

Curative 3D Conformal Radiotherapy of Non-Operated Prostate Adenocarcinoma at Pointe-a-Pitre University Hospital (Guadeloupe): About 29 Cases

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Abstract

Context: Technological advances have improved the toxicities of radiotherapy. We are evaluating the 3D technique in prostate cancer. **Materials and Methods:** Retrospective study from January 2015 to December 2015 with 29 files. Survival was calculated by Kaplan-Meier method. **Results:** We collected 29 patient records over the study period. The median age was 75 years with the following extremes: 54 years and 83 years. The median PSA level was 12 ng/ml with a range of 3.05 to 79 ng/ml. Gleason score analysis showed 6 patients (20.69%) with a score of 6 (3 + 3), 23 patients (79.31%) with a score of 7 including 12 patients (41.38%) with grade 3 and 11 patients (37.93%) with grade 4. The median dose delivered was 74 Gy, with a mean dose of 73.79 Gy and extremes of 70 Gy for the minimum and 76 Gy for the maximum. Hormone therapy was combined with radiotherapy in 17 patients (58.62%). Seven patients (24.14%) had grade 1 acute bladder toxicity and one patient (3.45%) had grade 2 acute toxicity. Late bladder toxicity was grade 1 in 5 patients (17.24%), grade 2 in 3 patients (10.34%) and grade 3 in 1 patient (3.45%). Late rectal toxicity, grade 2 in 3 patients (10.34%), grade 3 in 1 patient, was noted. Overall survival at 2 years was 100% and 89.65% at 5 years. Relapse-free survival at 2 years was 82.76% and 62.07% at 5 years. There were 3 deaths (10.34%) of which only one was related to prostate cancer. **Conclusion:**

*The first two authors contribute equally.

Radiotherapy, like surgery, is a fundamental option for the treatment of prostate cancers, particularly those that are locally advanced. It is gaining in importance with the improvement of techniques (IMRT, VMAT...) and new fractionations which contribute to the reduction of toxicities and the comfort of patients (shorter spread).

Keywords

Prostate Cancer, 3D Conformal Radiotherapy, Survival

1. Introduction

Prostate cancer is the second most diagnosed cancer in men after lung cancer with 13.7% of cases. It ranks first in terms of incidence in men over 55 years of age [1]. Mortality has been decreasing steadily since 1990, with the rate standardised on the world population falling from 18.1 to 10.2 per 100,000 HA between 1990 and 2012, thanks to improved treatment and access to screening for early diagnosis [2].

In Guadeloupe, over the period 2008-2012, the incidence and mortality were respectively 192.9 and 25.1 per 100,000 HA [3].

Its management is multidisciplinary, with surgery and radiotherapy as the main curative means. Thanks to the progress made by conformal radiotherapy, the results obtained are becoming similar in terms of disease control to those of surgery, as shown by several comparative series. Radiotherapy has therefore become a real alternative to surgery and should be offered to any patient with prostate cancer [4].

Despite the important advances, the availability of techniques is rather heterogeneous.

We report the epidemiological, clinical, therapeutic and prognostic results of patients treated with 3D conformal radiotherapy for prostate adenocarcinoma located at the University Hospital of Pointe-à-Pitre in Guadeloupe.

2. Materials and Methods

2.1. Study Setting

We conducted our study in the radiotherapy department of the Pointe-à-Pitre University Hospital, which is the only radiotherapy centre on the island.

During the period of our study (2015), the department had two Varian linear accelerators (clinac[®] ix and clinac[®] 2100).

2.2. Type of Study and Period

This was a retrospective descriptive study of prostate cancer cases treated at the radiotherapy department of the University Hospital of Pointe-à-Pitre (Guadeloupe) over the period January 2015-December 2015.

2.3. Study Population

Inclusion criteria

- Non-metastatic prostate cancer treated with radiotherapy \pm hormone therapy.
- Absence of any previous specific treatment for prostate cancer.
- Patients were selected according to whether the intake was entirely public that's why the number of patients is small.

Non-inclusion criteria

- Incomplete file or patient lost to follow-up
- All privately treated patients were excluded
- Treatment: Radiation therapy is said to be conformal when the dose of ionising radiation used is delivered homogeneously to a precisely defined tumor volume while sparing the surrounding healthy tissue and organs. A initial three-dimensional imaging for location and repositioning is used. The precise calculation of the dose to be delivered is achieved by computer-controlled multi-blade collimators.

2.4. Data Collection

The data was collected using archived medical records, from Aria software of Varian and Easily from CHU Guadeloupe. A data collection form was drawn up for this purpose.

2.5. Methods of Analysis

Data were entered and analysed in Epi info 7 on Microsoft Excel 2007.

Histograms and other figures were made with Microsoft Excel 2007.

For the quantitative variables (age, PSA, dose, follow up...) we assessed the minimum, maximum, mean and standard deviation. For all qualitative variables, the calculation of frequency and percentage was performed.

The Kaplan-Meier method was used for the survival curves at 2 and 5 years.

2.6. Ethical Considerations

We collected data using anonymised forms with strict confidentiality.

3. Results

The characteristics of the patients are summarized in **Table 1**. 29 patients were collected over a one-year period. All were treated with radiotherapy \pm hormone therapy. The mean age of the patients was 72.7 years, with a minimum of 54 years and a maximum of 83 years. The median age was 75 years. The most representative comorbidity was hypertension in 23 patients (79.31%). The main discovery circumstance was routine screening in 19 patients (65.52%). Rectal examination was abnormal in 15 patients (51.72%). The median PSA level was 12 ng/ml with a range of 3.05 to 79 ng/ml. Gleason score analysis showed 6 patients (20.69%) with a score of 6 (3 + 3), 23 patients (79.31%) with a score of 7 including 12 patients (41.38%) with grade 3 and 11 patients (37.93%) with grade

4. MRI was performed in 26 patients (89.66%) and was contraindicated in 3 patients. It revealed a capsular breakthrough (T3a) in 5 patients (19.23%), seminal vesicle involvement (T3b) in 4 patients (15.38%) and lymph node involvement in 1 patient (3.8%). CT scans were performed in 9 patients (31.03%) and scintigraphy in 25 patients (86.21%). There were no distant locations. The D'AMICO classification found 3 patients (10.34%) classified as low risk, 14 patients (48.28%) as high risk and 12 patients (41.38%) as intermediate risk. All our patients had received 3D conformal radiotherapy for curative purposes. It was combined or not with hormone therapy. The median time to treatment was 5.7 months (2.3 - 23). Pelvic irradiation was performed in 15 patients (51.72%). The median total dose delivered was 74 Gy, with extremes of 70 Gy for the minimum and 76 Gy for the maximum. In all our patients, a classical fractionation was used, *i.e.* 2 Gy per fraction, 5 days a week. Hormone therapy was combined with radiotherapy in 17 patients (58.62%). All patients in the D'AMICO high-risk group received long hormonal therapy and 3 patients in the intermediate-risk group received short hormonal therapy. At the end of treatment, patients were seen in consultation 2 to 3 months later and then once a year, alternating with the referring urologist, with a PSA level. The median follow-up after radiotherapy was 56 months (28 - 66). The median follow-up was 63 months (27.5 - 74.3). Toxicities were assessed according to RTOG criteria. Acute toxicity was defined as all toxicities occurring during treatment and up to 3 months after the end of treatment and all those occurring beyond 3 months were late. Seven patients (24.14%) had grade 1 acute bladder toxicity and one patient (3.45%) had grade 2 acute toxicity. All patients had tolerated treatment well in terms of digestion, with grade 1 symptoms in seven patients (24.14%). Late bladder toxicity was grade 1 in 5 patients (17.24%), grade 2 in 3 patients (10.34%) and grade 3 in 1 patient (3.45%). Late rectal toxicity, grade 2 in 3 patients (10.34%), grade 3 in 1 patient, was noted. Biological remission was achieved in 28 patients (96.55%), with only one patient showing biological progression. The median time to nadir was 23.5 months (2-52). During the follow-up, biological relapse was noted in 7 patients (24.14%) associated in 2 patients with a local focus on exploration (PET-choline) and in 3 patients with secondary bone locations. Overall survival at 2 years was 100% and 89.65% (26 patients) at 5 years (**Figure 1**). Relapse-free survival at 2 years was 82.76% (24 patients) and 62.07% (18 patients) at 5 years (**Figure 2**). There were 3 deaths (10.34%) of which only one was related to prostate cancer and the other 2 to pancreatic cancer and biliary cancer respectively.

4. Discussion

Prostate cancer is the most common cancer in France, accounting for 16% of all cancer cases and 28% of cases in men. The number of new cases observed in 2011 was 53,917 [2].

In the French West Indies, the incidence of prostate cancer and its mortality are higher than in metropolitan France (50% of incident male cases 140/100,000), this is related to the African ethnic origin of the majority of this island population

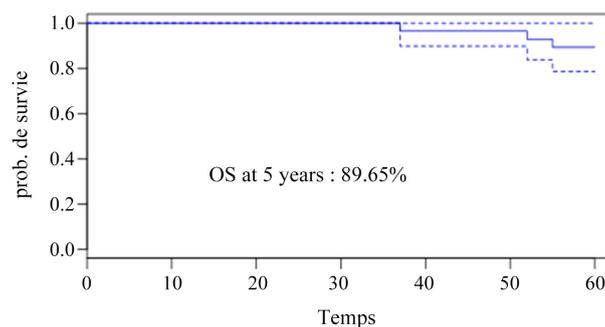


Figure 1. 5-year overall survival curve.

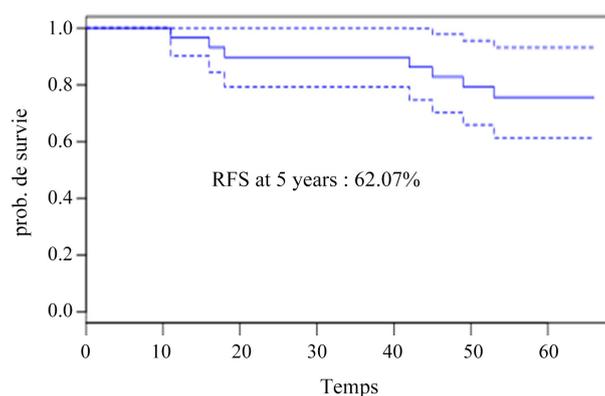


Figure 2. Relapse-free survival curve at 5 years.

Table 1. Characteristics of patients with localized prostate cancer.

Characteristics of patients	headcount (percent)
Median age (years)	75 (54 - 83)
HTA	23 (79.31%)
Diabetes	12 (41.38%)
heart disease	3 (10.34%)
CRI	1 (3.45%)
Systematic screening	19 (65.52%)
Urinary signs	10 (34.48%)
Performance status	
0	20 (69%)
1	8 (28%)
2	1 (3%)
TR abnormal	15 (51.72%)
Median PSA (ng/ml)	12 (3.05 - 79)
Gleason	
-6 (3 + 3)	6 (20.69%)
-7 (3 + 4)	12 (41.38%)
-7 (4 + 3)	11 (37.93%)
Classification of D'AMICO	
-High risk	14 (48.28%)
-Low risk	3 (10.34%)
-Middle risk	12 (41.38%)

CRI: Chronic renal insufficiency, PSA: prostate specific antigen, TR: rectal touch, HTA: high blood pressure.

and probably to environmental pollution by chlordecone [5].

The average age at diagnosis is 70 years (54,55). In sub-Saharan Africa, in the series by M. NDOYE [6] and M. GUEYE [7], the mean age was 71 and 69 years respectively. In our study, the mean age was 72.68 years.

Prostate cancer screening remains controversial. This controversy has been reinforced by the apparently conflicting specific mortality results of the 2 largest randomised studies: PLCO and ERSPC [8] [9]. However, prostate cancer screening has proven its ability to decrease disease-specific mortality. In our study, the main finding was individual screening in 19 patients (65.52%). This last result could be explained by the high prevalence of prostate cancer in the French West Indies.

All our patients had adenocarcinoma with a Gleason score of 7 in 69.31% of the population. In Mouhamadou Bachir Ba's study, 35.5% had a Gleason score of 7. However, the majority of his patients (70.9%) were at high risk of AMICO compared to 48.28% in our series [10].

Prostate MRI is a powerful examination for the detection of so-called "significant" lesions. Multiparametric MRI offers the greatest accuracy in the diagnosis and staging of prostate cancer [11] [12]. Its place before biopsy is suggested by Fourcade *et al.* who concluded that pre-biopsy prostate MRI and the PIRADS score appear to be good predictive tools for the diagnosis and assessment of prostate cancer aggressiveness. In addition to aiding diagnosis and extension assessment, MRI has an important role in defining target volumes.

It was performed in 26 patients (29.66%) in our series with informative results on local extension. Bone scintigraphy is the reference examination for the detection of bone metastasis [13]. The sensitivities and specificities of scintigraphy reach more than 90% - 95%, especially since the appearance of hybrid cameras, which make it possible to carry out a tomoscintigraphy (SPECT or Single Photon Emission Computed Tomography) coupled with a bone scan. The sensitivity of the bone scan depends mainly on the PSA level. It detects metastases significantly from a PSA threshold > 20 ng/ml. In our series, 25 patients (86.21%) were scanned.

Radiotherapy plays a key role in the therapeutic management of patients with prostate cancer at different stages of progression. This role has been further strengthened by a better understanding of radiobiology and technical advances that allow the delivery of larger doses with fewer side effects.

3D conformal radiotherapy followed on from 2D radiotherapy, and had allowed an increase in the dose to the prostate to 74 Gy. DEARNALEY *et al.* [14] compared a conformal technique with a conventional technique in 225 patients at a dose of 64 Gy. There was no significant difference in bladder toxicity, however rectal toxicity was a determining and limiting factor (56% grade 1 rectitis versus 37% and 12% versus 3% for grade 2).

No significant difference was observed in local control or overall survival [14].

The constant evolution of techniques has made conformal radiotherapy with intensity modulation (IMRT) the technique indicated for the treatment of pros-

tate cancer. IMRT reduces late toxicity compared with conventional RT at equivalent dose and increases the dose delivered to the tumour without significantly increasing toxicity [15].

However, in developing countries, 3D conformal radiotherapy is the most widely used technique.

The PROTECT trial, with more than 20% of patients presenting with intermediate stage at diagnosis, confirms the equivalence in specific survival between surgery and irradiation at 10 years.

In 2015, all 29 patients in our series had been treated with 3D conformal radiotherapy combined with hormone therapy in 17 patients (58.62%).

Lymph node irradiation has shown discordant results with no demonstrated benefit in the two phase III trials specifically evaluating its value (GETUG P01; RTOG94-13) (evidence level 2). Randomised trials demonstrating the value of irradiation in high-risk or locally advanced tumours have all included lymph node irradiation [15].

Pelvic irradiation concerned 51.72% of patients compared with 16.8% in the Pontvert study [16].

Hypofractionation is a real alternative with an enormous gain in machine time. In the high-risk group, an Italian study randomised 168 patients in a phase III trial to fractionated prostate RT at 80 Gy (2 Gy per fraction) compared with hypofractionated RT at 62 Gy (3.1 Gy per fraction) combined with 9 months of HT [17]. SSRB favoured hypofractionated therapy at 3 years (87% vs 79%, $p = 0.035$) in an initial analysis [17]. In a more recent publication with a follow-up of 70 months, neither local nor distant control was significantly improved in the hypofractionated arm compared with fractionated RT. The SSRB was improved by 10.2% but not significantly (85% vs 74%, $p = 0.065$) [17]. The English Conventional or Hypofractionated Highdose Intensity Modulated

Radiotherapy in Prostate Cancer (CHHiP) trial randomised over 12% of high-risk patients to a non-inferiority comparison of RT without pelvic irradiation between a standard 74 Gy/2Gy per fraction regimen and two hypofractionated doses of 60 Gy and 57 Gy at 3 Gy per session [18]. Neoadjuvant and concurrent (3 - 6 months) HT could be combined. The efficacy results for patients <75 years (85% of the population) in BRSC at 5 years are relatively similar between arms, 88.9%, 90.5% and 85.5% for 74, 60 and 57 Gy respectively [18].

Hormone therapy was superior to exclusive RT for local control, biochemical control, metastasis and overall survival at 10 years in the EORTC study: 40% vs 58% ($p = 0.0004$); RTOG 85-31: 38% vs 47% ($p = 0.0043$) [19] [20].

The indication for hormone therapy was met in patients in the intermediate unfavourable and high risk groups. Patients in the intermediate-favourable group only received exclusive radiotherapy. Indeed, Zumsteg *et al.* reported that patients in the intermediate group without poor prognostic factors (Gleason 3 + 4, less than 50% positive biopsies) had an excellent outcome when treated with exclusive radiotherapy [21].

Radiotherapy was well tolerated by patients, with no acute urinary or digestive toxicity of grade > 2 noted in our series. Indeed, acute urinary toxicity grade 1 and 2 were respectively 24.14% and 3.45% and digestive toxicity was grade 1 in 10 patients (34.48%). These results are lower than those reported by Pollack, Beckendorf and Peeters, which could be explained by the small number of patients [22] [23]. Late toxicity was relatively lower than in the literature.

The 5-year relapse-free survival in our series was 62.07%, which is comparable to that reported by Bolla, Mottet and Afshin of 75%, 64.7% and 65.1% respectively [24] [25].

Regarding 5-year overall survival, Bolla reported an OS of 78% and the RTOG 92-02 trial (phase III), conducted by Hanks *et al.*, reported an OS of 80% [24] [26]. The overall survival at 5 years was 89.65% in our study.

The limitations of our study lie in the fact that it is a retrospective series with a small number of patients.

Nevertheless, our series shows that 3D radiotherapy, apart from toxicities, gives good results in local control and survival.

5. Conclusion

Radiotherapy, like surgery, is a fundamental option for the treatment of prostate cancers, particularly those that are locally advanced. It is gaining in importance with the improvement of techniques (IMRT, VMAT...) and new fractionations which contribute to the reduction of toxicities and to the comfort of patients (shorter spread).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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