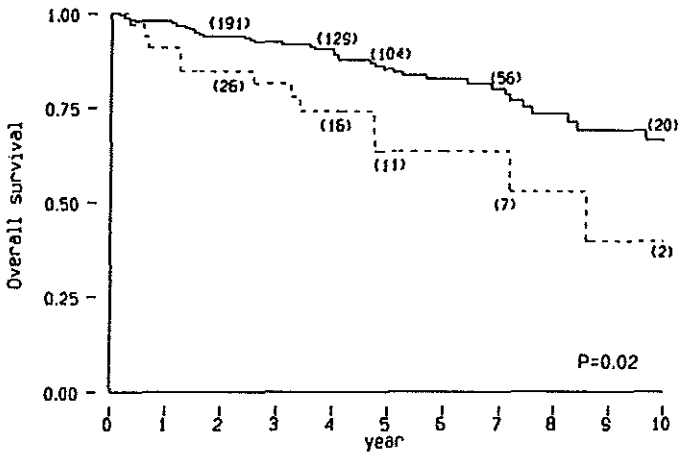
Figure 5: Kaplan Meier projections of overall survival in 240 patients without (_____), and 33 patients with (-----) vascular invasion. The numbers between parenthesis indicate the patients at risk at that time, the p-value indicates the significance of the difference between the curves, determined by the logrank-test.

97

Figure 6: Kaplan Meier projections of cancer specific survival in 240 patients without(___), and 33 patients with (-----) vascular invasion. The numbers between parenthesis indicate the patients at risk at that time, the p-value indicates the significance of the difference between the curves, determined by the lograrik-test.

DISCUSSION.

Vascular invasion and hematogenous dissemination. Vascular invasion is one of the first steps in the development of metastases [1]. The metastatic process starts with invasion of the tumor cells in the periglandular stroma; the next step is tumor angiogenesis, which facilitates the invasion of tumor cells into the vascular spaces, because these tumor-induced blood vessels are fragile and highly permeable, with a discontinuous basement membrane [11]. After invasion of the blood vessels the tumor cells are transported by the ciculatory system, and arrest in the capillary bed of the target-organ, where extravasation occurs and growth in the target-organ [1]. The process of vascular invasion was studied by Liotta [12], who identified 3 steps: 1:tumor cell attachment to components of the matrix via cell surface receptors; 2: secretion of hydrolytic enzymes which can locally degrade the matrix; 3: tumor cell locomotion into the vessel. The basement membrane is a meshwork of type IV collagen, which can be degraded by a type IV collagenolytic metalloproteinase that is identified in highly metastatic tumor cells [12,13]. Tumor cells with metastatic potential represent a subpopulation with special properties [11] : they are able to degrade the basement membrane and survive the traumata of dissemination. This explains why only 1 of 1000 tumor cells is able to produce a metastasis [1]. Vascular invasion correlates with high grade prostate cancer (Bahnson [5], Salomao [10], present series). The meta-static subpopulation may be relatively more numerous in poorly differentiated tumors, which occur more frequently in the later phases of the tumor development, after dedifferentiation. This hypothesis may explain why distant metastases are relatively infrequent after radical

prostatectomy, since it is known that hematogenous dissemination occurs in 25% of the patients during radical prostatectomy, due to intraoperative manipulation of the prostate [14,15]. Furthermore tumor cell clumps produce a significantly greater number of metastatic foci than a similar number of single tumor cells [15]; whether patients with intraoperative dissemination have tumor clumps or single cells in their circulation is not known, since the investigation was performed with electrophorese, following amplification of the tumor cell RNA by the polymerase chain reaction technique, and not by light microscopy [14]. It seems that the hematogenous dissemination that occurs during surgery due to manipulation of the tumor has less impact on progression than the vascular invasion found by light microscopy, because the latter is due to invasion of a selected subpopulation with a high metastatic potential, whereas the disseminated tumor cells during operation can be of several different tumor cell populations.

Neoangiogenesis. Although prostatic carcinomas are generally not considered to be very vascular tumors, neoangiogenesis is a frequent event. Bigler [16] and Brawer [17] found it to be present in 14 of 15 patients who underwent a radical prostatectomy for prostate cancer. Patients with prostate cancer had a significantly higher vascular density than those with benign prostatic hyperplasia (BPH); they also found a different microcirculation and different morphology in BPH, as compared to prostate cancer. In BPH the localization of capillaries was at the interface of the glands and the stroma; in tumors the distribution of capillaries was more at random, depending on the site of the tumor. In BPH the vessels were uniform in size and caliber, whereas in carcinoma they were variable in size with tiny or inconspicuous lumens [16]. Weidner compared the tumor angiogenesis in patients with prostatic carcinoma with and without metastases, by counting the microvessels within the initial invasive carcinomas [18], and found a significantly higher microvessel density in metastatic carcinomas. The microvessel counts correlated with increasing Gleason score, and added significant additional information for progression as determined by multivariate analysis. The observation that the microvessel density was greatest in poorly differentiated tumors, suggests that the highly angiogenic phenotype occurs relatively late in the natural history of the disease, as well differentiated tumors dedifferentiate to poorly differentiated tumors [18].

Incidence of vascular invasion. The incidence of vascular invasion in the present series was 12%. This incidence is considerably lower then reported by Bahnson [5] (51%), and Salomao [10] (53%). The reasons for this are probably differences in definition, and the fact that the radical prostatectomy specimen in the present study was evaluated in a routine matter, without elaborate sampling, and without extra attention for vascular invasion. No specimen was reviewed for this study. Bahnson differentiated between invasion of vascular and lymphatic vessels, and defined invasion as presence of tumor in the lumen or cellular reaction around or in the lymphatic or venous channel. A differentiation was made between rare (71%), multifocal (19%), and diffuse vascular invasion (10%) [5]. Multifocal and diffuse vascular invasion were present in 16% of his patients; this number approaches the 12% in the present series. Salomao defined vascular invasion as presence of tumor within endothelial-lined spaces, and did not differentiate between vascular or lymphatic channels. They did however differentiate between focal and extensive vascular invasion, the latter was present in 33%. In the present study vascular invasion was simply defined as presence of tumor within endothelial-lined spaces.

Prognostic significance of vascular invasion. The simplicity of the definition and the routine way in which the radical prostatectomy specimen was evaluated did not harm the prognostic significance. Clemente investigated vascular invasion in patients with lymph node negative mammary duct carcinoma and found an incidence of 6.9% after routine evaluation; vascular invasion was a highly significant prognostic factor for progression and survival. However when

a randomly selected part of the specimens was reviewed with special attention given to the presence of vascular invasion, the incidence rose to 20%, but the prognostic significance for survival was lost [2]. Bahnson reported a fourfold increased risk for progression in patients with vascular invasion, compared to those without, however after adjusting for grade and pathological stage, no additional prognostic value resulted [5]. In the present series vascular invasion was the most significant prognostic variable for CP, BP, and CSS, followed by capsular perforation, high grade and positive margins of resection, as determined by the multivariate analysis. In the univariate analysis vascular invasion was a significant prognostic factor for CP, LR, DM, BP, OS, and CSS.

Correlation of vascular invasion with other pathological variables. Vascular invasion is reported to correlate with high grade and advanced pathologic stage [5,10], and also with capsular perforation, seminal vesicle invasion, surgical margin status, and lymph node involvement [10]. In the present series vascular invasion correlated with all evaluated pathological variables (see table 2) except lymph node involvement. This is surprizing, since no differentiation was made between vascular and lymphatic channels in this study. This means that in some cases the vessel involved by vascular invasion is probably a lymphatic vessel, which should result in lymph node positive disease and therefore a positive correlation could be expected. The reason for the lack of a correlation may be that the lymph node positive patients in this study-group represent a highly selected group of patients, with very small metastases.

Determination of vascular invasion. In this series vascular invasion was evaluated during a routine work-up of the radical prostatectomy specimen. No special coloring of the slides beside the standard hematoxilin/eosine coloring was necessary, and no elaborate sampling was perfomed. Since the majority of the vascular invasion sites are in the area of the tumor, no painstaking revision of slides is necessary. This means that vascular invasion can be evaluated during the routine work-up of the radical prostatectomy specimen, without investing extra time and costs, and without delay of the pathologists report. Given the highly prognostic significance of vascular invasion, we underline the suggestion of the Cancer Committee of the College of American Pathologists of reporting vascular invasion for all prostatic specimens, using routine light microscopic examination [6].

CONCLUSIONS.

Vascular invasion determined in the radical prostatectomy specimen of patients operated for clinically localized and locally advanced prostate cancer is easy to evaluate , without investing extra time and costs. This variable correlates significantly with capsular perforation, seminal vesicle invasion, positive margins of resection, perineural invasion, histological grade and pathological stage. In the univariate analysis vascular invasion is strongly predictive for progression and decreased survival. In the multivariate analysis vascular invasion proved to be the most significant prognostic factor for progression and survival. Vascular invasion should be reported on a routine basis during examination of radical prostatectomy specimens.

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PART 3

LYMPH NODE POSITIVE PROSTATIC CANCER: INFLUENCE ON PROGRESSION

Deoxyribonucleic acid ploidy of core biopsies and metastatic lymph nodes of prostate cancer patients: impact on time to progression.

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DEOXYRIBONUCLEIC ACID PLOIDY OF CORE BIOPSIES AND METASTATIC LYMPH NODES OF PROSTATE CANCER PATIENTS: IMPACT ON TIME TO PROGRESSION

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ABSTRACT

We studied 98 patients with locally confined but lymph node positive prostatic cancer (1 stage T1, 29 stage T2, 55 stage T3 and 2 stage T4) who were not treated by radical prostatectomy. A retrospective analysis was done of deoxyribonucleic acid (DNA) ploidy of pretreatment core biopsies of the primary tumor and lymph node metastases. While DNA ploidy has been shown to be an important prognostic factor if applied to radical prostatectomy specimens, core biopsy specimens and nodal metastases have rarely been studied. Of the 98 patients 87 were evaluable for DNA ploidy: 45 (52%) had diploid, 13 (15%) had tetraploid and 29 (33%) had aneuploid tumors. The ploidy of the primary tumor and of the lymph node metastases correlated significantly with the rate of progression and interval to progression. Also, significant correlations were noted between the percentages of cells in the S phase or S plus G2 phases of the cell cycle and interval to progression.

Most patients in this study are part of the European Organization for Research and Treatment of Cancer protocol 30846, a prospective randomized study of early versus delayed treatment in lymph node positive, otherwise locally confined prostate cancer. This study is ongoing. Early endocrine treatment was associated with a significantly longer interval to progression. In a Cox regression analysis of the prognostic factors involved in this study, early endocrine treatment was more important than ploidy or proliferation patterns. Stage (T category) and histopathological grade did not show a correlation with progression. Followup is still too short and the numbers of patients are too small for relevant subgroup analysis.

DNA ploidy measurement by flow cytometry on archival (paraffin embedded) core biopsy and lymph node material is possible, and produces meaningful results in predicting the prognosis of prostatic cancer. Since this information can be made available before treatment decisions, its exact value in the management of locally confined prostate cancer can be determined.

KEY WORDS: DNA, neoplasm; prostatic neoplasms; ploidies; lymph nodes; biopsy

The patient material collected within the institutions involved in the European Organization for Research and Treatment of Cancer (EORTC) protocol 30846, which compares early versus delayed endocrine treatment in lymph node positive prostatic cancer, offers a unique opportunity to compare prognostic factors that relate the primary tumor and the lymph nodes in node positive prostate cancer patients. Most recent articles on deoxyribonucleic acid (DNA) ploidy of prostate cancer are related to radical prostatectomy specimens.[1-7] Only a few investigators report on the ploidy of lymph node metastases[3] and prostatic aspiration biopsies.[9-18] Recently, static cytometry on core biopsies was described,[19] whereas no information is yet available of flow cytometry on core biopsies. Only 1 report reviewed in the literature refers to a comparison between the ploidy of the primary tumor and lymph node metastases.[20]

DNA ploidy can be determined in fresh or paraffin embedded material. The latter method enables the analysis of larger series with several years of followup. Several investigators have described the technical difficulties encountered in determining DNA ploidy on histological biopsy specimens. To establish DNA ploidy as an important, clinically useful prognostic factor, it will be necessary to show prognostic relevance for ploidy

determinations on biopsy specimens rather than on radical prostatectomy specimens, which will only be available after treatment decisions have already been made. Considering the setup of EORTC protocol 30846 and the treatment policies followed at the involved institutions, radical prostatectomy is not done in the presence of lymph node metastases. Patients with positive lymph nodes are either randomized to early endocrine treatment versus delayed endocrine treatment or are treated according to their personal preference.

Considering the existing controversy on whether early or delayed endocrine treatment might be more effective, it will be important to be able to correct for relevant prognostic factors, such as ploidy. In fact, Myers et al produced long-term followup data comparing ploidy, and early and delayed endocrine treatment with progression and survival rates.[7] Unfortunately, our followup is short and amounts to an average of 32 months (range 2 to 115). For this reason the interval to progression is used as the end point for reporting in our study.

More and more evidence is accumulating that the size of the primary tumor and other related parameters are important prognostic factors, at least in locally confined disease. Tumor volume calculated on radical prostatectomy specimens correlates with the grade of malignancy, incidence of lymph node metastases, peripheral prostate specific antigen (PSA) levels

and incidence of metastases as shown by Stamey et al.[21] However, there is also evidence that the primary tumor progression rate and response to endocrine treatment are different from those of distant metastases. Carpentier et al have shown that while 20 patients who were observed prospectively showed progression to metastatic disease, only 2 of those had local progression during the same period (24 months).[22] Also, the EORTC Genitourinary Group protocol 30761 demonstrated different response and progression rates of the primary tumor as compared to distant metastases.[23] The different behavior of the primary tumor under treatment, especially under endocrine treatment, may also eventually limit the prognostic significance obtained from biopsies or radical prostatectomy specimens.

In our series the feasibility of using archival core biopsies for flow cytometry is studied, and the results are compared to ploidy in lymph node metastases in the same patients. Furthermore, the significance for the rate of progression and interval to progression of ploidy and S phase or S plus G2 percentages of cells is determined in primary carcinoma and lymph node metastases.

MATERIAL AND METHODS

Patients. Between 1981 and 1991, 98 patients with lymph node positive prostate cancer were studied; 87 of them had evaluable ploidy measurements and were included in this study. The lymph node status was determined by pelvic lymph node dissection in the area between the bifurcation of the common iliac artery, entrance of the lacuna vasorum, external iliac vein and obturator vessels. According to the tumor, nodes and metastasis system of 1978/1982, which is used throughout this report, 34 patients were classified as having stage N1, 48 stage N2 and 3 stage N3 disease.[24] In 2 patients the N category was unknown. The clinical stage was T1 in 1 patient, T2 in 29 patients, T3 in 55 patients and T4 in 2 patients. Four patients had a well differentiated (grade 1), 46 a moderately differentiated (grade 2) and 37 a poorly differentiated (grade 3) carcinoma. Mean patient age was 63.9 years (range 41 to 80). Of the 98 patients 81 are included in EORTC protocol 30846. This protocol was reviewed and approved by the Protocol Review Committee of the EORTC. In this study patients are randomized between immediate and delayed endocrine treatment. In the delayed group endocrine treatment is initiated at the time of objective progression. Since delayed endocrine treatment was only initiated after progression occurred, delayed endocrine treatment patients in this evaluation are untreated. This EORTC study is unfinished; survival data and other results of this protocol will be subject to reporting after completion of the protocol. A total of 17 patients received early endocrine treatment outside the EORTC protocol.

Followup. Patients were followed by their own urologist at 3-month intervals during the first 2 years and every 6 months during further followup. Followup consisted of physical examination, including digital rectal examination, ultrasonography of the prostate (not at all centers), and determination of serum alkaline phosphatase, prostatic acid phosphatase (PAP) or PSA levels. The latter was determined only after it became a routine laboratory investigation in 1987. Computerized tomography and bone scanning were done only on indication of increasing serum markers or specific complaints of the patients.[25, 26] Progression was defined as the occurrence of metastases, proved by physical examination, bone scans and imaging. An elevation of serum markers alone was not considered as progression.

Prognostic parameters. The prognostic parameters studied are the T category according to International Union Against Cancer criteria of 1982, histopathological grade according to the Mostofi system, early versus delayed endocrine treatment, ploidy, and the proportions of S phase cells and S plus G2 phase cells determined by DNA flow cytometry. PSA was not evaluated because it was not yet available for routine use at all participating centers at the initiation of this study. Therefore,

these data are incomplete and the numbers are too small to be meaningful.

Core biopsies. In each patient 4 biopsies were obtained transperineally, using a 14 gauge Tru-Cut* needle. The specimens were fixed in formalin and embedded in paraffin. All specimens were investigated by a reference pathologist and the histopathological grade (according to the Mostofi system) was determined. Biopsy material was available in 54 cases, 53 of which (98%) were evaluable.

Transurethral resection material. A total of 18 patients underwent resection of the prostate before entering the study. Of these patients 10 were evaluable for ploidy analysis. Unfortunately, no core biopsy material was available in these patients.

Lymph node metastases. This material was obtained by pelvic lymph node dissection in 72 patients. A total of 87 lymph nodes containing metastases and 39 normal lymph nodes was investigated.

DNA ploidy determinations. DNA flow cytometry of primary tumors and/or metastases was evaluable in 87 of 98 patients. The most undifferentiated part of the tumor was identified by light microscopy and used for DNA ploidy determination.

For the preparation of suspensions of cell nuclei, a modification of the basic Hedley method was used.[27] Sections (100 μ.) of the paraffin blocks were placed into fine mesh bags, which were placed into a cassette, and then dewaxed and rehydrated in a tissue processor. Enzymatic digestion was done with Subtilisin Carlsberg (Sigma Protease Type XXIV) and all centrifugation steps were omitted. In this manner cell loss was minimized, and nuclei suspensions with extremely low amounts of clumped nuclei and debris were obtained. The nuclei were stained with DAPI, final concentration 6 μM., and analyzed with a PAS II† flow cytometer. The representativeness for tumor cells of the tissues used for preparation of the cell suspensions from the blocks was determined in a contiguous 5 μm. section. In addition, the proportion of tumor cell nuclei was counted in an aliquot of the stained suspension of nuclei by light microscopy. The mean ratios of tumor cell nuclei per normal nuclei were 32% (range 2 to 95%) for prostatic biopsies and 75% (range 18 to 88%) for lymph node metastases, respectively. To confirm the ploidy of the near diploid aneuploid cell populations the DNA content of identified nuclei from normal and malignant cells was measured by means of a static image analysis system. Tumors were considered diploid if only 1 G1 peak was present. For determination of the DNA index in grossly aneuploid cell populations the first peak to the left was assumed to represent diploid cells. Samples with peaks in the tetraploid position (DNA index 1.95 to 2.05, more than 15% of the total cells) and a corresponding octoploid G2 peak were classified as tetraploid. This 15% boundary was arbitrarily chosen because no core biopsies from benign lesions of the prostate were available to determine the normal range of G2 values.

For the determination of the percentage of cells in the S plus G2 phases of the cell cycle the multicycle program by Rabinovitch was used. The "sliced-nuclei" option of the program applied provides a background fit model, which includes a compensation for the effects of cutting of nuclei during sectioning of the paraffin embedded samples.[27]

In suspensions of cell nuclei prepared from aneuploid primary tumors and aneuploid metastases the proportions of aneuploid nuclei as measured by flow cytometry were compared with the proportions of microscopically identified tumor cell nuclei. Mean values were 30 ± 29% (range 1 to 95) for flow cytometry, and 50 ± 30% (range 2 to 93) for microscopical counts. The difference in the individual tumors between the results of the 2 counts was highly significant (p <0.001). On the average, an aneuploid tumor with 30% aneuploid cells thus contains in addition 20% of diploid tumor cells. Particularly in tumors with

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† Partec, Münster, Federal Republic of Germany.

109

tetraploid DNA content, a large number of diploid tumor cells were observed. Cell loss can be excluded, since flow cytometry and measurement of tumor cell nuclei were done in the same cell nuclei suspension.

Statistical methods. Interval T to progression was estimated by the Kaplan-Meier technique.[24] Differences between curves were evaluated for statistical significance using the log-rank test. The prognostic variables were analyzed by the Cox regression analysis.

RESULTS

Among the 98 patients ploidy was not evaluable in 11: in 5 no adequate histological material was available and in 6 the DNA histogram was of poor quality. These patients were excluded from the evaluation of ploidy. In the overall analysis tumors are considered diploid if the primary tumor and lymph nodes or, in case of lacking information, 1 of the samples (either the primary tumor or the lymph nodes) was classified as diploid. In case of a mixed result the poorer ploidy was always used as definitive classification. In the 87 patients in whom either the ploidy of the primary and/or the ploidy of the lymph nodes were evaluable the tumors were classified as diploid in 45 (52%), tetraploid in 13 (15%) and aneuploid in 29 (33%). Figure 1 shows representative DNA histograms for diploid, tetraploid and aneuploid tumors.

The ploidy of the primary tumor was evaluable in 63 patients: 36 (57%) had diploid, 15 (24%) tetraploid and 12 (19%) aneuploid tumors. Among 87 evaluable lymph nodes in 71 patients the ploidy was determined as diploid in 54 (62%), tetraploid in 8 (9%) and aneuploid in 25 (29%). All samples from 39 normal lymph nodes were diploid.

In 46 patients the ploidy of the primary tumor and the lymph node metastases could be obtained. A comparison of the classification by ploidy is given in table 1. Of the diploid and aneuploid primary tumors 84% and 89%, respectively, had equally classified metastases. In each of the 25 diploid primary tumors and the 27 diploid lymph node metastases 1 aneuploid cell population was found. In the tetraploid primary tumors, however, a wide variation of the ploidy of the lymph node metastases is obvious. Nonrepresentative cell material of the primary tumor or further clonal development of the tetraploid lymph node metastases can be discussed. When diploid and tetraploid are combined into 1 group conformity is noted in 86% of the samples.

When ploidy was compared to T category, grade and nodal status, no statistically significant or clinically relevant correlations could be found. However, there was a trend toward more

extensive growing tumors being aneuploid more frequently than locally confirmed tumors. Aneuploid tumors were, however, equally distributed between moderately differentiated and undifferentiated lesions. No meaningful correlation with the N status (N1, N2, N3) was noted.

Prognostic factors and interval to progression. Of the 87 patients available 3 died of cancer of the prostate and 1 died intercurrently. Mean followup was 33.4 months (range 3 to 116). The results from the bivariate analysis of the various prognostic factors are listed in table 2.

T category and histopathological grade. Tumors of stages T1 and T2, and stages T3 and T4 were combined into 2 groups. The 4 patients with grade 1 tumors were combined with those with grade 2 tumors. No statistically significant differences for stage and grade were found.

Ploidy of the primary tumor. In 63 patients in whom the ploidy of the primary tumor was known the influence of the ploidy classification of diploid, tetraploid or aneuploid on interval to progression was tested. There was no significant difference in interval to progression between diploid and tetraploid (p = 0.47), and between tetraploid and aneuploid (p = 0.18) but a significant difference was found in the comparison of the diploid and aneuploid groups (p = 0.02). When the diploid and tetraploid groups were combined and tested against the aneuploid group, a significant difference was also noted (p = 0.023, fig. 2).

The percentage of cells in the S phase in primary tumor. As a measurement of proliferation, the percentage of cells in the S phase of the cell cycle was evaluated in the primary tumors of 54 patients. The mean values and range in relation to the different ploidy classifications are listed in table 3 together with the corresponding values for G2 cells of the cell cycle. It can be seen that the mean numbers of cells in the S phase increased from 0.7% in the diploid to 5.2% in the aneuploid cell populations. When a division is made into 2 groups, 1 group with an S phase percentage of cells of 4.0% or less and 1 group with an S phase percentage of more than 4%, a significant difference is found for interval to progression (p = 0.013). When the values for S phase and the G2 cells of the cell cycle were combined, and a division was made into 2 groups with percentages of S plus G2 cells of 6% or less and greater than 6%, again a significant difference was found for interval to progression (p = 0.0015, fig. 3).

Ploidy of lymph node metastases. A similar pattern was observed in the 71 patients with known ploidy of the lymph node metastases. When interval to progression was compared for diploid versus tetraploid and tetraploid versus aneuploid tumors, no significant differences were found (p = 0.84 and p =
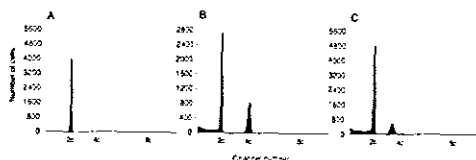

FIG. 1. DNA histograms representative of diploid (*A*), tetraploid (*B*) and aneuploid (*C*) tumors.

TABLE 1. *Ploidy value of 46 primary tumors and their lymph node metastases*

Primary Tumors	Lymph Node Metastases			
	Diploid No. (%)	Tetraploid No. (%)	Aneuploid No. (%)	Totals
Diploid	21 (84)	3 (12)	1 (4)	25
Tetraploid	5 (42)	2 (16)	5 (42)	12
Aneuploid	1 (11)	—	8 (89)	9
Totals	27	5	14	46

TABLE 2. *Bivariate analysis of various prognostic factors for interval to progression*

| Factors	No.	Chi-Square	P Value
Therapy (early vs. delayed endocrine therapy)	87	17.59	0.0001
Median age (65 or less vs. more than 65)	87	1.33	0.25
Primary tumor:			
Stage (T1 + 2 vs. T3 + T4)	87	0.005	0.94
Grade (1 + 2 vs. 3)	87	0.55	0.46
Ploidy (diploid + tetraploid vs. aneuploid*)	63	5.17	0.023
S phase (4% or less vs. more than 4%)	54	*6.16	0.013
G2 + S phase (6% or less vs. more than 6%)	54	10.92	0.001
Lymph node:			
Ploidy (diploid + tetraploid vs. aneuploid)	71	4.46	0.035
S phase (4% or less vs. more than 4%)	66	7.94	0.005
G2 + S phase (6% or less vs. more than 6%)	66	12.33	0.0004

* Median value.

110
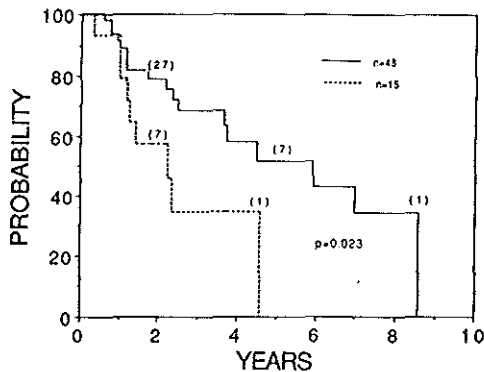
FIG. 2. Kaplan-Meier curves for interval to progression in 48 patients with diploid or diploid-tetraploid (———)and 15 with aneuploid (- - - - -) primary tumors. Numbers in parentheses indicate number of patients at risk at certain time.

TABLE 3. *Relationship between the percentage of cells in the S and G2 phases of the cell cycle and the ploidy classification in 54 primary tumors*

Ploidy	No.	S Phase* (range)	G2 Phase* (range)
Diploid	29	0.7 ± 0.7 (0.1–3.1)	2.3 ± 2.5 (0.2–13.2)
Tetraploid	12	3.4 ± 1.3 (1.8–5.9)	2.1 ± 1.6 (0.1–5.0)
Aneuploid	13	5.2 ± 3.4 (1.8–13.8)	4.3 ± 3.2 (0.2–9.6)

* Mean plus or minus standard deviation.

0.32). The difference between diploid and aneuploid tumors was again significant (p = 0.0391). Combining the diploid and tetraploid groups and testing them against the aneuploid group also resulted in a significant difference (p = 0.0348).

The percentage of cells in the S phase in lymph node metastases. A similar pattern is observed in the 66 patients with lymph node metastases in whom the percentage of cells in the S phase could be evaluated. The mean values and ranges are shown in table 4 in relation to ploidy. The values from 39 benign lymph nodes are included for comparison. The mean number of cells in the S phase increases from 1.4% for diploid to 3.9% for aneuploid cell lines. When a division is made between groups with S phase percentage of 4% or less and greater than 4%, a significant difference is found (p = 0.005) for interval to progression (table 2). By combining the percentages of S phase and G2 cells, and taking 6% as the dividing

line for the 2 groups, the significance for the interval to progression further increased (p = 0.0004).

Early versus delayed endocrine treatment. A highly significant difference in interval to progression resulted when patients receiving early endocrine treatment were compared to those in whom treatment was delayed (p = 0.0001, fig. 4). Since delayed treatment was only initiated at the time of progression, the patients in the delayed endocrine treatment group were untreated up to this point.

Regression analysis. A Cox multivariate regression analysis for the different prognostic factors for interval to progression revealed that therapy is the most important factor. This was the case for progression of the primary tumor and for progression to distant disease, with p values of 0.004 and 0.0057, respectively.

Irrespective of the treatment, the ploidy of the primary tumor was significantly correlated with progression (p = 0.0107). However, this was not the case for the ploidy of lymph node metastasis (p = 0.25). The S plus G2 phase percentage of cells (≦6.0% and >6.0%) showed significant differences for time to progression in lymph node metastases (p = 0.03), but not in the primary tumors (p = 0.35). Clinical stage and grade, in confirmation of the results of the monovariate analysis, did not reach significance in the regression analysis.

The 37 patients in the early endocrine treatment group were subjected to a separate regression analysis. In this group, ploidy was a significant predictor of progression in the primary tumor and in the lymph node metastases (p = 0.02 and p = 0.04). Also, the S plus G2 percentage was significant for lymph node metastases (p = 0.02) but not for the primary tumors (p = 0.095). Clinical stage and grade again did not reach significance.

DISCUSSION

DNA ploidy of the primary tumor in locally confined prostate cancer and in lymph node positive disease has been shown to be an important, if not the most important, prognostic factor. Relevant data are summarized in table 5.[2-5, 7, 8, 13, 29-33] However, most of the information on ploidy has been obtained on radical prostatectomy specimens. Obviously, this information is only available after treatment decisions have already been made. It is unknown at this moment how reliably DNA ploidy can be determined on biopsy material by flow cytometry, especially on core biopsies. Ideally, DNA ploidy determined on core biopsies should be compared for this purpose with DNA ploidy determined on radical prostatectomy specimens. In our study the policy was not to remove the prostate in case of the presence of lymph node metastases. These lymph node metastases were available for comparison with biopsy material of the primary tumor. This material and all clinical information were collected within a prospective randomized EORTC protocol. The data were under EORTC policy subject to external quality control.
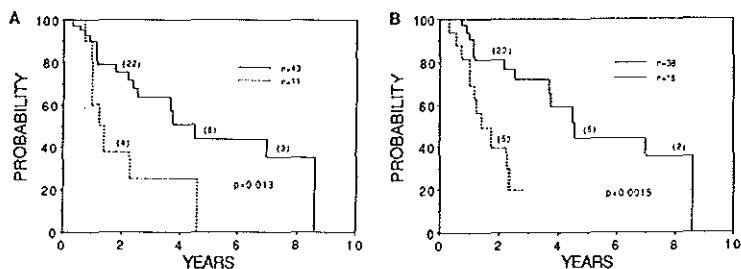

FIG. 3. Kaplan-Meier curves for interval to progression. Numbers in parentheses indicate number of patients at risk at certain time. *A*, 43 patients with S phase values of 4% or less (———) and 11 with values of 4% or more (- - - - -) in primary tumors. *B*, 38 patients with S plus G2 values of 6% or less (———) and 16 with values of more than 6% (- - - - -) in primary tumors.

111

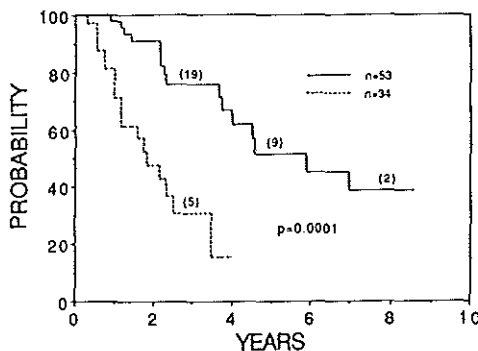| Ploidy	No.	S Phase* (range)	G2 Phase* (range)
Diploid	33	1.4 ± 0.7 (0.4–3.8)	1.3 ± 0.9 (0.2–3.3)
Tetraploid	7	2.1 ± 1.3 (0.1–4.5)	1.8 ± 1.7 (0.1–5.3)
Aneuploid	21	3.9 ± 3.1 (0.7–12.0)	3.0 ± 3.6 (0.3–16.2)
Benign	39	0.9 ± 0.6 (0.3–1.7)	0.5 ± 0.2 (0.1–1.5)

* Mean plus or minus standard deviation.

FIG. 4. Kaplan-Meier curves for interval to progression in 50 patients who received early (———) and 34 who received delayed (· · · · ·) endocrine treatment.

Our results show that the determination of DNA ploidy on core biopsy material is technically feasible. The results correlate with DNA ploidy obtained from lymph node metastases and with interval to progression. The distribution of DNA ploidy for primary tumors, primary tumor biopsies and lymph node metastases that were found in the literature are shown in table 5.[2-5, 7, 8, 13, 29-33] Our results have been added to this table. Obviously, there is considerable variation of the distribution of ploidy from series to series. Since tumor stage and grade are significantly related with ploidy,[17] differences in stage and grade by selection of the tumors studied must be one of the main reasons for the differences in ploidy composition of the various series. In our investigation patients with manifest distant metastases were excluded. The frequency of distant metastases in relation to ploidy of the prostate has been studied previously in 490 patients with newly detected carcinomas. The frequency increased from 7% in diploid and 17% in tetraploid tumors to 28% and 52% in those with 1 or multiple cell populations.[15] Thus, exclusion of patients with distant metastases in our series resulted in a predominance of diploid tumors but of relatively high grade and stages—43% of the tumors were poorly differentiated and 66% were stage T3 or more. Another possible explanation may result from the variation in the percentage of tetraploid cases in the different investigations. A reason for this finding is that there is no uniform definition for the assignment of tetraploidy. However, this uncertainty is more likely to influence the rate of diploid cases diagnosed. It is remarkable that the inter laboratory variability in DNA ploidy determination is slight. Still, technical variations and differences in interpretation may lead to a different allocation of ploidy in 10 to 15% of the cases.[34] The 15% boundary for tetraploidy in our study was chosen arbitrarily because no normal range of G2 values was known for core biopsy material. The boundary for stage D1 prostate carcinoma of the Mayo Clinic report was 13%, which therefore can only partly explain the lower proportion of tetraploid tumors in our study (15%) compared with the Mayo Clinic material (45%).[4]

We found that all tetraploid tumors contained large populations of diploid cell lines and that, in the analysis for prognostic importance, tetraploid tumors can best be combined with diploid tumors. Montgomery et al also found no significant difference in progression rates between diploid and tetraploid carcinomas.[31] The high percentage of aneuploidy as found previously in a large number of unselected high grade, high stage tumors[17] was not found in our study. Stephenson et al also studied lymph node metastases and found a rate of aneuploidy that is similar to our study.[8]

A major concern in using biopsy material to determine ploidy is whether the tissue or cells obtained are representative for the tumor as a whole. Pleomorphism has been shown by Müller et al[35] and several others to be the reason for under grading of radical prostatectomy specimens by means of core biopsies. In this situation grade 3 tumors may frequently be missed. The possibility of missing aneuploid tumors with core biopsies must be investigated further. Our data, which confirm a good correlation between the ploidy in biopsies and the ploidy in lymph node metastases, do not suggest an under determination of aneuploidy by core biopsy. The data are documented in table 1.

At least in Europe, aspiration biopsy of the prostate is still done frequently and is considered to be an important diagnostic tool. The possibility has been raised that cell sampling is more efficient and representative for the whole of a given tumor than core biopsy. Adolfsson et al found a significant correlation between ploidy and interval to progression in 146 untreated low grade, low stage tumors with the use of fine needle aspiration biopsy.[13]

In our study a significant correlation between DNA ploidy determined by means of archival material of core biopsies and interval to progression is described. This finding reproduces the results of studies using radical prostatectomy specimens for retrospective analysis and shows that the pretreatment evaluation of DNA ploidy by flow cytometry is feasible. In our series of lymph node positive patients the T category and grade of differentiation of the primary tumor were not shown to be relevant prognostic factors. Also, there was no strong correlation between DNA ploidy, and the T and G categories.

In our series the significance of proliferation for interval to progression was also found for the parameter of the proportion of cells in the S phase or S plus G2 phases of the cell cycle. A highly statistically significant separation was achieved when patients were separated according to a percentage of cells in the S phase or S plus G2 phases of 4% or less and more than 4%, and 6.0% or less and greater than 6.0%, respectively. These findings were confirmed in the lymph node metastases. More recent techniques allow the determination of the proliferating fraction of primary tumors by use of the antibody Ki-67 reacting with a protein that is not expressed in the G0 phase of the cell cycle. Subsequent to preliminary studies,[36] attempts to correlate this parameter to ploidy and to the percentage of cells in the S and G2 phases of the cell cycle are in progress. Scrivner et al did DNA flow cytometry and bromodeoxyuridine labeling on 44 fresh biopsies of prostatic carcinoma, of which 37 were evaluable.[37] They found a significant correlation between the bromodeoxyuridine labeling index and the DNA index but not between the labeling index and the percentage of cells in S plus G2 phases, as determined by flow cytometry. As an explanation in this study the high noise-to-signal ratio and the inability to discriminate between neoplastic and nonneoplastic cells was offered. No followup data on the patients recruited to this study are available.

Early endocrine treatment turned out to have the strongest impact on interval to progression of all parameters analyzed in this study. This finding is not surprising and confirms a previous report from this institution.[38] However, this difference was never demonstrated previously in a prospective randomized fashion. Myers et al studied DNA ploidy in 62 stage D1 cancer

112

Reference	No. Pts.	Material Investigated	Ploidy (%)			Tumor Stage	Prognostic Significance
			Diploid	Tetraploid	Aneuploid		
Dejter et al[2]	69	Radical prostatectomy	36 (97.3)	—	1 (2.7)	B	No—survival (after correction for stage, Gleason)
			9 (64.3)	—	5 (35.7)	C plus D1	
			5 (27.8)	—	13 (72.2)	D2	
Fordham et al[3]	72	Radical prostatectomy	35 (48.6)	—	37 (51.4)	T1, T2, T3, T4	Yes—survival
Winkler et al[4]	91	Radical prostatectomy	38 (42)	41 (45)	12 (13)	D1	Yes—progression and survival free of disease significant
Ritchie et al[5]	109	Radical prostatectomy	59 (54)	44 (40)	6 (6)	Not indicated	Yes—progression not significant
Nativ et al[92]	146	Radical prostatectomy	67 (46)	68 (47)	11 (7)	C	Yes—progression and cause-specific survival significant
Montgomery et al[31]	246	Radical prostatectomy	177 (68)	74 (28)	10 (4)	B	Yes—progression and cause-specific survival significant
Myers et al[7]	62	Radical prostatectomy	14 (50)	—	14 (50)*	D1	Yes—survival free of disease and progression significant
			9 (26)	—	25 (74)†	Nondiploid	
Zincke et al[33]	370	Radical prostatectomy	138 (37)	168 (46)	64 (17)	D1	Yes—survival and progression significant
Adolfsson et al[13]	146	Aspiration biopsy	69 (47)	69 (47)	8 (6)	T1, T2, T3	Yes—interval to progression significant
Stephenson et al[8]	82	Lymph node metastases	33 (40)	23 (28)	26 (32)	D1	Yes—overall survival significant at p = 0.01, free of disease survival not significant at p = 0.06, interval to progression not significant at p = 0.055
McIntire et al[29]	39	Transurethral resection chips	10 (91)	—	1 (9)	A1	Yes—progression significant at p <0.02
			13 (59) Nonaneuploid	—	9 (41)	A2	
Lundberg et al[30]	71, 57 evaluated	Transurethral resection chips, (25), transvesical resection (79)	19 (33)	23 (40)	15 (27)	Not indicated	No—survival not significant at p = 0.059
Present series	63	Tru-Cut biopsy	36 (57)	15 (24)	12 (19)	D1	Yes—interval to progression significant at p = 0.0229
	87	Lymph node metastases	54 (62)	8 (9)	25 (29)		Yes—interval to progression significant at p = 0.0343

* Early endocrine treatment.
† Delayed endocrine treatment.

patients treated with radical prostatectomy and early or delayed endocrine treatment, with a median followup of greater than 10 years.[7] The subgroup analysis showed a much more favorable outcome according to progression for the diploid early endocrine treatment group compared to other groups. Unfortunately, in our study the number of patients and the short followup are considered to be prohibitive for a meaningful subgroup analysis.

In conclusion, it can be stated that DNA ploidy can be determined from archival core biopsy material of prostate cancer and on lymph node metastases, and that the results correlate significantly with interval to progression. Besides DNA ploidy the percentage of cells in the S phase or S plus G2 phases of the cell cycle indicates a significant difference for interval to progression. Stage and grade in the presence of lymph node metastases were not significantly correlated with interval to progression in our study. Patients receiving early endocrine treatment were shown in a prospective randomized study to have a prolonged interval to progression compared to patients receiving delayed treatment. The question of whether early and delayed treatment will have an impact on cancer-related or overall survival may be answered in the future by this ongoing study. Our results encourage further studies of DNA ploidy on biopsy material to establish the role of this important prognostic factor in the pretreatment evaluation of patients with prostate cancer.

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113

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General Discussion.

GENERAL DISCUSSION.

INCREASING IMPORTANCE OF PROSTATE CANCER IN THE MALE POPULATION
The incidence of prostatic carcinoma in developed coutries is rising [1]. This increase in inciden-
ce appears to be due to the induction of screening programs, which leads to earlier detection of
prostate cancer, and increasing public and doctors awareness of the disease [2]. In 1991 14.1%
of all diagnosed malignant tumors in the Netherlands were prostatic carcinomas, and the
mortality/incidence ratio was 0.49, meaning that 50% of the patients actually died because of
their prostatic tumor [3]. Furthermore the age-adjusted mortality-rate for prostate cancer increa-
sed with 1% per year from 1950-1989 in the Dutch male population [4]. These numbers indicate
that prostate cancer can no longer be discounted as " the disease that strikes only old men who
will probably die of intercurrent causes ". Due to earlier detection the incidence of localized
disease at the time of diagnosis has increased from 27.7% in 1985, to 48.5% in 1990 [5]. This
increase has caused a rise in radical prostatectomy treatments in the past decade [1], since this is
the treatment of choise for patients with localized prostate cancer who are able to undergo
surgery and have a life-expectancy of at least 10 years. Generally patients under the age of 70,
who are in a good physical condition are considered candidates for radical prostatectomy. This
age limit may however be too low for a substantial part of the patients with newly diagnosed
prostate cancer. In the United States of America the average life-expectancy of a 75 years old
man is 12 years, and therefore men of 75 years old who are in an excellent condition (the
'biologic elite') may still be proper candidates for radical surgery [6].

STAGING ERRORS IN PROSTATE CANCER : INFLUENCE ON TREATMENT DECI-
SIONS
Like in most tumors, organ-confined disease has a better prognosis than tumor extension
outside the organ in prostate cancer patients. The resection of a wide margin of healthy tissue
around a tumor to achieve radical resection is a well established surgical oncological principle.
The anatomical structures surrounding the prostate allow however only a resection margin of a
few milimeters, which means that tumors with extraprostatic extension present a risk of
positive margins of resection and the associated risk of early local recurrence [7]. Because of
these difficulties radical prostatectomy is not considered standard treatment for patients with
locally advanced disease (T3 [8]); most of these patients are treated by radiotherapy. The discri-
mination between organ-confined and locally advanced prostatic tumors is therefore of major
importance in making a treatment decision. Unfortunately the staging techniques are not very
reliable in detecting extraprostatic extension (capsular perforation). In 43-75% of the tumors
staged as pT2 (organ-confined), the pathological evaluation of the radical prostatectomy
specimen shows capsular perforation (pT3) [9,10,11]. On the other hand, 17-30% of the T3 tumors
are overstaged, and appear to be locally confined [12,13,14]. These patients may be denied a
curative operation because of staging errors. Neither digital rectal examination [15], nor transrec-
tal ultrasonography [15,16,17], nor magnetic resonance imaging [17], nor preoperative PSA [18,19], nor
combinations of these techniques can accurately predict the presence of capsular perforation
[15,16,17]. Since the results of radiotherapy for progression and survival in prostate cancer patients
seem to be worse than the results obtained by surgery [20,21], the results of surgery for T3
prostate cancer should be carefully evaluated to determine the best treatment method for these
patients.

SURGERY IN LOCALLY ADVANCED PROSTATIC CARCINOMA

Only a few studies report on surgery for T3 carcinoma of the prostate. In all studies, except the one conducted by Jewett [22], a substantial part of the patients received adjuvant therapy, which can influence the progression-rates reported, since hormonal therapy is known to prolong the interval to progression [12,23,24,25,26,27,28,29,30]. The study by Jewett [22] was performed in 1958, when staging methods were less reliable: no lymph node dissection was done, so this patient-group may contain many patients with lymph node metastases unnoticed at the time of surgery. This may explain the poor overall survival of 12.5% after 10 years. We investigated the results of surgery as a monotherapy in T3 patients, and found an overall survival of 83% at 5 years, and a cancer specific survival of 90% at 5 years [13]. These results are comparable to those in patient-groups treated by surgery and adjuvant treatment, which indicates that hormonal adjuvant therapy does not prolong survival. Clinical progression occurred in 36% of the patients at 5 years, and biochemical progression (2 consecutive PSA-values >0.1 ng/ml postoperatively) in 63% at 5 years, in patients without adjuvant therapy [13]. Only the outcome for biochemical progression was worse in patients not treated by hormonal adjuvant therapy, which is no surprise, since the PSA-level drops to female levels after hormonal therapy, and rises only when the effect is terminated by the outgrow of androgen-independent tumor cell-populations. At that time the androgen sensitivity of the tumor is lost, and progression is inevitably. Patients treated by surgery only can have hormonal therapy when biochemical (or clinical) progression occurs, to suppress tumor growth, and to prolong the disease-free interval. During the analysis of the patients who received radical prostatectomy as a monotherapy for T3-carcinoma, the subgroup of patients with T3G3 turned out to have a very unfavourable prognosis with early progression. Patients with T3G1-2 tumors did not differ significantly in prognosis from patients with T<3 tumors, but 93% of the patients with T3G3 suffered progression, and most patients did so within the first 2 years post-surgery. We concluded that radical prostatectomy is not indicated in this group of patients, altough it can be tried in young patients. In that case we advise immediate adjuvant hormonal therapy, to delay progression.

Patients with pathological pT3 prostate cancer (preoperatively staged as organ-confined) treated by surgery only [10,11,31,32,33,34,35,36,37,38,39,40,41], have survival and progression-rates that are comparable to those of clinical T3 patients; only the local recurrence-rate is higher in pT3 patients. Patients treated by radiotherapy only for T3 prostate cancer [42,43,44,45,46,47,48,49,50,51,52] have lower survival and higher progression-rates than patients treated by surgery (see table 12,13, chapter 2). Therefore radical prostatectomy is beneficial in T3-patients with a good general condition, who are fit to undergo a surgery. Adjuvant therapy in pT3-patients seems to have a beneficial effect on clinical progression during the first 10 years of follow-up, but not for the years 10-15 post-surgery. There was however a substantial benefit for local recurrence in patients undergoing adjuvant radiotherapy (see table 13, chapter 2). No significant differences occurred in overall and cancer specific survival. A comparison for survival and progression in patients treated by surgery and for those treated conservatively (i.e. hormonal therapy at the time of progression or when the patient has complaints), cannot be made because the studies reporting conservative management contain either several stages in one group [53,54,55], or contain only patients with low and intermediate grade [53,56].

Despite the fact that T3-tumors are generally larger than organ-confined tumors, which should make the resection more difficult, the complication rate showed no statistically significant difference between T<3 and T≥3 tumors [57]. Intraoperative complications occurred in 3.7%, incontinence after one year was 11% (6% became dry after implantation of a sphincter-prothesis); potency was preserved in 43%, and 32% had stenosis of the anastomosis requiring dilata-

tion [57]. There was a trend towards a lower complication rate over the years, with a growing experiance. The mortality-rate was 1.5%. These mortality- and complication-rates seem acceptable.

THE IMPORTANCE OF PATHOLOGICAL VARIABLES FOR PROGRESSION AND SURVIVAL IN PROSTATIC CARCINOMA

Pathological variables are important indicators for the course of the disease after radical prostatectomy (chapter 5). Unfortunately the major treatment decision has already been made at that time, since the pathological variables are determined in the radical prostatectomy specimen. Efforts to determine some of these variables preoperatively were not always succesfull, due to the sampling errors of the biopsies. This is illustrated by the undergrading of 27%, when the grades of the preoperative biopsies were compared to those of the radical prostatectomy specimens. On the other hand, DNA-ploidy proved to be a significant prognostic factor when determined on pre-operative biopsie-material [61]. For daily practice the importance of the pathological variables may be that they can influence the decision to administer adjuvant therapy. In patients with T3G3 tumors for example, adjuvant therapy is adviseble because early progression can be expected.

In general pathological variables can be divided in two groups, 1: those concerning local tumor extension (capsular perforation, perineural invasion, seminal vesicle invasion, positive margins of resection, and pT-category); and 2 : those related to the biological agressiveness of the tumor (grade, vascular invasion, DNA-ploidy, pN-category).

In the univariate analysis all pathological variables evaluated were significant prognostic factors for clinical and biochemical progression, and all except perineural invasion and pN-category were significant for cancer specific survival. In the multivariate analysis however vascular invasion, capsular perforation, high grade, and positive margins of resection were the most important variables, indicating that both local extension and biological behaviour of the tumor are important for progression and survival (chapter 5). The role of local tumor extension was further evaluated for positive margins of resection (chapter 6). All positive margins of resection occurred in pathologically locally advanced carcinoma (pT3-4); but 53% of the patients with capsular perforation had negative margins of resection, indicating that radical surgery is possible in T3-disease. There was a significant correlation between positive margins and seminal vesicle invasion, capsular perforation, and apical positive margins. Saving the neurovascular bundle had no influence on the occurrence of positive margins: this means that the decision to save the bundle (this decision was taken intraoperatively) was made only when the risk of extracapsular extension (and therefore positive margins) was very low [7]. The event of positive margins of resection was a significant prognostic factor, independant of the pathological stage: patients with pT3-4 and positive margins had significantly more progression than those without positive margins.

Vascular invasion is only rarely reported in the litterature, despite the suggestion of the Cancer Committee of the College of American Pathologists to report this variable [58]. Only one study reports on vascular invasion [59], and in this study it is not a significant independent variable for progression. Salomao investigated the correlation of vascular invasion with other pathological variables, but did not test for prognostic significance for progression and survival [60]. In our study vascular invasion was the most significant variable in the multivariate analysis for clinical- and biochemical progression, and for cancer specific survival (chapter 7). There was a correlation with all other pathological variables, except with the pN-category. The lack of a correlation with the lymph node status is not understood, but is perhaps a consequence of the

selection of the patients with positive lymph nodes in this group of patients. Given the excellent prognostic value for disease recurrence and survival, vascular invasion can be considered one of the most important pathological variables, which gives an indication of the agressiveness of the tumor.

LYMPH NODE POSITIVE DISEASE AND PROGRESSION

Lymph node metastases are frequently found in locally advanced prostatic carcinoma, percentages of 33%-56% are reported [12,13,62,63]. These metastases cannot adequately be predicted by CT-scanning [63], or Magnetic Resonance Imaging [64]. Therefore a lymph node dissection with evaluation of frozen sections prior to the radical prostatectomy is essential to eliminate the possibility of lymphatic metastases. Once the pelvic lymph nodes are involved, the disease is no longer localized, but systemic, and local radical therapy can not control the disease [65]. We reported on 98 patients with lymph node positive disease, who did not undergo radical prostatectomy, but who were treated with early (immediate) or delayed (at the time of progression) hormonal therapy; most patients were part of the EORTC study 30846, which compares progression and survival for patients with early versus delayed hormonal therapy. Hormonal therapy proved to be the most important prognostic factor in this group; in patients with early treatment 50% had progression at 5 years, compared to about 100% in the untreated group. This is not surprizing, considering the short follow-up in this group of patients, and the fact that hormonal therapy is known to prolong the disease-free interval to progression [66]. The results for survival are not yet evaluable, given the short follow-up.

RECENT DEVELOPMENTS IN THE TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

The established treatments for the treatment of locally advanced prostate cancer are: radiotherapy, radical prostatectomy, and hormonal therapy at the time of progression. Recently there has been a revival of cryosurgery for ablation of the prostate in prostate cancer. Nowadays this technique is combined with ultrasonography [67], so that the formation of the ice-ball can be followed with real-time imaging. This should prevent damage to the rectal wall, because the procedure can be stopped when the ice-ball extends outside the prostate. Shinohara reported on a group of 102 patients undergoing cryosurgery of the prostate; 57% of these patients had locally advanced disease [68]. At 3-6 months postoperatively 23% had residual cancer in 1 or more biopsies, and in 71% prostatic epithelial elements were present. At 6 months postoperatively about 50% of the patients with T3a-b, and 70% of those with T3c had detectable PSA, despite the fact that all patients with locally advanced disease received complete androgen blockade for at least 3 months prior to cryosurgery. Lymph node dissections were only performed in patients who had a PSA>15 ng/ml, or who had a Gleason score ≥7; despite the high percentage of patients with locally advanced tumors, lymph node metastases were found in only 3 patients. Complications occurred in 51% of the patients; 23% required TUR of the necrotic prostatic tissue because of obstruction, 15% had some degree of incontinence, and 84% was impotent (of those potent preoperatively). These complication-rates are worse than those reported for radical prostatectomy [57]. Because follow-up is short, results for progression and survival can not be evaluated, however the high percentages of patients with residual disease, and detectable PSA at 6 months postoperatively indicate that the results may be discouraging. Basically cryosurgery of the prostate meets the same problems in treating patients with tumor extension outside the capsule as do radical prostatectomy and radiotherapy: the anatomical situation does not allow extension of the ice-ball (resection / radiation) in a

wide margin of healthy tissue around the prostate. Therefore this therapy has the same limitations as the established techniques. The administration of preoperative hormonal therapy does not result in significant downstaging of locally advanced disease to organ-confined disease, as discussed in chapter 2 (see table 6). It is not to be expected that cryosurgery will be the solution for patients with locally advanced prostate cancer, and neither radiotherapy, nor radical prostatectomy is the definite answer to the problem of locally advanced disease. A better therapy is urgently needed for this stage T3 prostate cancer, which is present in 12% to 40% of all newly diagnosed prostate cancer patients [69,70,71].

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CHAPTER 10
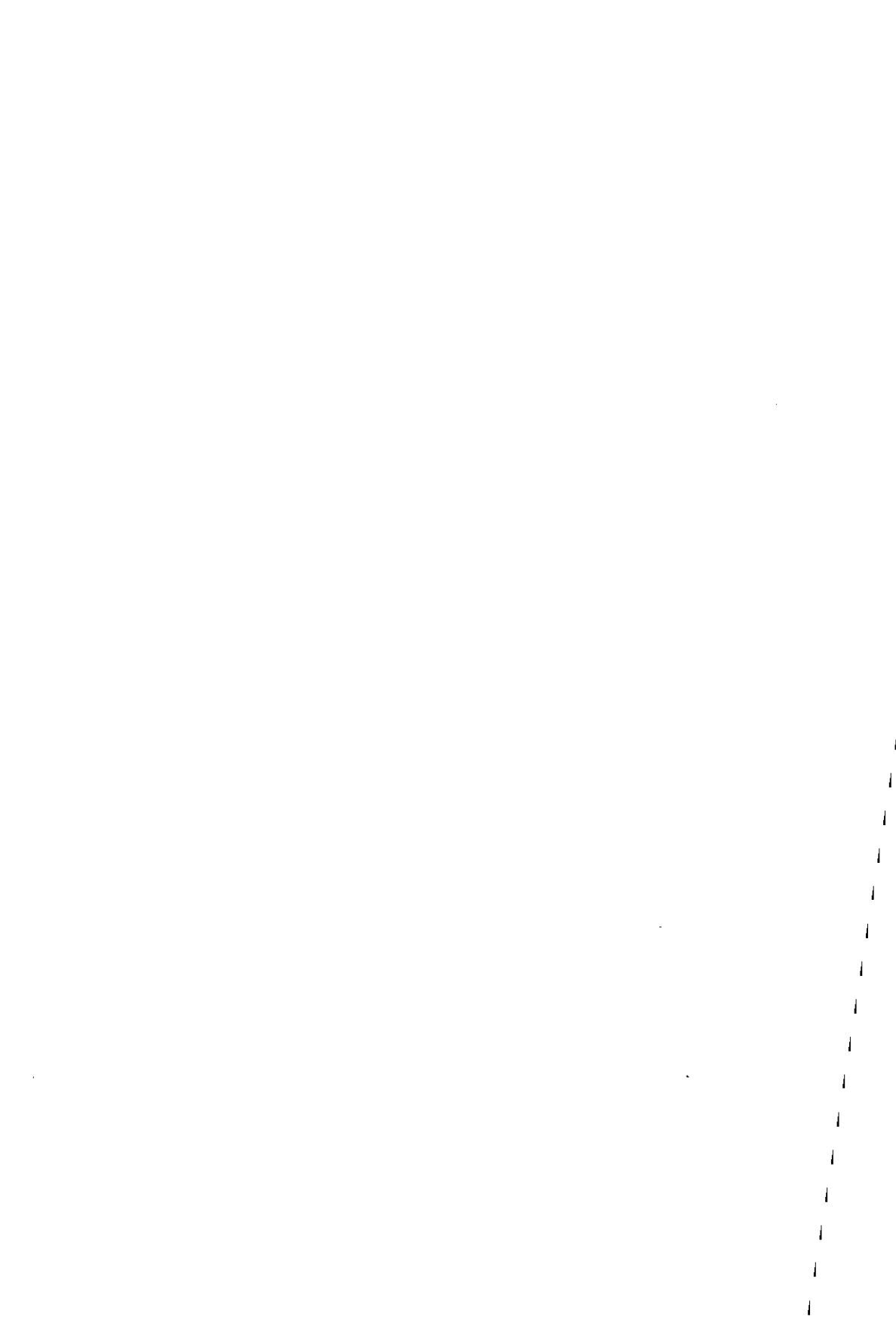
Summary and Conclusions.

SUMMARY AND CONCLUSIONS

The incidence and mortality of prostatic carcinoma is rising in developed countries. Nowadays prostate cancer makes up 14% of all diagnosed malignant tumors in men in the Netherlands, with a mortality/incidence ratio of 0.5, which means that 50% of the patients will die because of prostatic cancer. This means that prostatic carcinoma can no longer be considered a relatively benign tumor that strikes most men when they reach a high age; but it should be considered the second most common cause of death in men with malignant tumors (after pulmonary carcinoma). In the last decade the introduction of Prostate Specific Antigen (PSA) has stimulated the introduction of screening programs for prostate cancer, which has caused an increase in detection of patients with locally confined and locally advanced disease, who are candidates for radical, curative treatment. The optimal treatment for patients with locally advanced prostate cancer is however still a matter of debate, since the extension of tumor outside the prostate, and the anatomical situation of the surrounding structures may prevent radical excision. Therefore many urologists consider surgery unsuitable for locally extensive disease. This thesis evaluates the limits and possibilities of radical prostatectomy for locally advanced prostate cancer, by describing the progression and survival after radical surgery, the influence of pathological variables, and the complications of the procedure.
The history and contemporary developments in radical prostatectomy are described in chapter 1. In the last decade better understanding of the anatomy of the surrounding structures of the prostate has lead to modifications of the surgical technique, which resulted in a lower complication rate. This fact has promoted the use of radical prostatectomy, and has resulted in a steep increase of the number of radical prostatectomies performed.

Chapter 2 reviews the literature on the treatment of locally advanced carcinoma. The natural history and results of conservative (hormonal) therapy are correlated, since most patients receiving expectant treatment experience progression, requiring (hormonal) treatment. The results of radical prostatectomy for clinically advanced (stage T3/C) prostate cancer in terms of tumor control and survival are evaluated. This evaluation is difficult, since almost all studies deliver adjuvant (hormonal) therapy to a substantial part of their patient-population, which influences (short-term) progression-rates. There is however no influence of adjuvant hormonal therapy on survival. Overall survival ranged from 64%-95% at 5 years, from 12%-72% at 10-, and from 20%-51% at 15 years. Cancer specific survival ranged from 85%-92% at 5 years, from 79%-82% at 10-, and from 68%-70% at 15 years. Clinical progression (i.e. local recurrence and/or distant metastases) varied from 12%-45% at 5-, 39%-49% at 10-, and 50%-71% at 15 years. Biochemical progression is evaluated seperately, and means elevated PSA after surgery. The biochemical progression-rates vary from 48%-63% at 5-, and from 59%-62% at 10 years. Long-term results are not available, because PSA is only used on a routine basis since 1986 in most clinics. The results of radiation treatment of locally advanced prostate cancer are compared to those of radical prostatectomy. It appears that radiation therapy leads to higher progression and lower survival rates, indicating that this treatment is inferior to surgery. It must however be remembered that there are differences between the populations undergoing surgery and radiation therapy, which may account for some of these differences in tumor control and survival.
Many patients staged as locally confined disease turn out to have locally advanced disease (up to 70%). The results of tumor control and survival in pathological advanced disease (pT3)are also evaluated in this chapter. Because many patients with this condition receive radiation and/or hormonal adjuvant therapy, patient-groups treated with and without adjuvant therapy are evaluated seperately. Adjuvant therapy offers some advantage for progression, and especi-

ally for local recurrence. Also survival-rates are better after the administration of adjuvant therapy. However no prospectively randomized studies have been published yet, so these results have to be interpreted with caution. The results of preoperative hormonal therapy with the intention of downstaging the disease, are discouraging; the percentages of locally confined carcinoma after neoadjuvant therapy are about equal to the overstaging percentages in populations treated without preoperative hormonal therapy.

Chapter 3 describes the results of radical prostatectomy as a monotherapy in 100 patients with clinical T3-prostate cancer. In 39 patients lymph node metastases were found, and 2 patients had evidence of pT4-tumors at surgical exploration. These patients were not treated by radical prostatectomy, because of these findings. In 3 young patients with a single microscopic lymph node metastasis a radical prostatectomy was performed. Of the 59 patients who underwent radical prostatectomy 9 had positive lymph nodes, which were not detected on frozen sections. The pathological stage in patients without lymph node metastases was pT2 in 9 patients, pT3 in 39-, and pT4 in 2 patients. Only one of the 9 patients with lymph node metastases is free of progression. Progression occurred in none of the pT2 patients, in 27 of 39 patients with pT3, and in both patients with pT4. A total of 22 patients were free of clinical and biochemical progression at an average follow-up of 44 months. The data on T3-patients were compared to a group of 129 patients with T0 to T2 disease. There was a significant difference in interval to clinical progression between those groups (p=0.001), but this difference disappeared once the T3G3 patients were excluded. Prognostic factors analyzed were the pretreatment and posttreatment histological grade, pretreatment PSA and prostatic acid phosphatase levels, positive margins of resection, seminal vesicle invasion, and lymph node status. It was concluded that radical prostatectomy is an effective treatment in patients with T3G1-2 prostate cancer; the results for progression are comparable to those for patients with T0-T2 disease. In patients with T3G3 disease the results are however discouraging: 93% of the patients with T3pT3G3 suffered progression during the observation period. Effective adjuvant treatment is urgently needed in this patient-group.

In chapter 4 the mortality and morbidity associated with radical prostatectomy is investigated. In a group of 188 patients undergoing radical prostatectomy 3 patients died in the postoperative period (1.5%): 2 patients died of a pulmonary embolus, and one because of sepsis. There were 7 intraoperative complications: 4 cases of rectal injury, 2 external iliac vein injuries, and one ureter lesion. All injuries were recognized immediately and repaired without further consequences. The most common short-term complications were wound infection (17%), prolonged lymph drainage (17%), lymphocele (7%) and bleeding (6%). The long-term complications were incontinence (11% at one year postoperatively; 50% of these patients became continent after implantation of an artificial urinary sphincter), stenosis of the urethro-vesical anastomosis (32%, most patients were cured by one or two dilatations in the outpatient clinic), and impotence (57% after a bilateral nerve-saving procedure). There were no significant differences in complication-rates in patients with T3-disease compared to those with T<3-disease. The complication-rate decreased in more recent years with growing experience. Radical prostatectomy in locally advanced disease can therefore be performed with acceptable mortality and morbidity.

Chapter 5 is an account of the different pathological variables determined in the radical prostatectomy specimen, and their influence on tumor progression and survival. In 273 patients the

radical prostatectomy specimen was evaluated for: pathological stage, histological grade, capsular perforation, positive lateral and apical margins of resection, seminal vesicle invasion, perineural invasion, and vascular invasion. Furthermore the lymph node status was evaluated. The frequency of the pathological variables was: pT-category: pT0: 2%, pT1: 0%, pT2: 29%, pT3: 63%, pT4: 5%; histological grade: G0: 2%, G1: 14%, G2: 62%, G3: 22%; capsular perforation: present: 64%, absent: 36%; positive lateral margins: present: 34%, absent: 66%; positive apical margins: present: 41%, absent: 59%; seminal vesicle invasion: present: 29%, absent: 71%; perineural invasion: present: 76%, absent: 24%; vascular invasion: present: 12%, absent: 88%.Positive lymph nodes were present in 10% of the patients.

For the patient-group as a whole the progression and survival rates at 5-, 10-, and 15-years were; for clinical progression: 27%,53%, and 63%; for local recurrence: 11%, 24%, and 24%; for distant metastases: 21%, 41%, and 53%; for biochemical progression: 52% at 5 years; for overall survival: 82%, 63%, and 55%; and for cancer specific survival: 92%, 82%, and 82%. In the univariate analysis all evaluated pathological variables were significant prognostic factors for clinical and biochemical progression, and all except perineural invasion and the pN-category were significant for cancer specific survival. In a multivariate analysis vascular invasion was the most significant variable for clinical and biochemical progression and cancer specific survival; other significant prognostic factors for clinical progression were: capsular perforation, high grade, and positive lateral margins of resection. For biochemical progression capsular perforation was the only other significant prognostic factor, and for cancer specific survival only positive lateral margins were significant beside vascular invasion. The other evaluated variables added no significant prognostic information. It was concluded that the evaluation of pathological variables is usefull to estimate the risk for progression and survival, and especially vascular invasion, capsular perforation, high grade, and positive lateral margins of resection.

In chapter 6 the influence of positive margins of resection on local and distant progression, and the correlation with the other pathological variables is evaluated. Positive lateral margins of resection correlates significantly with advanced stage, high grade, the presence of seminal vesicle invasion, capsular perforation, and positive apical margins. There was no correlation between the saving of the neurovascular bundles and the occurrence of positive margins. Positive lateral margins of resection was an independant prognostic factor for local and distant progression; there was no significant difference in progression in patients with pT0-2 and pT3-4 and negative margins, but there was when these groups were compared to patients with pT3-4 with positive margins. Contrary to positive lateral margins, positive apical margins of resection did not influence progression. This may be due to the definition used: positive apical margins were defined as the presence of tumor in the most distal slice taken from the radical prostatectomy specimen. This finding resulted in a change in the protocol for evaluation of the apical margin: from that time on the apical slice of the specimen is cut in several slices, in the sagital plane, to get a more clear impression of the tumor extent in the apical margin.

Chapter 7 reports on the influence of vascular invasion on progression and survival, and describes the correlation between vascular invasion and the other pathological variables. Vascular invasion is defined as the presence of tumor cells in endothelial-lined spaces; no differentiation is made between vascular and lymphatic vessels. Vascular invasion occurred in 12% of the patients.The presence of vascular invasion correlated significantly with the presence of capsular perforation, seminal vesicle invasion, positive lateral and apical margins of

resection, perineural invasion, high grade, and advanced stage, but not with the presence of lymph node metastases. There was no significant difference in preoperative PSA-value in patients with and without vascular invasion. Vascular invasion was a significant prognostic factor for clinical and biochemical progression, local recurrence, distant metastases, overall survival, and cancer specific survival. In the multivariate analysis vascular invasion was the most significant prognostic factor for clinical and biochemical progression, and cancer specific survival. Vascular invasion can be determined during the routine work-up of the radical prostatectomy specimen, without investing extra time and costs; therefore it should be reported on a routine basis during examination of the radical prostatectomy specimen.

Chapter 8 deals with the patient-group who did not undergo radical prostatectomy because lymph node metastases were found during the lymph node dissection. Those patients were treated by early or delayed hormonal therapy (most patients were enrolled in EORTC protocol 30846, which evaluates the influence of early versus delayed hormonal therapy for progression and survival). Patients treated with early hormonal therapy had a significantly longer interval to progression, but follow-up is still too short and patient numbers too small for a relevant subgroup analysis. Furthermore the DNA ploidy was determined in the prostatic biopsies and the lymph node metastases (DNA ploidy determination was performed in the Karolinska Institute, Stockholm, Sweden, department of Radiobiology, chairman: prof. B. Tribukait), to evaluate if this produces relevant prognostic information. Also the percentage of cells in the S- and G2 phase of the cell cycle was determined. In 98 patients the ploidy was evaluable in 87 cases; tumors were diploid in 52%, tetraploid in 15%, and aneuploid in 33%. In the primary tumor 57% diploid, 24% tetraploid, and 19% aneuploid tumors occurred; in the lymph node metastases these numbers were: 62%, 9%, and 29%. No statistically significant relation was found between the ploidy-status and T-category, grade, and lymph node status. Therapy, ploidy, percentage of cells in the S-phase, and S- and G2-phase were significant prognostic factors for progression. In the multivariate analysis therapy, ploidy of the primary tumor (but not ploidy of the lymph node metastases), and percentage of cells in the S-and G2-phase of the lymph node metastases (but not of the primary tumor), were significant prognostic factors for progression. It was concluded that ploidy of core-biopsies and lymph node metastases are significant prognostic factors for progression, and that early hormonal therapy prolongs the interval to progression. The relevance of ploidy performed on core-biopsies is that prognostic information, which may influence treatment decisions is available before the actual start of the treatment.

CONCLUSIONS

Radical prostatectomy is possible in patients with clinically locally advanced prostatic carcinoma (stage T3), with acceptable mortality and morbidity. The results for progression are comparable to those in patients with locally confined (T2) tumors, when patients with T3G3 are excluded. This group of T3G3 patients represents a subgroup with very high progression-rates after radical prostatectomy; therefore radical prostatectomy is not recommanded in these patients.
Pathological variables determined in the radical prostatectomy specimen (capsular perforation, positive margins of resection, seminal vesicle invasion, perineural invasion, vascular invasion, grade, pT-category) are relevant prognostic factors for progression and survival. Vascular invasion is the most significant prognostic factor, and should be determined on a routine basis

during examination of the radical prostatectomy specimen.

DNA-ploidy can be determined in paraffin-embedded core-biopsies, and is a significant prognostic factor for progression. In patients with lymph node metastases immediate hormonal therapy prolongs the interval to progression, the effects on survival are not yet known, because follow-up is too short.

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Samenvatting en Conclusies.

SAMENVATTING EN CONCLUSIES

De incidentie en mortaliteit van prostaatkanker stijgt in ontwikkelde landen. Van alle maligne tumoren in mannen (in Nederland) is 14% prostaatkanker; de incidentie/mortaliteits verhouding is 0.5: dit betekent dat 50% van de mannen die prostaatkanker hebben, hieraan zal sterven. Dit betekent dat prostaatkanker niet langer beschouwd mag worden als een relatief goedaardig carcinoom, dat voornamelijk mannen op hoge leeftijd treft, bij wie dit weinig consequenties heeft, maar dat prostaatkanker na bronchuscarcinoom de meest voorkomende doodsoorzaak is in mannen met maligne tumoren. In de afgelopen 10 jaar heeft de introductie van Prostaat Specifiek Antigeen (PSA) geleid tot het starten van screening programma's voor prostaatkanker. Hierdoor worden meer lokaal beperkte en lokaal uitgebreide carcinomen gevonden, welke in aanmerking komen voor curatieve behandeling. De optimale behandeling van patienten met lokaal uitgebreide carcinomen is nog onderwerp van discussie, omdat de uitbreiding van de tumor buiten de prostaat, en de anatomisch situatie van de omliggende structuren een radicale excisie onmogelijk kan maken. Daarom achten veel urologen chirurgische behandeling ongeschikt voor patienten met lokaal uitgebreide prostaatkanker. Dit proefschrift evalueert de grenzen en mogelijkheden van radicale prostatectomie als behandeling voor lokaal uitgebreid prostaatcarcinoom, d.m.v. beschrijving van de progressie en overleving na radicale chirurgische resectie, de invloed van pathologische variabelen, en de complicaties van de operatie.

De geschiedenis en de recente ontwikkelingen van de radicale prostatectomie worden beschreven in hoofdstuk 1. In de afgelopen 10 jaar heeft een beter begrip van de anatomie van de omliggende structuren geleid tot veranderingen in de chirurgische techniek, waardoor nu minder complicaties voorkomen. Dit feit heeft de toepassing van radicale prostatectomie gestimuleerd, hetgeen geresulteerd is in een sterke toename van het aantal radicale prostatectomieën.

Hoofdstuk 2 geeft een overzicht van de literatuur over de behandeling van lokaal uitgebreid prostaatcarcinoom. Het natuurlijk beloop en de resultaten van conservatieve (hormonale) behandeling hangen samen, omdat de meeste patienten die zonder behandeling gevolgd worden, progressie krijgen, welke behandeld wordt met hormonale therapie . De resultaten van radicale prostatectomie als behandeling voor lokaal uitgebreid prostaatcarcinoom (stadium T3/C) in termen van tumor controle en overleving worden geëvalueerd. Deze evaluatie wordt gecompliceerd door het feit dat in de meeste studies een aanzienlijk deel van de onderzochte populatie adjuvante (hormonale) behandeling krijgt, hetgeen de (korte termijn) progressie beïnvloed. Er is echter geen invloed van adjuvante hormonale therapie op overleving. De totale overleving varieert van 64%-95% na 5 jaar, van 12%-72% na 10-, en van 20%-51% na 15 jaar. De kanker specifieke overleving varieert van 85%-92% na 5 jaar, van 79%-82% na 10-, en van 68%-70% na 15 jaar. Klinische progressie (= lokaal recidief en/of metastasen op afstand) varieert van 12%-45% na 5 jaar, van 39%-49% na 10-, en van 50%-71% na 15 jaar. Biochemische progressie wordt afzonderlijk geëvalueerd, en bestaat uit verhoogd PSA na operatie. Biochemisch progressie tradt op in 48%-63% na 5 jaar, en in 59%-62% na 10 jaar. Lange termijn resultaten zijn niet beschikbaar, omdat PSA pas sinds 1986 routinematig wordt bepaald. De resultaten van radiotherapie als behandeling voor lokaal uitgebreid prostaatcarcinoom worden vergeleken met die van radicale prostatectomie. Radiotherapie lijkt te leiden tot meer progressie en slechtere overleving van patienten met lokaal uitgebreid prostaatcarcinoom, zodat operatie een betere behandeling lijkt voor deze groep patienten. Er moet echter wel

bedacht worden dat er verschillen (in maligniteitsgraad, leeftijd, conditie) zijn tussen de populaties van patienten die radiotherapie en radicale prostatectomie ondergaan, waardoor een gedeelte van de slechtere resultaten van radiotherapie verklaard kan worden.

Veel patienten die gestageerd zijn als hebbende lokaal beperkt carcinoom (stadium T2), blijken een lokaal uitgebreide tumor te hebben (tot 70%). De progressie en overleving van patienten met pathologisch lokaal uitgebreid prostaatcarcinoom (pT3) worden in dit hoofdstuk geëvalueerd. Omdat veel patienten met dit stadium adjuvante radiotherapie en/of hormonale therapie krijgen, worden patienten-groepen behandeld met en zonder adjuvante therapie apart geëvalueerd. In deze retrospectieve studie biedt adjuvante therapie enig voordeel voor wat betreft progressie, en vooral ten aanzien van lokaal recidief. Ook overlevings percentages lijken beter na het geven van adjuvante behandeling. Er zijn echter geen prospectieve gerandomizeerde studies gerapporteerd, dus deze resultaten moeten met enige reserve geïnterpreteerd worden. De resultaten van preoperatieve (neoadjuvante) hormonale therapie, met het doel de tumor lokaal beperkt (en dus beperkt tot de prostaat) te maken zijn ontmoedigend; het percentage lokaal beperkte tumoren na neoadjuvante therapie is ongeveer gelijk aan het percentage overstagering in de populatie patienten die geen preoperatieve hormonale therapie ontvangen.

Hoofdstuk 3 beschrijft de resultaten van radicale prostatectomie als enige behandeling (zonder adjuvante therapie) in 100 patienten met klinisch T3 prostaatkanker. In 39 patienten werden lymfeklier metastasen gevonden, en 2 patienten bleken intraoperatief T4 tumoren te hebben. I.v.m. deze bevindingen ondergingen deze patienten geen radicale prostatectomie. In 3 jonge patienten met een enkele microscopisch kleine lymfeklier metastase werd wel een radicale prostatectomie verricht. Van de 59 patienten die een radicale prostatectomie ondergingen, hadden 9 patienten positieve lymfeklieren, welke gemist waren tijdens het vriescoupe onderzoek. Het pathologische stadium van de patienten zonder lymfeklier metastasen was pT2 in 9 patienten, pT3 in 39-, en pT4 in 2 patienten. Slechts één van de 9 patienten met lymfeklier metastasen heeft geen progressie gekregen. Progressie trad op in geen van de patienten met pT2, in 27 van de 39 patienten met pT3, en in beide patienten met pT4. In totaal hadden 22 patienten geen klinische of biochemische progressie na een gemiddelde follow-up van 44 maanden. De gegevens van de T3-patienten werden vergeleken met die van een groep van 129 patienten met stadium T0-T2, welke eveneens behandeld werden met een radicale prostatectomie. Er was een significant verschil in interval tot klinische progressie tussen deze groepen (p=0.001), maar dit verschil verdween als de patienten met T3G3 uitgesloten werden. De geanalyseerde prognostische factoren waren: pré- en post-operatieve histologische gradering, préoperatieve serumspiegels van PSA en Prostaat Zure Fosfatase, positieve snijvlakken, zaadblaas invasie, en lymfeklier status. De conclusie is dat radicale prostatectomie een effectieve behandeling is voor patienten met T3G1-2 prostaatkanker; de progressie is vergelijkbaar met die van patienten met T0-T2 tumoren. Bij patienten met T3G3 tumoren zijn de resultaten echter slecht: 93% van de patienten met T3pT3G3 prostaatkanker krijgt progressie tijdens de geobserveerde periode. Effectieve adjuvante behandeling is dringend nodig voor deze patienten-groep.

In hoofdstuk 4 worden de met radicale prostatectomie geassocieerde mortaliteit en morbiditeit onderzocht. In een groep van 188 patienten die een radicale prostatectomie ondergingen, overleden er 3 in de postoperatieve periode (1.5%): 2 patienten overleden t.g.v. een longembolie, en een patient t.g.v. sepsis. Er traden 7 intraoperatieve complicaties op: rectumperforaties in 4 patienten, beschadiging van de vena iliaca externa in 2 patienten, en één ureterlaesie. Alle

laesies werden direct ontdekt en hersteld, zonder verdere consequenties. De meest voorkomende complicaties waren: wondinfectie (17%), langdurige lymfe drainage via de wonddrain (17%), lymfocèle (7%), en bloeding (6%). De lange termijn complicaties waren: incontinentie (11% na een jaar postoperatief, 50% van deze patienten werd continent na de implantatie van een sfincter prothese), stenose van de urethro-vesicale anastomose (32%, de meeste patienten waren genezen na een of twee poliklinische dilataties), en impotentie (57% na een bilateraal zenuwsparende operatie). Er waren geen significante verschillen in aantal complicaties tussen patienten met T3 tumoren en patienten met T<3 tumoren. Het percentage complicaties nam af in de latere jaren van de studie, met toenemende ervaring. Radicale prostatectomie in patienten met lokaal uitgebreid prostaatcarcinoom kan verricht worden met een acceptabele mortaliteit en morbiditeit.

Hoofdstuk 5 is een evaluatie van de verschillende pathologische variabelen die in het radicale prostatectomie preparaat onderzocht worden, en hun invloed op progressie en overleving. In 273 patienten werd het radicale prostatectomie preparaat geëvalueerd voor: pathologisch stadium, histologische gradering, kapsel perforatie, positieve laterale en apicale snijvlakken, zaadblaas invasie, perineurale invasie, en vasculaire invasie. Verder werd de lymfklier status geëvalueerd. De frequentie van de pathologische variabelen was: pT-categorie: pT0: 2%, pT1: 0%, pT2: 29%, pT3: 63%, pT4: 5%; histologische gradering: G0: 2%. G1: 14%, G2: 62%, G3: 22%; kapsel perforatie: aanwezig: 64%, afwezig: 36%; positieve laterale snijvlakken: aanwezig: 34%, afwezig: 66%; positieve apicale snijvlakken: aanwezig: 41%, afwezig: 59%; zaadblaas invasie: aanwezig: 29%, afwezig: 71%; perineurale invasie: aanwezig: 76%, afwezig: 24%; vasculaire invasie: aanwezig: 12%, afwezig: 88%. Lymfklier metastasen waren aanwezig in 10% van de patienten.
Voor de gehele groep waren de progressie en overlevings percentages na 5-, 10-, en 15 jaar: klinische progressie: 27%, 53%, en 63%; lokaal recidief: 11%, 24%, en 24%; metastasen op afstand: 21%, 41%, en 53%; biochemische progressie: 52% na 5 jaar; totale overleving: 82%, 63%, en 55%; en kanker specifieke overleving: 92%, 82%, en 82%. In de univariate analyse waren alle onderzochte pathologische variabelen significante prognostische faktoren voor klinische en biochemische progressie, en alle variabelen behalve perineurale invasie en de pN-categorie waren significant voor kanker specifieke overleving. In de multivariate analyse was vasculaire invasie de meest significante prognostisch faktor voor klinische en biochemische progressie en kanker specifieke overleving; de andere significante prognostische faktoren voor klinische progressie waren: kapsel perforatie, slecht gedifferentieerd carcinoom, en positieve laterale snijvlakken. Voor biochemische progressie was kapsel perforatie de enige andere significante prognostische faktor, en voor kanker specifieke overleving waren alleen positieve laterale snijvlakken significant naast vasculaire invasie. De andere geëvalueerde variabelen voegden geen significante prognostische informatie toe. Geconcludeerd kan worden dat de evaluatie van pathologische variabelen nuttig is om het risico voor progressie en overleving in te schatten, en dat vooral vasculaire invasie, kapsel perforatie, slecht gedifferentieerd carcinoom, en positieve laterale snijvlakken belangrijke prognostische informatie geven.

In hoofdstuk 6 wordt de invloed van positieve snijvlakken op lokale progressie en progressie op afstand geëvalueerd, en wordt de correlatie van deze variabele met de andere pathologische variabelen onderzocht. De aanwezigheid van positieve laterale snijvlakken correleert met de aanwezigheid van een hoog tumor-stadium, slecht gedifferentieerd carcinoom, zaadblaas invasie, kapsel perforatie, en een positief apicaal snijvlak. Er was geen verband tussen het

sparen van de neurovasculaire bundels en het optreden van positieve snijvlakken. Positieve laterale snijvlakken waren een onafhankelijke prognostische faktor voor lokale progressie en progressie op afstand (metastasen); er was geen significant verschil in progressie tussen patienten met pT0-2 en pT3-4 tumoren zonder positieve snijvlakken, maar wel tussen deze groepen en patienten met pT3-4 en positieve snijvlakken. In tegenstelling tot laterale positieve snijvlakken, beïnvloeden apicale positieve snijvlakken de tijd tot progressie niet. Dit is mogelijk het gevolg van de gebruikte definitie: positieve apicale snijvlakken werden gedefinieerd als tumor in het meest distale sneevlak van het radicale prostatectomie preparaat. Deze bevinding heeft geresulteerd in een aanpassing van het protocol voor de beoordeling van het apicale snijvlak; tegenwoordig wordt het meest distale gedeelte van het preparaat in diverse plakjes opgesneden, in het sagitale vlak. Dit maakt een betere beoordeling van het apicale snijvlak mogelijk.

Hoofdstuk 7 rapporteert over de invloed van vasculaire invasie op progressie en overleving, en beschrijft de correlatie van deze variabele met de andere pathologische variabelen. Vasculaire invasie wordt gedefinieerd als de aanwezigheid van tumor cellen binnen ruimtes welke worden omgeven door endotheel; er wordt geen onderscheid gemaakt tussen bloed- en lymfe- vaten. Vasculaire invasie was aanwezig in 12% van de patienten. De aanwezigheid van vasculaire invasie correleert met de aanwezigheid van kapsel perforatie, zaadblaas invasie, positieve laterale en apicale snijvlakken, perineurale invasie, slecht gedifferentieerd carcinoom, en een hoog tumor-stadium, maar niet met de aanwezigheid van lymfeklier metastasen. Er was geen significant verschil in de préoperatieve PSA-waarde tussen patienten met en zonder vasculaire invasie. Vasculaire invasie is een significante prognostische variabele voor het optreden van klinische en biochemische progressie, lokaal recidief, metastasen op afstand, totale overleving, en kanker specifieke overleving. In de multivariate analyse was vasculaire invasie de meest significante prognostische faktor voor klinische en biochemische progressie, en kanker speci- fieke overleving. Vasculaire invasie kan bepaald worden tijdens de routinematige evaluatie van het radicale prostatectomie preparaat, zonder extra tijd en kosten te investeren; daarom zou het routinematig gerapporteerd moeten worden bij het onderzoek van radicale prostatectomie preparaten.

Hoofdstuk 8 beschrijft de patienten-groep die geen radicale prostatectomie onderging, omdat tijdens de lymfklierdissectie positieve lymfklieren werden gevonden. Deze patienten werden behandeld met onmiddelijke of uitgestelde hormonale therapie (de meeste patienten maakten deel uit van de EORTC-studie 30846, welke de invloed van onmiddelijke versus uitgestelde hormonale therapie vergelijkt voor progressie en overleving in patienten met lymfklier metasta- sen bij prostaat carcinoom). De patienten welke behandeld werden met onmiddellijke hormona- le therapie hadden een significant langer interval tot progressie, maar de follow-up is te kort, en de patienten-aantallen te klein, om een relevante subgroep analyse te doen. Verder werd de DNA-ploidy bepaald in de prostaatbiopten en de lymfklier metastasen (de DNA-ploidy bepa- ling werd uitgevoerd in het Karolinska Instituut, Stockholm, Zweden, op de afdeling Radiobi- ology, hoofd: prof. B. Tribukait) om te onderzoeken of dit relevante prognostische informatie zou opleveren. Ook werd het percentage cellen in de S-en G2-fase van de cel cyclus bepaald. In 87 van de 98 patienten was de ploidy te evalueren; 52% van de tumoren waren diploid, 15% tetraploid, en 33% aneuploid. In de biopten van de primaire tumor was 57% van de tumoren diploid, 24% tetraploid, en 19% aneuploid; in de lymfklier metastasen waren deze percentages respectievelijk 62%, 9%, en 29%. Er was geen statistisch significante relatie tussen de ploidy-

status en het tumor-stadium (T-categorie), de maligniteitsgraad, en de lymfklier status. De therapie, de ploidy, het percentage cellen in de S-fase, en de S-en G2-fase waren significante prognostische faktoren voor progressie. In de multivariate analyse waren therapie, ploidy van de primaire tumor (maar niet van de lymfklier metastasen), en percentage cellen in de S-en G2-fase van de lymfklier metastasen (maar niet van de primaire tumor), significante prognostische faktoren voor progressie. De conclusie luidt dat ploidy bepaald op prostaatbiopten en in lymfklier metastasen een significante prognostische faktor is voor progressie van prostaatkanker, en dat onmiddelijke hormonale therapie het interval tot progressie verlengt. De betekenis van ploidy bepaald in prostaatbiopten is dat hiermee prognostische informatie verkregen kan worden, voordat belangrijke beslissingen worden genomen t.a.v. de behandeling van patienten.

CONCLUSIES

Radicale prostatectomie is mogelijk bij patienten met klinisch lokaal uitgebreid prostaat carcinoom (stadium T3), met acceptabele mortaliteit en morbiditeit t.g.v. de operatie. De resultaten t.a.v. progressie zijn vergelijkbaar met die van patienten met lokaal beperkte tumoren (T2), mits patienten met T3G3 tumoren worden uitgesloten van operatie. Patienten met T3G3 prostaatcarcinoom vormen een subgroep met een zeer hoog risiko voor progressie na radicale prostatectomie; daarom wordt radicale prostatectomie afgeraden voor deze groep patienten. De pathologische variabelen welke bepaald worden in het radicale prostatectomie preparaat (kapsel perforatie, positieve snijvlakken, zaadblaas invasie, perineurale invasie, vasculaire invasie, histologische graad, en pT-categorie) zijn relevante prognostische faktoren voor progressie en overleving. Vasculaire invasie is de meest significante prognostische faktor, en zou routinematig bepaald moeten worden tijdens het pathologisch onderzoek van het radicale prostatectomie preparaat.
DNA-ploidy kan bepaald worden op paraffine behandeld materiaal van prostaatbiopten, en is een significante prognostische faktor voor progressie. In patienten met lymfklier metastasen verlengt onmiddellijke hormonale therapie het interval tot progressie, de effecten op overleving zijn nog niet bekend, daar de follow-up op dit moment nog te kort is.

Data checklist for enrollment of patients in the prospective study.

PID# ⌐⊥⊥⊥⊥⊥⊥⊥⌐ NAAM : _____ GEB : __ ___ ____

Hoofdstuk klinische stagering.

02 Diagnosedatum :   maand ⎯⎯⊥⊥⌐ ⌐⊥⊥⎯ jaar

03 Diagnose n.a.v. ⎯⎯⎯⎯⎯⎯⊥⊥⌐
  - 1 Prostaat klachten
  - 2 Rectaal onderz. toeval
  - 3 Incidenteel (TUR)
  - 4 Prost.screening studie
  - 5 Verhoogd PSA

04 Voorafg.beh.prost.probl. ⎯⎯⊥⊥⌐
  - 0 Geen
  - 1 Hormonaal
  - 2 TUR-prostaat
  - 3 Radiotherapie
  - 4 Anders

05 Performance (WHO klasse) ⎯⎯⊥⊥⌐
  - 0 Normaal
  - 1 - 4 klasse 1 tm 4

06 Nacht. erecties ⎯⎯⎯⎯⎯⊥⊥⎯ 0 Nee, 1 Ja

07 Erecties met sex.stimulatie ⎯⊥⊥⎯ 0 Nee, 1 Ja

08 Sexueel actief ⎯⎯⎯⎯⎯⎯⊥⊥⎯ 0 Nee, 1 Ja

09 Bereikt orgasme ⎯⎯⎯⎯⊥⊥⎯ 0 Nee, 1 Ja

10 Herkomst ⎯⎯⎯⎯⎯⎯⎯⊥⊥⌐
  - 1 Eigen poli
  - 2 Rotterdam
  - 3 Regio
  - 4 Elders
  - 5 Buitenland

Hoofdstuk rectaal toucher.

11 Tumor palpabel links ⎯⎯⎯⊥⊥⌐
  - 0 Nee
  - 1 <= 1/2 kwab
  - 2 > 1/2 kwab

12 Tumor palpabel rechts ⎯⎯⊥⊥⌐
  - 0 Nee
  - 1 <= 1/2 kwab
  - 2 > 1/2 kwab

13 Kapsel doorbraak ⎯⎯⎯⎯⊥⊥⌐
  - 0 Nee
  - 1 Rechts
  - 2 Links
  - 3 Beiderzijds

14 Vesicula invasie ⎯⎯⎯⎯⊥⊥⌐
  - 0 Nee
  - 1 Rechts
  - 2 Links
  - 3 Beiderzijds

15 Fixatie, ingroei ⎯⎯⎯⎯⊥⊥⌐
  - 0 Nee
 - 1 Blaashals, rectum, ext.sphincter
  - 2 Levator, bekken

147

16 Indien TUR-p ────────┴─┴─┤
```
┌ 1 Geen maligniteit
  2 TUR-pT <= 5%
  3 TUR-pT > 5%
└ 9 Onbekend
```

17 T-categorie (TNM 92) ────┴─┴─┴─┴─┤
```
┌ T0;Tx;T1a;T1b;T1c;T2a;T2b;T2c;
└ T3a;T3b;T3c;T4a;T4b
```

18 IVP, echo ──────────┴─┴─┤
```
┌ 0 Normaal
  1 Stuwing 1 kant
  2 Stuwing bdz
└ 9 Niet gedaan
```

19 Botscan ──────────┴─┴─┤
```
┌ 0 Normaal
  1 Hotspots, meta's
  2 Hotspots deg.afw.
  3 Hotspots, andere afw.
  4 Toename hotspots t.o.v. eerdere
    scan
└ 9 Niet gedaan
```

20 Bot; X-ray/MRI/CT ────┴─┴─┤
```
┌ 0 Negatief
  1 Blastische meta's
  2 Lytische meta's
  3 Degeneratieve veranderingen
  4 Andere afwijkingen
└ 9 Niet gedaan
```

21 Bot biopsie ────────┴─┴─┤
```
┌ 0 Negatief
  1 Positief
└ 9 Niet gedaan
```

22 CT/Echo/MRI abdomen ────┴─┴─┤
```
┌ 0 Normaal
  1 Reg.klieren verdacht
  2 And.klieren verdacht
  3 Reg.en and. klieren verdacht
  4 Niet lymfogene meta's
  5 Andere afwijkingen
└ 9 Niet gedaan
```

23 Punct.Cyt nav CT/Echo/MRI ──┴─┴─┤
```
┌ 0 Negatief
  1 Positief
└ 9 Niet gedaan
```

24 Volume prostaat echo ──┴─┴─┴─┴─

25 Serum kreatinine ──┴─┴─┴─┴─

26 Alkalische fosfatase ──┴─┴─┴─┴─

27 Testosteron ──┴─┴─┴─┴─

28 PSA ──┴─┴─┴─┴─

29 Prostaat biopsie rechts ——————⌐ 0 Negatief
                                           1 pos.G1
                                           2 pos.G2
                                           3 pos.G3
                                           4 pos.zonder G
                                           9 Onbekend

30 Prostaat biopsie links ——————⌐ 0 Negatief
                                           1 pos.G1
                                           2 pos.G2
                                           3 pos.G3
                                           4 pos.zonder G
                                           9 Onbekend

31 Cyt.punctie prostaat rechts ———⌐ 0 Negatief
                                           1 Verdacht
                                           2 Positief
                                           9 Onbekend

32 Cyt.punctie prostaat links ———⌐ 0 Negatief
                                           1 Verdacht
                                           2 Positief
                                           9 Onbekend

33 Graad maligniteit TUR ——————⌐ 1 G1
                                           2 G2
                                           3 G3
                                           9 Onbekend

Hoofdstuk operatie.

34 Operatiedatum   maand ——⎿⏌⏌⏌⎿⏌⏌⏌—— jaar

35 Operateur ————————⌐ 1 FHS
                                           2 Gast
                                           3 Staf
                                           4 Assistent
                                           5 Anders

36 Lymfklier dissectie ——————— 0 Nee, 1 Ja

37 Palpatie rechts ———————⌐ 0 Negatief
                                         1-8 verdachte lymfklier(en)

38 Doorsnede grootste klier ——— 0 - 98 mm, 99 onbekend

39 Palpatie links ————————⌐ 0 Negatief
                                         1-8 verdachte lymfklier(en)

40 Doorsnede grootste klier ——— 0 - 98 mm, 99 onbekend

41 Vriescoupe rechts ——————⌐ 0 Negatief
                                         1-8 verdachte lymfklier(en)

42 Vriescoupe links ——————⌐ 0 Negatief
                                         1-8 verdachte lymfklier(en)

43 Radicale prostatectomie ——————⌐ ⌐ ⌐ 0 Nee, 1 Ja

52 Poging zenuwsp.operatie ——————⌐ ⌐ ⌐
- 0 Nee
- 1 Rechts
- 2 Links
- 3 Beiderzijds

44 Complicatie peroperatief ——————⌐ ⌐
- 0 Geen
- 1 Vaatletsel
- 2 Darmletsel
- 3 Ureterletsel
- 4 Anaesthesiologie
- 5 Overleden
- 6 Anders

45 Geschat bloedverlies ——————⌐ ⌐ ⌐ ⌐ ⌐ ml.

PID# ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ NAAM : _____ GEB : __ __ ____

Hoofdstuk pathologische anatomie.

46 Paraff.coupe lymfkl. rechts ──⌊_⌊──
```
0 Negatief
1 1 klier <= 2 cm
2 1 klier > 2 cm en <= 5cm
  of meerdere klieren <= 5 cm
3 klier meta > 5 cm
4 extra regionale klier positie
```

47 Afmetingen grootste klier ──⌊_⌊_⌊── 0 - 98 mm; 99 Onbekend

48 Paraff.coupe lymfkl. links ──⌊_⌊──
```
0 Negatief
1 1 klier <= 2 cm
2 1 klier > 2 cm en <= 5cm
  of meerdere klieren <= 5 cm
3 klier meta > 5 cm
4 extra regionale klier positief
```

49 Afmetingen grootste klier ──⌊_⌊_⌊── 0 - 98 mm; 99 Onbekend

50 Grootte metastase in lymfklier ⌊_⌊──
```
1 Sol meta <= 2 mm
2 Sol meta > 2 mm en < 20 mm
3 Sol meta >= 20 mm en <= 50 mm
4 Mult meta <= 2 mm
5 Mult meta > 2 mm en <= 50 mm
6 Meta > 50 mm
```

51 pN categorie (TNM 92) ──────⌊_⌊── pN0,pN1,pN2,pN3

53 Tumor links ──────────⌊_⌊──
```
0 Nee
1 <= 1/2 kwab
2 > 1/2 kwab
```

54 Tumor rechts ─────────⌊_⌊──
```
0 Nee
1 <= 1/2 kwab
2 > 1/2 kwab
```

55 Kapsel doorbraak ────────⌊_⌊──
```
0 Nee
1 Rechts
2 Links
3 Beiderzijds
```

56 Vesicula invasie ────────⌊_⌊──
```
0 Nee
1 Rechts infiltratie
2 Links infiltratie
3 Beiderzijds infiltratie
```

57 Fixatie cq ingroei ───────⌊_⌊──
```
0 Nee
1 Blaashals, rectum, ext.sphincter
2 Levator, bekken
```

58 pT-categorie (TNM 92) ────⌊_⌊_⌊──
```
T0;Tx;T2a;T2b;T2c;
T3a;T3b;T3c;T4a;T4b
```

59 G categorie ——————————————⌐ 0 Negatief
                                          1 G1
                                          2 G2
                                          3 G3

60 Vasculaire infiltratie ——————⌐ 0 Negatief
                                          1 Positief

61 Perineurale infiltratie —————⌐ 0 Negatief
                                          1 Positief

62 Resectievlak ———————————⌐ 0 Vrij van tumor
                                          1 Niet vrij van tumor

63 Resectievlak apex ——————————⌐ 0 Vrij van tumor
                                          1 Niet vrij van tumor

64 Kapsel infiltratie ——————————⌐ 0 Geen
                                          1 Tot aan kapsel
                                          2 Invasie kapsel
                                          3 Door kapsel (in peripr.vet)

Complicaties (binnen 2 mnd. postop.)

65 Infectie wond ————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

66 Drain > 2 weken ————————————— |_|_| — 0 Nee, 1 Ja

67 Extravasaat op CU na 3 weken —|_|_|— 0 Nee, 1 Ja

68 Drainage lymfocele ————————— |_|_| — 0 Nee, 1 Ja

69 Bloeding ————————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

70 Fistel ————————————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

71 Pneumonie ——————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

72 Thrombose ——————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

73 Embolie ————————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

74 Stuwing nier ————————————— |_|_| — 0 Nee, 1 Ja

75 Myocardinfarct —————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

76 Na verw. cath. incont. ———— |_|_| ⌈ 0 Nee
                                    | 1 tm 7 weken = duur in weken
                                    ⌊ 8 8 of meer weken

77 Anastomose dilatatie ———— |_|_| — 0 Nee, 1 Ja

78 Andere ——————————————————— |_|_| — 0 Nee, 1 Ja, 2 Overleden aan

79 Aantal P.C. gegeven ————— |_|_|_|

80 Dagen catheter a demeure —— |_|_|_|

81 Therapie achteraf ————————— |_|_| ⌈ 0 Geen
                                      | 1 Orchidectomie
                                      | 2 Endocrien
                                      | 3 Bestraling
                                      ⌊ 4 Anders

82 Dagen opname ————————————— |_|_|_|

83 PSA ——————————————————————— |_|_|_|_|
   (1e binnen 3 mnd. postop.)

Data checklist follow-up visits of patients in the prospective study.

PID# ⌐⌐⌐⌐⌐⌐⌐⌐⌐ NAAM : _____ GEB : __ ___ ____

02 Follow up datum :   maand ———⌐⌐⌐ ⌐⌐⌐———— jaar

03 Performance (WHO klasse) ———⌐⌐⌐ ⌐ 0 Normaal
                                     1 - 4 Klasse 1 tm 4

04 Pijn ————————————————⌐⌐⌐ ⌐ 0 Nee
                                 1 Perineaal
                                 2 Bot
                                 3 Elders
                                 4 Meerdere plaatsen

05 Nacht. erecties ——————————⌐⌐⌐— 0 Nee, 1 Ja, 9 Onbekend

06 Erecties met sex.stimulatie ——⌐⌐⌐— 0 Nee, 1 Ja, 9 Onbekend

07 Sexueel actief ————————⌐⌐⌐— 0 Nee, 1 Ja, 9 Onbekend

08 Bereikt orgasme ————————⌐⌐⌐— 0 Nee, 1 Ja, 9 Onbekend

09 Incontinent ————————————⌐⌐⌐ ⌐ 0 Nee
                                   1 Ja, <= 2 verb/dag
                                   2 Ja, > 2 verb/dag
                                   3 Sph. proth. droog
                                   4 Sph. proth. lekt

10 Obstructieve mictie ————————⌐⌐⌐ ⌐ 0 Nee
   (eventueel therapie)   1 Ja, dilataties
                                     2 Ja, operatie
                                     3 Ja, andere therapie
                                     4 Ja, geen therapie

11 Status localis na Rad.Prost. ——⌐⌐⌐ ⌐ 0 RT normaal
                                        1 RT verdenking recidief
                                        2 Echo verdenking recidief
                                        3 Recidief/bevestigd biopsie
                                        9 Geen RT gedaan

12 Rectaal toucher zonder RP. ———⌐⌐⌐ ⌐ T0;T2a;T2b;T2c;
   (TNM 92)   T3a;T3b;T3c;T4a;T4b

12a Geschat volume RT [cm3] ——⌐⌐⌐⌐⌐

12b⌐ Totaal volume TRUS ———⌐⌐⌐⌐⌐ cm3
    Volume adenoom TRUS ———⌐⌐⌐⌐⌐ cm3
    Laesie1 (max.afm.) —⌐⌐⌐⌐ x ⌐⌐⌐⌐ mm
    Laesie2 (max.afm.) —⌐⌐⌐⌐ x ⌐⌐⌐⌐ mm

Op indicatie :

13   X-Thorax. ——————————⌐⌐⌐ ⌐ 0 Negatief
      dd : __ ___ __   1 Positief metastasen
                                 2 Andere afwijkingen

14   Botscan. ——————————⌐⌐⌐ ⌐ 0 Normaal
      dd : __ ___ __   1 Hotspots, meta's
                                 2 Hotspots deg.afw.
                                 3 Hotspots andere afwijkingen
                                 4 Toename hotspots tov eerdere
                                   scan

157

```
15    Bot: X-ray/MRI/CT ───────────┤ └┘├─ 0 Normaal
      dd :  __  ___  __                  1 Blastische meta's
                                         2 Lytische meta's
                                         3 Degeneratieve veranderingen
                                         4 Andere afwijkingen
```

```
16    CT/Echo/MRI abdomen ─────────┤ └┘├─ 0 Normaal
      dd :  __  ___  __                  1 Reg. klieren verdacht
                                         2 And. klieren verdacht
                                         3 Reg. en and. klieren verd.
                                         4 Niet lymfog. metastasen
                                         5 Andere afwijkingen
                                         6 Lokaal recidief
```

```
17    M-cat. (TNM 92) ─────────────┤ └┘├─ 0 M0
      dd :  __  ___  __                  1 M1a, niet regionale lymfklieren
                                         2 M1b, bot-metastasen
                                         3 M1c, andere metastasen
```

Behandeling.

17a Motivatie voor in te stellen behandeling : _____

_____

18 Orchidectomie ─────────────────┤ └┘├─ 0 Nee, 1 Ja

19 Anti-androg. ──────────────────┤ └┘├─ 0 Nee, 1 Ja

20 Horm.anders (LHRH) ────────────┤ └┘├─ 0 Nee, 1 Ja

21 Chemotherapie ─────────────────┤ └┘├─ 0 Nee, 1 Ja

22 Bestraling prost. regio ───────┤ └┘┘ 0 Nee, 1 Ja

23 Bestraling elders ─────────────┤ └┘├─ 0 Nee, 1 Ja

24 TUR ───────────────────────────┤ └┘├─ 0 Nee, 1 Ja

25 Anders ────────────────────────┤ └┘├─ 0 Nee, 1 Ja

26 In trialverband ───────────────┤ └┘├─ 0 Nee, 1 Ja

27 Alkalische fosfatase ──────┤ └┘┘ └┘┘
   (alleen prikken op indicatie !)

28 Testosteron ──────────┤ └┘┘ └┘┘ └┘┘
   (alleen prikken op indicatie !)

28 PSA ───────────────────────┤ └┘┘ └┘┘

```
33 Poli controle ─────────────────┤ └┘├─ 00 AZR, korte termijn
                                       01-12 AZR controle na .. mnd.
                                       96 Verwijzing naar elders
                                       97 Elders
                                       98 Ontslag
                                       99 Onbekend
```

DANKWOORD

CURRICULUM VITAE

The author was born on june 17, 1961, in Delft, The Netherlands. After graduation from the Groen van Prinsterer college in Vlaardingen in 1979 (Gymnasium β), he studied medicine at the University of Leiden from 1979-1988. During his student years he participated in the clinical investigation of a micro-processor controlled uroflowmetry system. After his graduation from the medical school, he performed as a general practitioner during his military service years (1988-1989), in the 'stafcompagnie of the first Army-Corps' in Apeldoorn. In 1990-1991 he worked as a resident not in training (AGNIO) at the Urology department of the Academic Hospital Rotterdam (chairman: Prof.Dr. F.H. Schröder). In these years the study resulting in this thesis was initiated.
After being admitted for the Urological training program, he spent two years (1992-1993) as a resident in training in the department of Surgery of the Leyenburg Hospital in The Hague (chairman: Dr. Oosterwijk). In 1994 started his residency in Urology in the Academic Hospital Rotterdam (chairman: Prof.Dr. F.H. Schröder), and the Sophia Childrens Hospital (head: Dr Nijman).
He is married to Lillian van Oosterbos, and has three children.

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