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Article original

A retrospective analysis of the results of p(65) + Be neutrontherapy for the treatment of prostate adenocarcinoma at the cyclotron of Louvain-la-Neuve. Part I: survival and progression-free survival

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ABSTRACT

Purpose. – To retrospectively evaluate survival, progression-free survival (PFS) and biological response in a series of patients irradiated with mixed neutron/photon beams for locally advanced prostate cancer in our institution.

Patients and methods. – Three hundred and eight patients were treated between January 1990 and December 1996. Fifty-five of these were recruited for pT3 or pN1 tumors after radical prostatectomy. Neoadjuvant androgen deprivation was given in 106 patients. The treatment protocol consisted of a mixed photon/neutron irradiation in a two-to-three proportion, up to a total equivalent dose of 66 Gy (assuming a clinical RBE value of 2.8). Pre- and post-treatment PSA determinations were available in practically all cases. Study endpoints were overall survival (OAS) and progression-free survival (PFS). The Cox proportional hazard regression model was used to investigate the prognostic value of baseline characteristics on survival and progression-free survival were a progression was defined as local, regional, metastatic or biological progression. Mean age was 69 years (49–86); mean pretreatment PSA was 15 (0.5–330) in all patients and 14 (0.5–160) in those receiving neoadjuvant hormonotherapy; seven patients only had an initial PSA ≤ 4 ng/mL; 15% were T1, 46% were T2, 28% were T3 or pT3 and 4% were T4 (7% unspecified); WHO grade of differentiation was I in 38%, II in 38% and III in 14% (5% unspecified).

Results. – The median follow-up was 2.8 years (0–7.8). Five-year overall survival (OAS) was 79% (95% CI: 71–87%) and 5-year progression-free survival (PFS) was 64% (95% CI: 54–74%) for the entire series. PFS in patients with an initial PSA ≥ 20 ng/mL was the same. PFS could be predicted by two optimal Cox regression models, one including histological grade ($p = 0.003$) and initial PSA ($p = 0.0009$) as cofactors, the other including histological grade ($p = 0.003$) and T stage ($p = 0.02$). The main prognostic factors for overall survival were PSA and age. Biological responses with PSA < 1.5 ng/mL, < 1 ng/mL and < 0.5 ng/mL at any time after treatment were documented in 70%, 61% and 47% of the patients, respectively.

Conclusion. – Five-year OAS was 79%, PFS was 64%, and biological response was 70% for prostate cancer patients treated with mixed photon/neutron beams as applied at Louvain-la-Neuve, which are good results as compared with the literature. The usual prognostic factors were confirmed.

fast neutrons / prostate adenocarcinoma / radiotherapy

RÉSUMÉ

Analyse rétrospective des résultats de la neutronthérapie p(65) + Be dans le traitement du cancer de la prostate au cyclotron de Louvain-la-Neuve. 1re partie : survie globale et survie sans progression.

Objectif de l'étude. – Évaluation rétrospective de la survie, de la survie sans progression tumorale et de la réponse biologique dans une série de patients irradiés par une association de neutrons et de photons pour un cancer localement évolué de la prostate.

Patients et méthodes. – Trois cent huit patients ont été traités entre janvier 1990 et décembre 1996. Cinquante-cinq étaient atteints d'un cancer classé pT3 ou pN1 après prostatectomie radicale. Une hormonothérapie adjuvante a été

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délivrée à 106 patients. Le traitement a consisté en une association de photons et de neutrons dans une proportion deux tiers–un tiers, jusqu'à une dose équivalente de 66 Gy (avec une efficacité biologique relative de 2,8). Une dosage pré- et post-thérapeutique du PSA a été réalisé dans pratiquement tous les cas. La survie globale et la survie sans progression tumorale ont été calculées. Le modèle de Cox a été utilisé pour étudier les facteurs pronostiques de la survie et de la survie sans progression locale, régionale, métastatique ou biologique. L'âge médian était de 69 ans (extrêmes : 49–86 ans) ; la concentration moyenne préthérapeutique du PSA était de 15 (extrêmes : 0,5–330) dans l'ensemble de la population et de 14 (extrêmes : 0,5–160) chez ceux ayant reçu une hormonothérapie néoadjuvante ; sept patients seulement avait initialement un PSA ≤ 4 ng/mL ; 15 % des tumeurs étaient classées T1, 46 % T2, 28 % T3 ou pT3 et 4 % T4 (7 % non précisés) ; le grade de différentiation OMS était de I chez 38 % des patients, II chez 38 % et III chez 14 % (5 % non précisés).

Résultats. – La durée médiane de surveillance était de 2,8 ans (extrêmes : 0–7,8 ans). Le taux de survie globale à cinq ans était de 79 % (intervalle de confiance à 95 % : 71–87 %) et le taux de survie sans progression tumorale de 64 % (54–74 %) pour l'ensemble de la population. Le taux de survie sans progression tumorale des patients qui avaient initialement une concentration de PSA > 20 ng/mL était le même. Le taux de survie sans progression tumorale peut être prédit avec le modèle de Cox par seulement deux cofacteurs, le grade histologique (p = 0,003) et le PSA initial (p = 0,0009), les autres cofacteurs significatifs étant le grade histologique (p = 0,003) et le stade T (p = 0,02). Les facteurs pronostiques principaux de la survie globale sont le PSA et l'âge. Une réponse biologique avec une concentration de PSA toujours inférieure à 1,5 ng/mL, 1 ng/mL et 0,5 ng/mL a été respectivement observée chez 70, 61 et 47 % des patients.

Conclusion. – Des taux de survie globale de 79 %, de survie sans progression tumorale de 64 %, et de réponse biologique de 70 % ont été obtenus chez des patients atteints de cancer de la prostate, cancer traité par une association de protons et de neutrons à Louvain-la-Neuve, ce qui constitue un bon résultat par rapport à ceux de la littérature. Les facteurs pronostiques usuels ont été retrouvés.

adénocarcinome de la prostate / neutrons rapides / radiothérapie

At the time the neutrontherapy facility became operational in Louvain-la-Neuve (LLN) in 1978, an American cooperative randomized study (protocol RTOG 77–04) was enrolling patients with clinical stage C or D1 prostate adenocarcinoma, comparing a mixed neutron-photon irradiation to a conventional photon treatment. This protocol was part of a series of collaborative neutron therapy trials launched in the 1970s by the RTOG for various tumor systems.

The rationale for testing fast neutrons as a new therapeutic modality stemmed from the observation of a lower OER than for x- or gamma rays; at the time hypoxia was considered the major cause for tumor resistance to radiotherapy [5, 7, 9]. Further arguments for their use in prostate adenocarcinoma appeared later on, e.g., an apparently more favorable RBE for well-differentiated, slowly growing tumors ascribed to the decreased cell-cycle dependency of the biological response to fast neutrons [28].

The results of RTOG 77–04 were first published in 1985, and updated in 1987 and 1993 [17, 18, 24]. Ninety-five patients had been randomized with a 2:1 randomization distribution in favor of the experimental arm; 91 were eligible for analysis. A substantial advantage in overall survival and disease-specific survival was reported with mixed neutron-photon beams. This advantage was confirmed in the two subsequent updates.

A second trial (protocol NTCWG[1] 85-23, NCI) enrolled 178 patients with T2–4, N0–1, M0 adenocarcinomas of the prostate from April 1986 to October 1990; conventional photons were compared to neutrons only [25]. Five-year actuarial survival was identical but actuarial loco-regional failure was significantly less in the neutron arm (11 vs 32%, $p < 0.01$). Also, actuarial 5-year post-treatment PSA failure was only 17% after neutrons versus 45% after photons ($p < 0.001$).

The positive results of both trials encouraged the LLN team to focus on prostatic cancer and the recruitment steadily increased year after year, topping at 83 patients in 1996. The publication of a high frequency of severe complications in the centers equipped with a non-isocentric neutron beam [1] was not considered relevant to the local situation since the many years of experience already accumulated had demonstrated the good tolerance of the patients treated in LLN with mixed neutrons and photons beam. For example, a 0% frequency of severe complications was reported in 62 patients treated with stage C prostatic cancer between 1978 and 1988 [23]. In addition, the vertical beam was equipped with a new multileaf collimator, operational from March 1992 [6].

PURPOSE

This study was designed to retrospectively evaluate the clinical (PFS and OAS) and biological (PSA) results obtained with this neutron facility.

[1] Neutron Therapy Collaborative Working Group, USA.

Table I. Definition of field margins.

	Pelvic fields (type I)	*Large prostate (type II)*	*Small prostate*
AP/PA			
Cranial limit	Lower 1/3 sacro-iliac articulations	2 cm above femoral heads	Just above femoral heads
Caudal limit	Inf. ischion	Inf. ischion	Inf. ischion
Lateral limits	1.5 cm from pelvic rim	Pelvic rim	Mid-foramen obturator
LAT			
Sup. limit	Same as AP/PA	Idem	Idem
Inf. limit	Same as AP/PA	Idem	Idem
Ant. limit	Anterior border of pubic articulation	Idem	Idem
Post. limit	Mid-rectum (baryum enema), ± mid S2	Idem	1–1.5 cm less

PATIENTS AND METHODS

Demographic data

A total of 533 patients have been treated since 1978 in Louvain-la-Neuve (LLN) (neutron part of the treatment) and Louvain-en-Woluwe (LeW) (photon part of the treatment), most with a mixture of neutrons (three fractions/week, anterior and posterior field) and 18 MV photons (two fractions/week, lateral fields). Clinical staging and regular PSA serum levels were systematically available since January 1990. The present analysis was therefore restricted to the 308 patients irradiated between January 1990 and December 1996.

The following parameters were retrospectively collected: age, initial PSA, PSA at follow-up, initial hemoglobin level, associated chronic disease, method of diagnosis, histological grade (good, moderate and bad differentiation (from Broder [4]), clinical T, N and M stage (AJCC 1992 4th ed.), type of surgery if any, initial or subsequent hormonotherapy, time of progression, second primary, survival status and cause of death. Missing data were obtained from the files of the referring urologist or the general practitioner.

The Gleason score, total or partial, was not always available in this retrospective review, partly because of the multi-centric origin of patients. Therefore, the three-grades classification was preferred.

Patients referred for post-operative radiotherapy (pT3) were coded according to their presurgical clinical T and N stage.

Treatment technique

The classical box technique was used, generally starting with pelvic fields for 25 fractions followed by a cone-down on the prostate for the last eight fractions, for a total of 33 fractions. The patients were treated alternatively with AP/PA fields (neutrons) delivering 0.70 Gy/day, 3 days a week, and lateral fields (photons) delivering 2 Gy/day the 2 other days. AP/PA fields were given by rotating the patient from a supine to a prone position and irradiating at 176 cm SSD. Lateral fields were given in a supine position at 100 cm SSD.

Neutron-absorbed doses were specified by combining the gamma (5–7% at LLN) [30] and the neutron component and applying a clinical RBE of 2.8. The neutron fractions of 0.70 Gy were combined with the x-ray fractions of 2 Gy to a total of 66 Gy equivalent. Field margins were routinely checked by simulation and confirmed by portal films at the first irradiation session. Dose calculations were carried out on a 2D Mevaplan treatment planning unit (Siemens) modified for absorbed-neutron dose calculations [29] and without correction for heterogeneities. A single cross-section was used at the isocenter level. In vivo dosimetry was occasionally carried out as control of the computer dosimetry and found in excellent agreement in all cases (unpublished material).

Two irradiation protocols were used: pelvic fields followed by a prostate boost (type I) or large prostate followed by the same prostate boost (type II). The latter protocol was indicated in patients with a small tumor and low PSA, in patients with a negative lymphadenectomy or in patients referred for postoperative irradiation (pT3) but ineligible in EORTC[2] 22911 trial. In all other cases a pelvic irradiation preceded the prostate boost. Field margins were defined as specified in *table I*.

The pelvic fields were intended to include obturator, hypogastric, internal iliac and common iliac lymphatic nodes as well as the prostate. The large prostatic fields were intended to cover essentially the obturator nodes together with the prostate. The prostatic boost covered the prostate only. The field limit definitions were derived from the RTOG protocols, similar also to those usually specified in EORTC protocols.

Tomodensitometry for treatment planning and tridimensional dosimetry were not used during treatments concerning this retrospective study. Radiation fields were

[2] European Organisation for Research and Treatment of Cancer, Brussels.

designed during a conventional radioscopic simulation with a bladder catheter for opacification and a rectum enema opacification with barium sulfate. As described in *table I*, for lateral fields, always treated with photons, the posterior limit was placed at mid-rectum without use of blocks or multi-leaf collimation. For the anterior and posterior part of pelvic fields (type I in *table I*), personal collimation was used to protect normal tissue mainly in the external and caudal part of these fields, outwards of the obturator holes and parallel to the iliac lymph node chain (based on bony landmarks). This was realised with a multi-leaf collimator for neutron therapy and with Cerrobend blocks for the photon therapy.

Patients referred to the department during arrest periods of the cyclotron (maintenance, breakdown) were either delayed until it resumed operation, or treated with photons only. Also, various treatment circumstances lead to an alteration of the neutron/photon ratio with a not inconsiderable proportion of patients receiving a lesser dose from the neutron and more from the photon beams. However, a minimum of 20 Gy were always given with 18 MV photons (usually by the lateral fields). The total group received thus the same total dose of 66 Gy equivalence but with some variation in the neutron/photon ratio.

The neutron/photon proportion was calculated by dividing the equivalent neutron dose, i.e., the neutron-absorbed dose corrected by the clinical RBE of 2.8, by the absorbed photon dose. The value of this clinical RBE was derived from a series of radiobiological experiments [2, 10-13].

Statistical analysis

Three endpoints have been used and estimated by the Kaplan-Meier method: overall survival, progression-free survival (PFS) and biological response (i.e., PSA status after treatment). Different groups of patients were compared using the logrank test. The Cox regression model was used for multivariate analyses.

The impact of the variable proportion of neutrons was assessed on these three endpoints as well as the impact of initial PSA value, neoadjuvant hormonotherapy, field size and PSA nadir after radiotherapy. In order to adjust the analysis for possible prognostic factors, the prognostic value of all available baseline variables was subsequently tested by univariate and multivariate techniques.

Overall survival was measured from the first day of radiation therapy to the date of death, whatever the cause; patients still alive at last follow-up were censored at this date in the survival analysis. Progression-free survival was measured from the first day of irradiation to the date of first documented progression, either clinical (local, regional, metastatic) or biological (PSA). Patients who died in remission, as well as patients in remission at the last follow-up were censored at the date of death or last follow-up. Biological response was defined as the reduction of PSA below 1.5 ng/mL (Hybritech); a subsequent elevation above 1.5 ng/mL was scored as a biological progression. Lower PSA nadir–1 and 0.5 ng/mL–were also tested, searching for a threshold value predictive of long-term biochemical control.

RESULTS

Demography

Three hundred and eight patients have been included in this retrospective analysis; details of the variables for which information was solicited are displayed in *table II*

Table II. Demography.

	Number (%) (Total=308)
Age (years): median (min-max)	69 (49–86)
Chronic disease	
None	80 (26)
Cardiovascular	112 (37)
Respiratory	25 (8)
Cardiovascular+respir.	25 (8)
Other	31 (10)
Unspecified	35 (11)=308
Method of diagnosis	
Biopsy	230 (75)
Turp	40 (13)
Other (adenectomy, etc.)	26 (8)
Unspecified	12 (4)=308
Histological grade	
Well differentiated	117 (38)
Moderately differentiated	116 (38)
Poorly differentiated	44 (14)
Unspecified	31 (10)=308
Clinical T stage	
T0	2 (1)
T1	45 (15)
T2	143 (46)
T3	86 (28)
T4	9 (3)
Unspecified	23 (7)=308
Clinical N stage	
N0	284 (92)
N1	6 (2)
N2	3 (1)
Unspecified	15 (5)=308
Clinical M stage	
M0	290 (94)
Unspecified	18 (6)=308
Prostatectomy	
No	237 (77)
Yes	55 (18)
Unknown	16 (5)=308
Adenectomy	
No	258 (84)

Table II. (continued)

	Number (%) (Total=308)
Yes	34 (11)
Unknown	16 (5)=308
Turp	
No	239 (78)
Yes	55 (18)
Unknown	14 (4)=308
Lymphadenectomy	
No	249 (82)
Yes	43 (14)
Unknown	16 (5)=308
Initial hormonotherapy	
No	189 (62)
Yes	106 (34)
Unknown	13 (4)=308
If yes, type of first hormonotherapy	
Androgen blockade	17
LHRH analogue	11
Combined androgen blockade	53
Orchiectomy	18
Unknown	7
If second, type of hormono	
Androgen blockade	6
LHRH analogue	6
Combined androgen blockade	4

This was an unremarkable series in terms of age (median 69 years old, range 49–86) or clinical stage (cT2: 46%–cT3: 28%), but the range of PSA extended to unusually high values compared to recent radiotherapy series (maximum 330 ng/mL). Ten patients were lost to follow-up as far as their surviving status is concerned. The demographic data are summarized in *table II*.

Survival

The results are shown in *table III*. The 5-year overall survival estimate with a median follow up of 2.3 years (min 0, max. 7.8 years) and the 5-year PFS was 79% with a standard error of 4% (95% CI: 71–87%) *(figure 1)* and 64% with a standard error of 5% (95% CI: 54–74%) *(figure 2)*, respectively.

Univariate analysis

Table IV summarizes the results of the univariate analysis for prognosis factors. Histological grade *(figure 3)*, T stage *(figure 4)*, initial PSA and initial hormonotherapy influenced PFS significantly. Age, initial PSA and initial hormonotherapy influenced overall survival. Initial PSA was stratified in four categories showing relevant survival differences: 0–10, 10–20, 21–100 and > 100 ng/mL for the patients without neoadjuvant hormonal therapy *(figure 5)* (see below). The neutron-photon proportion had no impact on OAS or DFS *(figure 6)*.

Table III. Survival results.

Progression	
no	222 (72)
yes	60 (19)
unspecified	26 (9)=308
Hormonotherapy for progression	
no	7
yes	40
unspecified	13
second primary	
no	265 (86)
yes	11 (4)
unspecified	32 (10)
Type of second primary	
colon, rectum	2
lung	3
stomach	1
pancreas	1
leukemia	1
biliary tract	1
thyroid	1
skin	1
Survival status	
dead	36 (12)
alive	262 (85)
lost to follow-up	10 (3)
Cause of death	
prostate cancer	11
infection	2
second primary	3
cardio-vascular	13
cirrhosis	1
car accident	2
unknown	4
Time between RT treatment and last date known to be alive or date of death (years) Med (Min-Max)	2.3 (0–7.8)
Hemoglobin (g/L)	14 (10–19)
Initial PSA (ng/L)	15 (0.5–330)
Initial PSA in patients in which a value is available before any therapeutic intervention (hormones, surgery, etc).	14 (0.5–160)
Percentage neutrons in pelvic dose	60 (0–72)
Percentage neutrons in large prostate dose	60 (0–72)
Percentage neutrons in small prostate dose	61 (0–73)

Multivariate analysis

PFS could be predicted by two optimal Cox regression models, one including histological grade ($p = 0.003$) and initial PSA ($p = 0.0009$), one including histological grade ($p = 0.003$) and T stage ($p = 0.02$) as cofactors. Both models are valid, presumably because of a correlation between the initial PSA and the clinical stage. Stratification of the population according to the type of treatment (large pelvis, type I or large prostate loge, type II) did not reveal additional prognostic factors. The main prognostic factors for overall survival were initial PSA and, quite logically

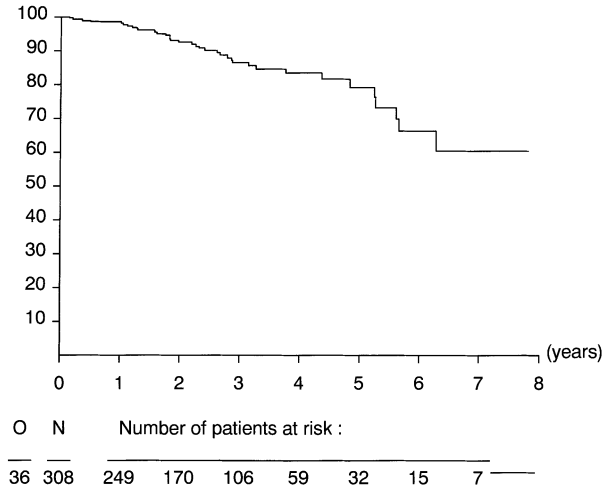

Figure 1. Kaplan-Meier curve for overall survival.

in an elderly population, age at the time of treatment. Only one third of the recorded deaths were due to prostate cancer (11/36).

Initial PSA value

In the whole series of patients, PSA was only a significant prognostic factor when categorized as < 100 ng/mL versus > 100 ng/mL. When lower values were chosen as a cut-off, this factor was not significant anymore. This is probably due to the fact that in patients treated with hormonotherapy before irradiation, the PSA recorded as 'initial' was measured after hormonotherapy, and may have been influenced by medical treatment. If we exclude patients pretreated with hormonotherapy, the prognostic value of PSA is also observed with lower cut-off values, but the number of patients is not sufficient to carry out multivariate analyses on this patient subset.

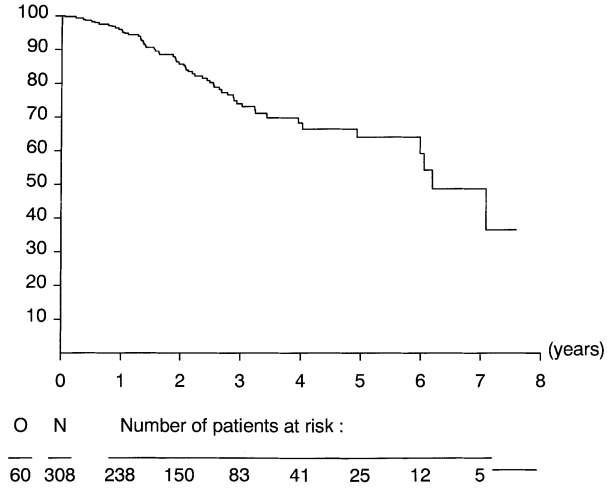

Figure 2. Kaplan-Meier curve for disease free survival.

Table IV. Univariate analysis.

	Progression-free survival	*Overall survival*
Age at time of treatment	NS	0.01
Age (=70 vs >70)	NS	0.02
Associated chronic disease	NS	NS
Histological grade	0.002	NS
T stage	0.008	NS
Initial PSA	0.0014	0.004
PSA=100 vs PSA>100	0.016	0.01
Initial hormonotherapy	0.05	0.05

The total group of 308 patients was broken down into two categories: those who had received hormonotherapy prior to irradiation (106 patients) and those who had not (189 patients). The information was not available in 13 patients. However, a pre-therapeutic PSA value was only available in 170 out of these 189 patients. In this group, the initial PSA level was a strong predictor of outcome with 4-year PFS of $92 \pm 6\%$ (< 10 ng/mL), $68 \pm 9\%$ (10–20 ng/mL) and $61 \pm 9\%$ (>20 ng/mL), respectively ($p = 0.0176$). The number of patients in the low PSA group was not sufficient to calculate a 5-year PFS with adequate confidence, the reason why the PFS has been calculated at 4 years *(figure 3)*. In the group which received hormonotherapy prior to irradiation, the PSA value recorded as 'initial' must have been already influenced by the medical treatment in some cases.

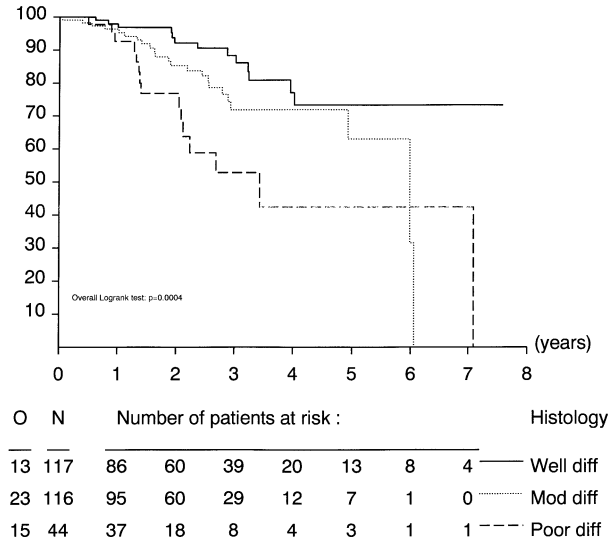

Figure 3. Time to progression according to pathological grade.

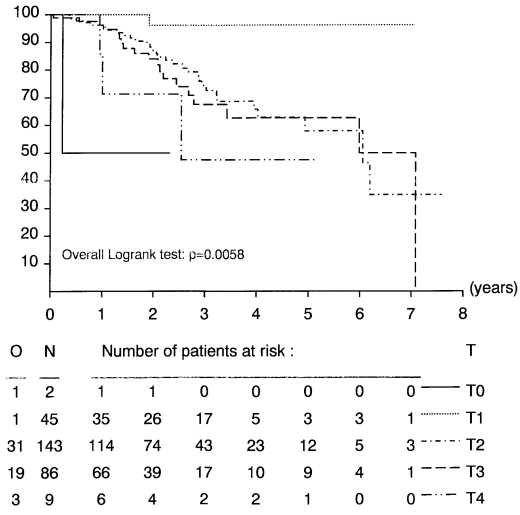

Figure 4. Time to progression according to T stage.

Influence of the proportion of neutrons over total dose

As a continuous variable or in different categories tried, for example: 0%, 1–50% 50.1–60%, 60.1–65%, > 6% neutrons in pelvis *(figure 6)*, the proportion of neutrons had no impact on PFS, on overall survival or on the biological response to therapy, whether the patients were treated on pelvic- (type I) or on large prostatic fields (type II), neither on univariate nor multivariate analysis.

Influence of neoadjuvant hormonal therapy

Initial hormonotherapy was found to have an important effect on the biological response ($p < 0.001$). It had, however, no significant effect on overall or progression-free survival. Initial hormonotherapy was usually discontinued after irradiation, though at variable times. The lack of a systematic approach to pre-radiotherapy hormonotherapy does not allow for conclusions regarding its adjuvant effect.

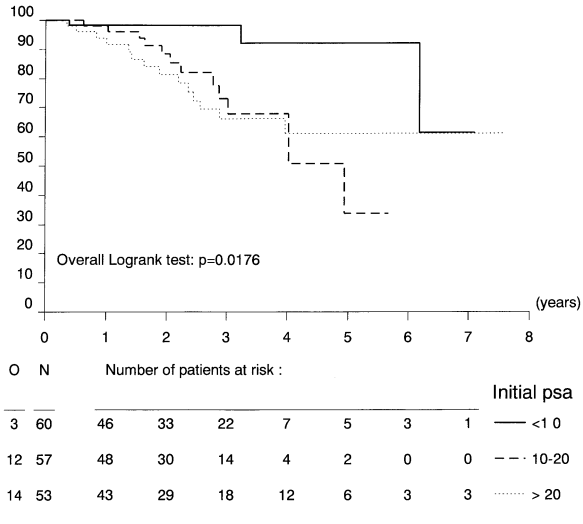

Figure 5. Kaplan-Meier curves to progression free survival in patients without initial hormonotherapy.

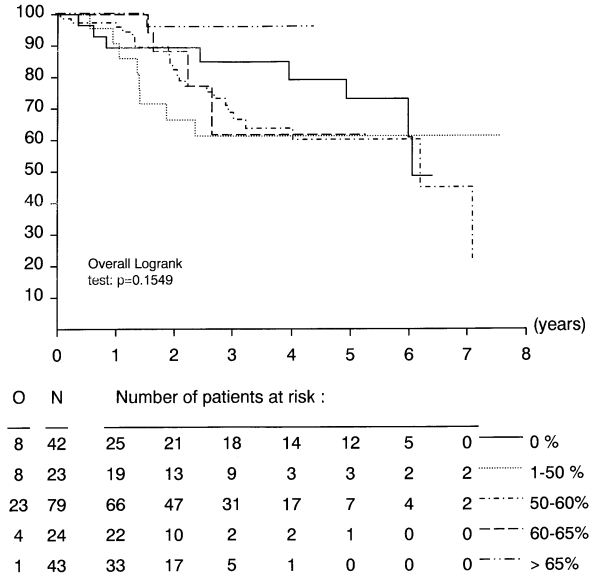

Figure 6. Time to progression according to % neutrons in pelvis.

Biological response, i.e., PSA smaller than 1.5 ng/mL at any time during follow-up, was documented in 201/284 (i.e., 70% of the patients). The proportion of neutrons had no influence on this parameter. A biological response defined as a PSA smaller than 0.3 ng/mL was also tested. Even in this case, the proportion of neutrons seemed to have no impact on the biological response. On the contrary, initial hormonotherapy strongly influenced the biological response ($p = 0.001$) but this was not translated either into overall survival or PFS.

PSA nadir after radiotherapy

The actuarial biological progression for the group of patients reaching a nadir ≤ 1.5 ng/mL is shown in *figure 7*. Other nadir values of <=1 ng/mL (reached in 61 % of patients) and ≤ 0.5 ng/mL (47% of patients) were also tested. Even at these very low PSA nadir values, biochemical failures were observed early after treatment.

In an attempt to better understand the structure of the patient population reaching low or very low PSA nadir values, the series has been divided in a number of subgroups. Out of the 189 patients who did not receive an initial hormonal treatment, 110 had a nadir PSA > 0.5 ng/mL and 76 had a nadir PSA ≥ 0.5 ng/mL (data were unavailable in three patients). The 5-year PFS

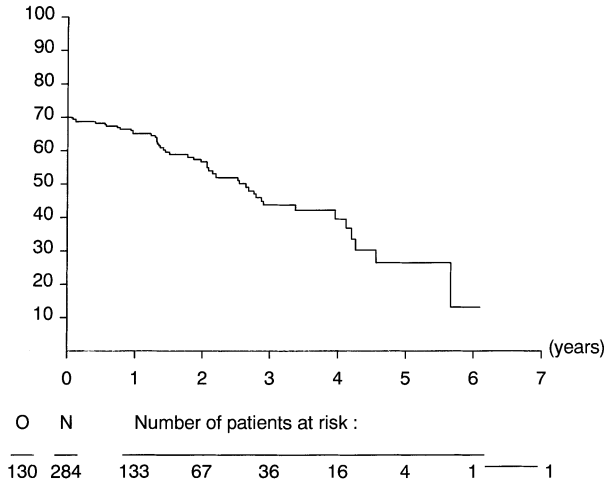

Figure 7. Biological progression cut-off value 1.5 ng/mL.

were 81% (95% CI: 69–93%) and 53% (95% CI: 31–75%), respectively ($p = 0.029$) *(figure 8)*.

In the group of 76 patients, the initial PSA was in the range 0.5–100, with a median of 12.8 ng/mL; the range of age was 51–78 with a median of 68 years. It had no remarkable features when compared to the entire series, except the fact that 46% of them (35 patients) were recruited in the neutron program for pT3 tumors after prostatectomy. The PSA nadir of 0.5 ng/mL was therefore explained by the surgical removal of the gland rather than by the irradiation, which is further confirmed by the observation that only three patients had an initial prostatectomy in the group of 110 who did not reach the nadir. This leaves us with 41 patients only reaching the threshold of 0.5 ng/mL after irradiation alone, without radical surgery (see *table V*). This group is too small to carry out a meaningful PFS analysis.

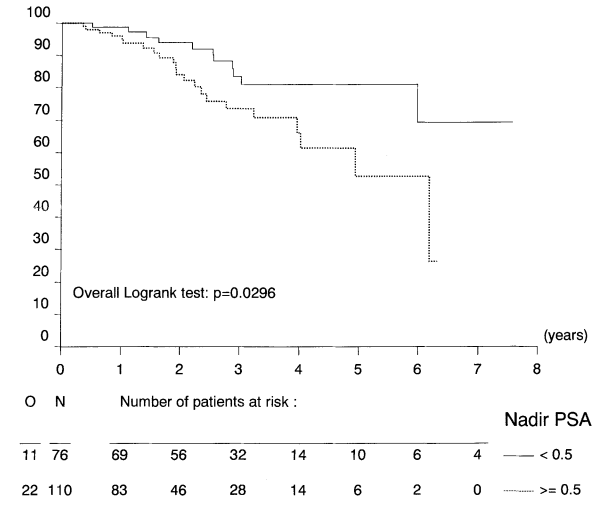

Figure 8. Kaplan-Meier curves for progression-free survival in patients without initial hormone therapy.

Table V. Influence of radical prostatectomy (RP) on PSA nadir in the 189 patients who did not receive initial hormone therapy.

	RP (n)	*no RP (n)*	*Total (n)*	*5-y PFS*
Nadir < 0.5 ng/ml	35	41	76	81±6%
Nadir > 0.5 ng/ml	3	107	110	53±11%**
Total	38	148	186*	

* Data were unavailable in 3 patients (total 189); ** $p = 0.029$.

Tolerance to treatment depended on the field size with more frequent and lasting acute digestive effects (chiefly diarrhea) in patients treated with type I protocol (pelvis). Late effects have not been recorded according to an internationally accepted classification but have been retrospectively assessed by a quality-of-life questionnaire directly sent to the patient. In addition, local urologists or general practitioners were interviewed for any grade III or IV (EORTC-RTOG scale) urological or rectal complications. Three patients required corrective surgery for late effects of neutrontherapy: one radical ileitis, one bowel obstruction and one persistent hematuria. The corresponding neutron-photon proportion for these three patients was 44, 56, and 60%, respectively. No toxic deaths were observed during the follow-up period, which complete the previous analysis carried out in 1990 [23]. The quality-of-life analysis of the present series will be discussed in a separate paper.

DISCUSSION

Demographic data regarding the population treated at LLN indicate that the present series consists of a large proportion of elderly patients presenting with a locally advanced prostate adenocarcinoma. The mean age was 69, 15% only were staged T1 and only seven patients had a PSA less than 4 ng/mL at diagnosis (excluding patients with neoadjuvant hormonotherapy). It was therefore not unexpected that the 5-year overall survival and the 5-year progression-free survival only reached 79% and 64%, respectively. However, since the LLN series included a substantial proportion of elderly patients, 26 out of the 36 observed deaths were due to intercurrent causes, unrelated to cancer or to treatment side effects.

In a multivariate analysis, significant prognostic factors for progression-free survival were 1) initial serum PSA; 2) grade of differentiation; and 3) clinical stage, quite a common finding in prostate cancer series treated with radiotherapy. Overall survival was only influenced by the

initial serum PSA, which confirms its excellent value as a surrogate for stage and grade, and by age, which is not unexpected.

Comparisons with other series are difficult to perform because of the several possible biases which might influence the results.

Clinical staging is often deceiving, with a systematic understaging in 30–50% of patients, as demonstrated in many surgical series. The rate of understaging depends on the thoroughness of the staging procedure and, among other factors, on the skill of the urologist carrying out the endorectal ultrasonography and the quality of his equipment. Subjectivity is also not absent from the clinical staging by digital rectal examination. The CT scan often used for lymphatic staging is also inaccurate with far more under- than overstaging and is useless for local tumor staging. MRI was not used in this series.

The grade of differentiation likewise depends on the skills of the anatomopathologist, on the number of biopsies taken in the prostate and, particularly, in the care taken to biopsy all quadrants appropriately.

The only objective and reproducible parameter is the PSA. It has been repeatedly reported as an acceptable surrogate to grade and stage. Therefore, our series can be tentatively compared to other series with a similar, unfavorable PSA distribution.

Data from the M.D. Anderson Cancer Center, for example, show a 70% difference in relapse or rising PSA between patients with a pretreatment PSA of 4 or less and those with a level greater than 20 ng/mL. For the latter, the actuarial relapse rate or rising PSA reaches 80% at 4 years. The outcome of patients in intermediate PSA categories are in the 40–50% range [31]. Kuban et al. have reported similar results but with a much longer follow-up as serum samples from patients treated in the seventies and the eighties were kept in storage [15]. The MGH series [34] analyzed early (T1–T2) and late (T3–T4) stages according to the initial PSA level with a cut-off at 15 ng/mL. In both groups, a PSA > 15 ng/mL predicted a close to 0% biochemical relapse-free survival at 4 years. When the initial PSA was < 15 ng/mL, about 60% of T1–2 tumors were biochemical relapse-free at 4 years versus about 40% only for T3–4 tumors. Patients from these series were treated with 'conventional' radiotherapy, i.e., with total doses in the range 68–70 Gy and without the very tight margins currently used in conformal techniques.

Recent reports on dose-escalation trials suggest an improved PFS with photon doses higher than 75 Gy. Zelefsky et al. reported a 79% 4-year PFS in an intermediate risk group (high PSA or high grade or ≥ T2c) and close to 60% in an unfavorable risk group (more than one of these factors) treated with a dose range of 75.6–81 Gy [33]. Hanks et al. reported a 73% 5-year PFS (labeled bNED in the original publication) in a group with a PSA in the range 10–19.9 ng/mL and receiving ≥ 75.75 Gy in the prostate gland [14]. In the less favorable group with a PSA ≥ 20 ng/mL and treated at the same dose levels, the 5-year PFS dropped to 30% (Kaplan-Meier estimate). Data from the M.D. Anderson study are more favorable, particularly in the poor prognostic factor groups (Gleason ≥ 8 or pretreatment PSA > 20 ng/mL or T–T4), but the follow-up is shorter and the group is relatively small [22].

The actuarial PSA control of 64% at 5 years observed on the present series compares well with these data. In the subgroup of patients with an initial PSA > 20 ng/mL (less than half the population), the actuarial PSA control was not significantly different from this figure, which can be considered as a favorable result. Conversely, the results in the subgroup with PSA < 20 ng/mL (more than half the population), also not significantly different from the total group, cannot be considered as favorable. However, several patients received neoadjuvant hormonal therapy in this group which explains, at least partly, this disappointing observation.

The level of post-irradiation PSA which must be reached to achieve long-term biochemical control has been the subject of much debate, but a nadir in the range of 0.5–1 ng/mL has been proposed as a target value after radiotherapy [16, 26, 32]. The progression-free survival of this series was thus calculated in the strata reaching a value of 0.5 ng/mL at any time after neutron therapy. Results were quite disappointing since, even when reaching this very low nadir, long-term control could not be maintained in all patients. A substantial proportion of these, however, received neoadjuvant hormonotherapy, which depressed serum PSA levels quickly and efficiently. In addition, nearly half of the patient with a nadir < 0.5 ng/mL did so because they had a prostatectomy first (pT3 patients). The breakdown of the present series in different subgroups – see *table IV* – indicated that 41 out of the 148 patients who did not receive neoadjuvant hormones and/or were not recruited for a pT3, eventually reached a PSA nadir ≤ 0.5 ng/mL. These are the potential candidates for long-term control of the disease, or at least those in which this value will be maintained for a long time, perhaps as long as 5 years [27].

Results at LLN are also in line with those reported in the NTCWG 85–23 randomized trial comparing fast neutrons (20.4 Gy neutron dose) versus conventional photons (70 Gy). However, an absolute comparison of the present series with the latter is difficult since the pretreatment PSA was not routinely measured in the randomized trial; only T3–T4 tumors or high-grade T2 were eligible [25]. On the other hand, post-treatment PSA values became gradually available as the follow-up increased; at 5 years, they were judged 'elevated' in 17% of neutron-treated

patients versus 45% in the photon group ($p < 0.001$). Severe complications were more frequent in the neutron arm but restricted to those facilities without a variable multi-leaf collimator and full isocentric neutron gantry (i.e., UCLA, M.D. Anderson, Cleveland, OH); these subsequently stopped treating patients of any sort. An important difference between the present series and the NTCWG 85–23 trial was the protocol of neutron irradiation used. In both cases, high-energy neutrons with a depth-dose distribution similar to a modern megavoltage unit were used but the LLN protocol continued to use mixed beam therapy whereas the randomized trial compared neutrons alone versus photons.

The decision of the LLN team to stick to the mixed photon-neutron protocol was linked to the early RTOG publications and to local, technical factors. The RTOG 77-04 trial, the first randomized trial with neutrons in prostate cancer, compared photons only with mixed beam therapy. The initial results and their further updates strongly militated in favor of the mixed beam treatment [17, 18, 24]. In addition, the LLN medical facility shared the cyclotron with nuclear physics and astrophysics research and only 3 days a week were dedicated to radiotherapy.

It is worth noting that the mixed photon-neutron beam protocol has also been adopted by the Karmanos Cancer Institute at Wayne State University. Their isocentric, multirod-shaped neutron beam allows for a state-of-the art conformation to prostate cancer. The neutron component of their treatment, however, is slightly less than the one used at LLN. Forman and Porter recently reported on biochemical control according to the pretreatment PSA value [8]. Four-year PFS for patients with a pre-RT PSA level < 10, 10–20 or > 20 ng/mL were 92, 85 and 38 %, respectively. The LLN data, again, compare favorably with these results.

In an attempt to determine the true influence of the neutron component on the present results, overall survival and progression-free survival were also analyzed after stratification for various photon-neutron proportions. The total dose has been unchanged throughout the whole period but, depending on the cyclotron availability (machine breakdown, unplanned arrests, maintenance, etc.) some variations of the respective neutron and photon doses were accepted. This can not be compared to a randomization procedure, and the small numbers allow for imbalance between the groups, but the selection was always unintentional. The analysis has been disappointingly negative. As a continuous variable or in categories (0%, 1–50%, 50–60%, 60–65%, > 65% neutrons) the proportion of neutrons had no impact on the progression-free survival or on overall survival, nor on the biochemical response to treatment (PSA nadir). Corrections for initial hormonotherapy did not alter this negative outcome ($0.2 < p < 0.9$). The lack of impact of neutron proportion on the results is probably related to the too-small number of patients in each subgroup, mainly the group with low neutron/photon proportion, as seen in details on *figure 6*. For example, only 27 patients had less than 30% of neutrons. We are thus thinking that it remains possible that the good survival results in this study despite the generally high initial PSA level may be related to the use of neutrons and not only to the inclusion of 62% of patients with low T stage (T0 to T2), of 76% of patients with well to moderately differentiated tumours and of 34% of patients treated with neoadjuvant hormonal treatment. However, with the relatively short median follow-up (2.8 years, 0–7.8) in this analysis, the survival results must be carefully interpreted.

A new approach to locally advanced prostate adenocarcinoma is neoadjuvant hormonotherapy. The EORTC and RTOG randomized trials both indicated that a significant survival benefit was brought by the combination of androgen deprivation with conventional radiotherapy. A randomized Canadian trial reported on a significantly lower positive biopsy rate 2 years after combined treatment [19]. The age structure of the present series is very similar to the population enrolled in the EORTC 22 863 trial [3]. Also, only grade 3 T1–T2 or all grade T3–T4 were eligible. The 5-year disease-free survival was 48% in the radiotherapy group versus 85% in the combined treatment group. Results from the RTOG 86–10 protocols are less encouraging, although the combined treatment arm does also significantly better: 39% 5-year DFS versus 20% with radiation only [20, 21]. Androgen deprivation was, however, much shorter in the RTOG protocol (about 4 months) than in the EORTC one (3 years).

Regarding androgen deprivation, the 106 patients treated at LLN with neutrons and who received neoadjuvant hormonotherapy had about the same PFS as the 189 who did not receive such a treatment. It is, however, not possible to draw conclusions from this experience because much variation existed regarding the actual protocol of treatment (various drugs, total androgen blockage versus simple anti-androgen treatment, variable duration) and also because it is not unlikely that those patients receiving hormonal therapy also had the most advanced stages. The question of the use of neoadjuvant hormonotherapy in neutron therapy is still to be elucidated.

In conclusion, mixed neutron-photon therapy yielded favourable results regarding both overall survival and progression-free survival, comparing well with the range reported in other series treated with conventional radiotherapy. It is not impossible that the subgroup with unfavorable prognostic factors, namely a PSA > 20 ng/mL, actually did better with an actuarial progression-free survival close to 65% at 5 years.

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