



Intensity-modulated radiotherapy for prostate cancer with seminal vesicle involvement (T3b) : multicentric retrospective analysis

Flora Goupy

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Flora Goupy. Intensity-modulated radiotherapy for prostate cancer with seminal vesicle involvement (T3b) : multicentric retrospective analysis. Life Sciences [q-bio]. 2018. dumas-02145665

HAL Id: dumas-02145665

<https://dumas.ccsd.cnrs.fr/dumas-02145665>

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THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1
sous le sceau de l'Université Bretagne Loire

Thèse en vue du
DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

présentée par

Flora GOUPY

Née le 10 Décembre 1989 à St-Nazaire

**Radiothérapie avec
modulation
d'intensité des
cancers de prostate
avec envahissement
des vésicules
séminales (T3b): une
étude multicentrique
rétrospective**

**Thèse soutenue au Centre Eugène
Marquis, Rennes
Thèse soutenue au Centre Eugène
Marquis, Rennes
Le 31 Mai 2018**

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REMERCIEMENTS :

Pr BENSALAH Karim : Merci d'avoir accepté de présider mon jury de thèse et de votre disponibilité.

Dr SUPLOT Stéphane : Merci d'avoir participé à cette étude multicentrique et d'avoir permis une accessibilité facile aux dossiers patients de la cohorte nantaise après les avoir sélectionnés. Merci de me recevoir prochainement en stage de radiothérapie pour mon dernier semestre d'interne au sein de votre service au Centre René Gauducheau.

Dr LE PRISÉ Élisabeth : Merci pour la riche formation professionnelle et humaine que j'ai pu recevoir au sein de votre service lors de mon internat. Le Centre Eugène Marquis restera toujours pour moi ma maison mère de formation. En vous souhaitant une très bonne continuation pour la suite de votre parcours.

Pr DE CREVOISIER Renaud : Merci de m'avoir confiée ce travail de recherche et permis grâce à votre réseau de professionnels d'étendre mon recueil à cinq autres institutions. Merci pour les innombrables heures accordées à la réalisation de ce travail et m'avoir accompagnée pour ma thèse d'exercice en tant que directeur de thèse.

Merci aux Dr PASQUIER David, Dr LATORZEFF Igor, Dr SCHICK Ulrike, Dr MONPETIT Érik, G. MARTINAGE pour leurs participations à ce recueil multicentrique.

Merci au Dr LE PROUST Bernadette pour son aide dans la relecture des imageries IRM de prostate.

Merci au Dr CASTELLI Joël pour son aide à la réalisation des statistiques et des figures de l'étude.

Merci à l'équipe des manipulateurs et des physiciens, en particulier Chloé HERVÉ et Nicolas PERICHON pour l'aide apportée à ce travail.

Merci à l'ensemble de professionnels de santé et aux patients que j'ai pu rencontrer tous le long de ma formation qui m'ont tant appris et me font aimer ma vocation au quotidien.

Merci à Kévin AHRWEILLER, à ma famille et à mes amis de m'avoir accompagnée dans ces études de médecine.

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Abstract

Objectives: No studies have reported data of external beam radiotherapy for specifically prostate cancer with seminal vesicle involvement (ISV). The objective of this study was to analyze the dose distribution and the clinical outcome in a large series of patients having received IMRT for T3b prostate cancer.

Materials and methods: This retrospective analysis included all patients having received IMRT and androgen deprivation therapy for T3b prostate cancer, between 2008 and 2017 in six French institutions, with available MRI images and dosimetric data. A dosimetric analysis was performed, in particular regarding the ISV. Recurrences, survivals and toxicities (CTCAE v4.0) were analyzed.

Results: A total of 276 T3b patients was included. The mean follow-up was 35 months. The mean (range) prescribed doses to the prostate and to the ISV were 77 Gy (70-80) and 68 Gy (46-80), respectively. The dose constraints recommendations were exceeded in less than 12% of patients for the rectum and the bladder. The 5 year risks of biochemical and clinical recurrences and cancer specific death were 24.8%, 21.7% and 10.3% respectively. The 5 year risks of local, pelvic lymph node and metastatic recurrences were 6.4%, 11.3% and 15%, respectively. Lymph node involvement was the only significant prognostic factor on clinical recurrence (HR 2.90, $p=0.005$) and cause specific survival (HR 4.45, $p=0.017$). Grade ≥ 2 acute and 5 year late toxicity rates were 13.2% and 12% for digestive toxicity, and 34% and 31.5% for urinary toxicity. The dose to the pelvic lymph node was predictive of late digestive toxicity.

Conclusion: IMRT for T3b prostate cancer allows delivering a curative dose in the ISV in the majority of cases, with a moderate digestive toxicity but a higher urinary toxicity. Local control appears relatively high and the main pattern of recurrence is metastasis. Lymph node involvement increases both the risk of digestive toxicity and recurrence.

Introduction

The standard of care of locally advanced prostate adenocarcinoma is radiotherapy combined with 2 to 3 years of androgen deprivation therapy (ADT) (1,2). The T3 stage includes both T3a stage defined as cancer extracapsular extension and T3b as cancer invasion of one or both seminal vesicles (ISV) (3). Even if the “T” staging of D’Amico risk group classification (4) is based on digital rectal examination (DRE), magnetic resonance imaging (MRI) is recognized as the most useful and accurate modality to detect, characterize and stage prostate cancer for almost a decade. In particular, if the MRI sensitivity is low for ISV detection (around 60%), its specificity is however particularly high (around 95%), according to a meta-analysis including 34 studies (5). The prediction of ISV, confirmed by surgery, is thus statistically increased by adding MRI at clinical-based models such as Partin tables or CAPRA score, with AUC increasing from 0.75 to 0.82, and from 0.75 to 0.83, respectively (6). Among new diagnostic localized prostate cancer, the incidence of T3 stage at DRE is estimated around 7% in the NCI’s Surveillance, Epidemiology, and End Results (SEER) database (7). On MRI, the incidence of T3a and T3b stages has been reported around 20% and 10%, respectively (8–10). After radical prostatectomy, pathological ISV ranged from 5% to 18%, depending on the studies and patient selection (11–18).

The increasing number of T3b prostate cancer rises the issues of both the radiation technique and the clinical results of external beam radiotherapy (EBRT), in terms of toxicity and carcinologic results. Thus, delivering high curative dose in the ISV by EBRT is particularly challenging for respecting the dose constraints in the rectum and the bladder (19–21). In prostate cancer, intensity-modulated radiotherapy (IMRT) has shown to dramatically improved dose distribution compared to “standard” 3D conformal RT (3D-CRT), allowing therefore prostate dose escalation (≥ 76 Gy), while not increasing toxicity (22–24). To our knowledge, no study reported clinical results of EBRT and in particular IMRT, specifically for T3b cancer. The possibility of escalating the dose in the ISV, while respecting the dose constraints in the organs at risk (OAR), is therefore not clearly established.

The objectives of this retrospective multicentric study was, in case of IMRT for T3b prostate cancer, to analyze the dose received by the ISV and the OARs, and the patient outcome.

Patients and methods

Inclusion criteria, initial staging, treatment and follow-up

Our retrospective analysis included all patients with T3b N0-1 M0 prostate adenocarcinoma having received IMRT in combination with ADT, in six French institutions (Rennes, Nantes, Lille, Toulouse, Brest and Vannes) between 2008 and 2017, with available MRI images, dosimetric and clinical data. Only patients with ISV on MRI pre-therapeutic were included (T3b stage). Patients treated with prostatectomy were excluded. All the patients had prostate biopsy showing adenocarcinoma. Seminal vesicle (SV) biopsy was performed in a subset of patients only. The initial staging included DRE, PSA measurements, Gleason score, pelvic computed tomography, pelvic MRI and Tc99m bone scintigraphy.

The multiparametric prostate MRI included T1- and T2-weighted (T1- and T2-WI), diffusion-weighted imaging (DWI) and dynamic contrast enhanced imaging with 1.5 Tesla magnet without an endorectal coil. On T2-WI, ISV was defined as SV disruption or loss of the normal architecture, focal or diffuse areas of low signal intensity, low signal intensity causing a mass effect, or evident tumor at the prostate base extending to SV. On DWI, ISV was defined as low focal signal lesions relative to benign prostate tissues on apparent diffusion coefficient maps within the SV. Asymmetric or irregular SV wall enhancement was also considered as ISV on dynamic T1-WI (25). Approximately 50% of MRI images were subjected to a second independent reading by an expert radiologist (35 years of experience). The length of ISV was defined on MRI in three thirds in the cranio-spinal axis. The lymph node involvement (N1) was defined as pelvis node ≥ 8 mm or lombo-aortic node ≥ 10 mm in the smallest diameter on MRI (26).

The patients needed to be treated with a curative intent. The total dose delivered to the prostate and the ISV had therefore to range from 70 to 80 Gy and 46 to 80 Gy respectively, at a standard fraction of 2 Gy. The target delineation and dose distribution had to be performed according to the French Study Group on Urogenital Tumors (GETUG) guidelines (21,27). Patients underwent simulation and treatment in the supine position. Intravenous iodine contrast was required. At the time of simulation, there was no recommendations concerning bowel or bladder filling. During treatment, patients had to keep a full bladder. The target volume and

OARs (bladder, rectum, bulb and femoral heads) were delineated on CT slices, whose spacing was 2 or 3 mm. The planning target volume (PTV) margins were defined as 5 to 10 mm around the prostate and SV, except in the posterior direction, where the margin was limited to 5 mm. The rectal wall was generated with a thickness of 5 mm from the external manually delineated rectal contour. The rectal length was defined as 1 cm below the PTV. The bladder wall was generated with a thickness of 7 mm from the external manually delineated bladder contour. The dose volume histogram had to respect the GETUG recommendations (21,27), for the rectum $V60 \text{ Gy} \leq 50\%$, $V72 < 25\%$ with a maximum dose of 76 Gy, for the bladder $V60 \text{ Gy} < 50\%$, $V70 < 50\%$ with a maximum dose of 80 Gy, and for the femoral heads $V55 < 5\%$. IMRT could use 6 to 23-MV X-rays beams.

The follow-up consisted in clinical assessments and PSA measurements repeated every 6 months. Imaging (pelvic MRI, CT scan and bone scan) was performed in case of biochemical progression or suspicion of clinical recurrence.

Endpoints and statistical analysis

The dosimetric charts were analyzed to report the doses received by each PTV and clinical target volume (CTV) for the prostate, not-involved SV and ISV (considering each third of the SV), not-involved and involved pelvic lymph node. The doses to the rectum and bladder were reported according to the recommendations of the GETUG (21,27), RTOG (28) and QUANTEC (29). Pearson correlation coefficients (r) were calculated to search correlation between the doses to the OARs and the volumes or the doses of the target volumes, in particular the length of the ISV. Significant correlations with $r > 0,5$ were only reported.

The follow-up was defined as the time between the date of first day of RT and latest news. Follow-up was calculated using reverse Kaplan-Meier estimation (30).

Biochemical recurrence was defined as a PSA level equal to or greater than the PSA nadir plus 2 ng/mL or the initiation of salvage ADT (31). Clinical recurrence was defined either by local recurrence, pelvic lymph node recurrence or metastasis. DFS was defined as the time between the date of first day of RT and one of the following event, when occurring: biochemical recurrence, clinical recurrence or death. Kaplan-Meier analysis was used to calculate the risk of biochemical and clinical recurrences, prostate cancer and overall deaths. Univariate and

multivariate Cox regression analysis were performed to identify predictors of recurrences and survivals. Log-rank test was used to test the impact of categorical parameters. The following parameters were tested for recurrences and survivals: age, T stage at DRE, PSA, Gleason score, number of D'amico risk factor, MRI parameters such as extracapsular extension, bilateral prostate or SV involvements, length of ISV, pelvic lymph node involvement, pathological parameters such as number of positive biopsy in the prostate and SV when performed, dosimetric parameters such as the doses received by the target volumes and ADT duration.

Acute and late digestive and urinary toxicities were scored in accordance to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The toxicities were acute when occurred within 90 days after the start of RT and late otherwise. Logistic regression tests were used to identify quantitative parameters related to acute toxicity. Kaplan-Meier analysis were used to calculate the risk of late toxicity. Univariate and multivariate Cox regression analysis were performed to identify predictors of late toxicity (grade ≥ 2). The following parameters were tested for toxicity: age, arterial hypertension, cardiovascular disease, diabetes, anticoagulant treatment, history of pelvic surgery, T stage at DRE, MRI parameters such as bilateral SV involvement, length of ISV, pelvic lymph node involvement, dosimetric parameters such as the doses received by the target volumes and the OARs.

Statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA), and R version 3.4.3 (GNU Project, Lucent Technologies).

Results

Patients, tumor and treatment characteristics

A total of 276 patients was analyzed. Patients and tumor characteristics are detailed in Table 1. Details are provided regarding in particular MRI tumor characteristics.

The median and mean (range) prescribed doses to the prostate, to the not-involved SV and ISV at MRI, to the not-involved pelvic lymph nodes and involved lymph nodes at MRI were 77 Gy and 77 Gy (70-80), 50 Gy and 57 Gy (46-80), 76 Gy and 68 Gy (46-80), 50 Gy and 49 Gy (46-55) and 50 Gy and 52 Gy (46-74), respectively. The prescribed doses to the ISV and the not-

involved SV were equal to or greater than 70 Gy for 64% and 22% of patients, respectively. The pelvic lymph nodes without lymph node involvement were treated at a prophylactic dose in 90% of cases. The mean radiotherapy duration was 56 days (range: 14-77).

The IMRT technic was based on the use of five-field beam in 30% of patients, volumetric modulated arc therapy in 45%, and tomotherapy in 25%. Image-guided radiotherapy (IGRT) for prostate was used in 71% of patients.

The dosimetric characteristics of the prostate, the ISV and non-involved SV by each third of SV are displayed in Table 2 and Figure 1 (Rennes series only, 106 patients). The dosimetric characteristics for the rectum and the bladder are displayed in Table 3 (whole series). The prostate PTV D95 was correlated to the rectum V72 ($r=0.53$, $p<0.01$). The percentages of cases not respecting the dose constraints for the rectum and the bladder are also displayed in Table 3, ranging from 0% to 12% of patients depending on the OAR and the recommendation.

The mean duration of ADT was 23 months (3-99).

Carcinologic results and prognostic analysis

The mean follow-up was 35 ± 3 months. Five-year biochemical and clinical recurrences rates were 24.8% (95% confidence interval (CI): 15.0-34.6%) and 21.7% (95% CI: 12.5-30.9 %), respectively (Figure 2). Regarding clinical recurrence, 5-year local, pelvic lymph node and metastatic recurrence rates were 6.4% (95% CI: 0.6-12.2%), 11.3% (95% CI: 3.7-18.9%) and 15% (95% CI: 7.8-22.2%), respectively (Figure 3). Five-year DFS, cause specific survival and overall survival rates were 65.8% (95% CI: 55.6-76.0%), 89.7% (95% CI: 82.9-96.5%) and 78.8% (95% CI: 70.2-87.4%), respectively (Figure 2).

In multivariate analysis, the only significant prognostic factor was lymph node involvement for biochemical recurrence (hazard ratio (HR) 2.94, 95% CI: 1.47-5.87, $p=0.002$), for clinical recurrence (HR 2.90, 95% CI: 1.38-6.08, $p=0.005$), for DFS (HR 1.89, 95% CI: 1.08-3.32, $p=0.026$) and for cause specific survival (HR 4.45, 95% CI: 1.30-15.21, $p=0.017$) (Figure 4).

Digestive and urinary toxicity rates and predictors of toxicity

Acute digestive toxicity rates were 86.8% for grades 0-1, 11% for grade 2, and 2.2% for grade 3. Not-involved SV dose was the only significant predictor of acute grade ≥ 2 digestive toxicity (HR 1.08, 95% CI: 1.04-1.13, $p < 0.001$). Five-year late digestive grade ≥ 2 toxicity rate was 12% (95% CI: 6.8-17.2%). Five patients (1.8%) presented late digestive grade 3 toxicity and none had grade 4 toxicity. In multivariate analysis, significant predictors of grade ≥ 2 late digestive toxicity were pelvic nodes dose (HR 1.13, 95% CI: 1.05-1.22, $p = 0.002$) (Figure 5) and age (HR 1.09, 95% CI: 1.03-1.16, $p = 0.007$).

Acute urinary toxicity rates were 66% for grades 0-1, 31.4% for grade 2 and 2.6% for grade 3. One patient stopped the radiotherapy course because of grade 3 urinary toxicity. Five-year late urinary grade ≥ 2 toxicity rate was 31.5% (95% CI: 23.3-39.7). Five patients (1.8%) presented late urinary grade 3 toxicity and none had grade 4 toxicity. No parameter was identified as predictor of acute or late urinary toxicity.

Discussion

This retrospective multicentric study is the only one reporting the experience of IMRT for T3b prostate cancer. Involved SV were treated to a curative dose (≥ 70 Gy) in the majority of cases (64%). The dose-volume recommendations were exceeded in less than 12% of patients for the rectum and the bladder. Digestive toxicity (grade ≥ 2) appeared moderate with acute and 5 year late toxicity rates of 13% and 12%, respectively. Urinary toxicity was higher, with acute and 5 year late toxicity rates of 34% and 31%, respectively. Overall, the 5 year risk of biochemical recurrence was 25%, corresponding to a low risk of local recurrence (6%) but to a high risk of metastases (15%). At 5 years, the risk of prostate cancer death was 10%.

Escalating the dose in the ISV exposes potentially the patient to an increased risk of toxicity. In our study, IMRT allowed dose escalation in ISV while respecting the dose constraints for the OARs in more than 85% of cases. The dose to the ISV depended however on the involved third of the SV, the distal involved third receiving less dose than the proximal third close to the prostate (Figure 1). Moreover, the non-involved SV received also a high dose (mean dose ≥ 63 Gy) (Table 2), depending also on the non-involved SV third (Figure 1). By escalating the dose (≥ 76 Gy) in the prostate only by IMRT, the literature shows that 5 year digestive and urinary

toxicity rates range from 5% to 15%, and from 10% to 24%, respectively (22,23,32–35). Regarding digestive toxicity, these results appear therefore comparable to our study (5 year rate of 12%). Our rate of urinary toxicity appears however quite higher (5 year rate of 31.5%), despite the systematic use of IMRT and the use of IGRT in the majority of cases. Reducing SV PTV below 5 mm when treating with IMRT combined with daily IGRT appears however not indicated to reduce toxicity. Indeed, SV presents deformations and move independently from the prostate, with a motion magnitude larger than the prostate even if the increasing tumour infiltration in the SV has been shown to reduce their mobility (36,37).

The large majority of reported treatment for T3b prostate cancer is based on surgical experience, likely in selected patients (Table 4). We found only four studies reporting specific results for T3b prostate cancer treated by radiation, based on the combination of EBRT and brachytherapy (BT) (38–40) or BT only (41) (Table 4). Our carcinologic results appear thus comparable with surgical series for pT3bN0 cancer, where the 5-year biochemical DFS rate ranges from 21% to 70% (66% in our study), the 5-year cause specific survival rate ranges from 94% to 98% (90% in our study) and the 5 year overall survival rate ranges from 86% to 93% (79% in our study) (11–16,42–46). ADT impacts also on the results as strongly demonstrated in case of RT and also shown in case of surgery. Indeed, Moschini *et al* found, in their very large series of 3279 T3b patients, that ADT improved DFS (HR=0.5), cause specific survival (HR=0.62) and overall survival (HR=0.75) (42). It must be pointed out however that such retrospective comparison between treatments must be considered with cautious due in particular to biases in patient and tumor selections (highest PSA and Gleason score in our RT series compared to the reported surgical studies).

Our results can also be compared to series of “overall” locally advanced prostate cancer treated with the most “standard” treatment combining EBRT (with or without prostate dose escalation) and long duration ADT. The 5-year biochemical DFS and cause specific survival rates appear comparable, ranging from 62% to 82% and from 91% to 95% in the literature *versus* 66% and 90% in our study, respectively (47–51).

The best mean for dose escalation is BT. Indeed, the superiority of the combined treatment over EBRT only has been demonstrated in series comprising both intermediate and high risk prostate cancer, in terms of biochemical control in three randomized studies (52–55), of metastases and even of overall survival in large national database (56). More recently, in high risk prostate cancer and after adjustment for prostate cancer prognostic factors, other medical

conditions, and socio-economic factors, the combination of BT to EBRT or radical prostatectomy have been shown to provide higher overall survival than EBRT combined with ADT for high risk prostate cancer (57). The proportion of T3 cancer treated by surgery was however small in this study. A limited number of four studies comprising a relative small number of patients (≤ 80) reported results of combined BT for T3b prostate cancer (Table 4) (38–41). Despite technique considerations with difficulties to ensure needles to the distal parts of SV, more than 80% of the entire SV volume received a dose escalation (39). Our carcinologic results appears slightly lower than those reported with the combined treatment with 5-year DFS and cause specific survival rates ranging from 70% to 82% and around 95% *versus* 66% and 90% in our study, respectively. Rades *et al* found in particular that BT dose escalation in SV compared to BT without dose escalation increased of 22% the 3 year DFS (39). These BT series excluded however the patients with lymph nodes involvement at imaging.

In surgical studies, the lymph node involvement has been shown to be the most significant prognostic factor of biochemical recurrence (HR=2.1), DFS (HR=2.88) and cause specific survival (HR=2.4) (13,17). Indeed, in case of ISV, the incidence of lymph node involvement is particularly high, ranging from 12% to 38% in the surgical series (12,13,15,17,42,43,58,59) (and 26% in our series identified on MRI). The lymph node involvement was also identified in our study as a significant prognostic factor of biochemical recurrence (HR=2.94), clinical recurrence (HR=2.90), DFS (HR=1.89) and cause specific survival (HR=4.45). Others poor prognosis factors like high Gleason score (≥ 8), high tumor infiltration on prostate biopsy, extracapsular extension and bilateral ISV were also identified as independent poor prognostic factor in several surgical and BT series (11,13,17,40,60), but not in our experience.

Our studies comprises several limitations. The follow-up is short (35 months), explained by the recent generalization and accessibility of MRI at initial staging. It implies that urinary toxicity must be interpreted with precaution knowing the possibility of late events. Moreover the analysis is retrospective, justifying the analysis of high grade of toxicity only (grade ≥ 2). Finally, a very small proportion of patients (8%) had SV biopsy confirming the ISV. Our patients are however likely to have true pathological ISV, as suggested by the high specificity of MRI for ISV (5).

Conclusion

We reported the most important series of EBRT for T3b prostate cancer. IMRT combined with IGRT allows delivering a high curative dose (≥ 70 Gy) in the ISV, while rarely exceeding dose constraints. Late digestive toxicity was low but urinary toxicity was slightly increased, compared to the literature reporting high dose to the prostate only. Local control appears high and the main pattern of recurrence is metastasis, mostly related to lymph node involvement at diagnosis. More follow-up is needed to confirm the results due to the relative recent use of MRI allowing characterizing ISV. The combined MRI Linac may even more improves the results by a better IGRT targeting.

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PATIENTS CHARACTERISTICS	
Age (years) *	69 (42-86)
Comorbidities (%)	
Arterial hypertension	41
Cardiovascular disease	23
Diabetes	13
Anticoagulant treatment	29
History of pelvic surgery	31
D'AMICO TUMOR CHARACTERISTICS	
PSA (ng/mL) *	27 (2-217)
T Stage at DRE (%)	
T1	11
T2	35
T3	54
Gleason score (%)	
≤ 6	7
7 (3+4)	27
7 (4+3)	24
8	24
9-10	18
Number of high risk factor (%)	
One (T3 only)	21
Two	65
Three	14
BIOPSY CHARACTERISTICS	
Total prostate biopsy *	12 (2-24)
Positive prostate biopsy *	8 (1-21)
Patients with SV biopsy (%)	8
Positive SV biopsies (%)	86
MRI TUMOR CHARACTERISTICS (%)	
Extracapsular extension	73
Bilateral prostate involvement	68
Bilateral involved SV	41
Length of involved SV	
Proximal 1/3	64
Proximal 2/3	20
Entire SV	16
Lymph node involvement	26

Table 1: Patient and tumor characteristics

*mean value (range); DRE: digital rectal examination; SV: seminal vesicle

PROSTATE		
PTV D95	74 (70-76)	
CTV D99	75 (70-80)	
INVOLVED SEMINAL VESICLES		
	PTV D95	CTV D99
Overall ISV	72 (53-79)	73 (54-80)
If ISV limited at proximal 1/3	73 (58-79)	74 (54-80)
If ISV limited at proximal 2/3	74 (63-77)	75 (65-78)
If ISV for the entire SV	67 (54-72)	69 (55-78)
NOT INVOLVED SEMINAL VESICLES		
	PTV D95	CTV D99
Overall not involved SV	63 (49-77)	66 (50-78)
If not ISV limited at distal 2/3	63 (49-77)	65 (50-78)
If not ISV limited at distal 1/3	63 (51-76)	68 (53-77)

Table 2: Dosimetric characteristics of the prostate and the seminal vesicles (non-involved and involved) depending on the length of seminal vesicle involvement on MRI (Rennes sub-group only, 106 patients)

Mean value (range) in Gy; Dx: dose recieved in x% of the targetvolume; PTV: planning target volume, CTV: clinical target volume, ISV: involved seminal vesicles on MRI

V_x	MEAN VALUES AND % OF PATIENTS OVER THE THRESHOLD V_x VALUE	RECTUM	BLADDER
V50	Mean value (range) (Gy)	37 (10-94)	38 (6-96)
	% of patients with V50 \geq 50% &	10	-
V60	Mean value (range)	23 (5-61)	26 (2-71)
	% of patients with V60 \geq 50 % °#	0	7
	% of patients with V60 \geq 35 % &	6	-
V65	Mean value (range) (Gy)	18 (3-47)	21 (2-60)
	% of patients with V65 \geq 50 % #&	-	5
	% of patients with V65 \geq 35 % #	1	-
	% of patients with V65 \geq 25 % &	12	-
V70	Mean value (range) (Gy)	12 (1-27)	16 (0-51)
	% of patients with V70 \geq 50 % °	-	0
	% of patients with V70 \geq 35 % #&	-	6
	% of patients with V70 \geq 20 % #&	8	-
V72	Mean value (range) (Gy)	9 (0-22)	-
	% of patients with V72 \geq 25 % °	0	-
V75	Mean value (range) (Gy)	3 (0-14)	9 (0-40)
	% of patients with V75 \geq 25 % #&	-	5
	% of patients with V75 \geq 15 % #&	0	-
	% of patients with V75 \geq 5 % (61)	21	-

Table 3: Dosimetric characteristics for the rectum and the bladder according to the recommendations (in the whole series)

V_x: Dose-volume threshold recommendations (volume of organ receiving at least x Gy in %) according to the GETUG (°) (21,27), RTOG (#) (28), QUANTEC (&) (29) recommendations

TREAT MENT	STUDIES	N	PATIENTS AND TUMOR CHARACTERISTICS				ADJUVANT TREATMENT			CARCINOLOGIC RESULTS				
			Age (Y)	PSA (ng/m)	Gleason score (%)*	N1*	ADT	RT	ADT and RT	Follow-up (months)	DFS (%)	MFS (%)	CSS (%)	OS (%)
Surgery	Moschini (42)	3279	65	22	6: 17% 7: 46% 8-10: 37%	38%	36%	14%	8%	148	5-Y: 50 10-Y: 36	-	5-Y: 94 10-Y: 86	5-Y: 90 10-year: 73
	Hubanks (11)	1132	66	10	6: 27% 7: 49% 8-10: 24%	No	30%	12%	-	127	10-Y: 41	10-Y: 81	5-Y: 96 10-Y: 89	10-Y: 59
	Pierorazio (12)	989	60	10	6 : 10% 7 : 55% 8-10 : 35%	25%	28%	5%	-	160	5-Y: 38 10-Y : 25	5-Y: 83 10-Y: 70	5-Y: 94 10-Y: 81	-
	Secin (13)	387	62	11	6-7: 83% 8-10: 17%	24%	No	No	No	68	5-Y: 38	-	5-Y: 96 10-yY: 85	-
	Siddiqui (14)	382	66	4	6: 27% 7: 48% 8-10: 25%	No	50%	No	No	120	5-Y: 70 with ADT and 32 without 10-Y: 60 with and 16 without	5-Y: 93 with ADT and 88 without 10-Y: 88 with ADT and 78 without	5-Y: 98 with ADT and 97 without 10-year: 94 with ADT and 87 without	10-Y: 75% with ADT and 69% without

	STUDIES		Age (Y)	PSA (ng/m)	Gleason score (%)*	N1*	ADT	RT	ADT and RT	Follow-up (months)	DFS (%)	MFS (%)	CSS (%)	OS (%)
	Jang (15)	350	67	16	6-7: 37% 8-10: 63%	20%	No	No	No	69	5-Y: 21	-	-	-
	Bastide (16)	199	64	13	6: 11% 7: 75% 8-10: 25%	No	38%, 15 mont hs	46%	25%, 12 mont hs	60	5-Y: 48	-	-	5-Y: 93
	Pagano (43)	180	64	9	6-7: 50% 8: 20% 9-10: 30%	12%	No	No	No	27	5-Y: 60	-	-	-
	SWOG 8794 (44)	139	65	-	-	No	No	51%	No	146	5-Y: 49 10-Y: 22	5-Y: 74	-	5-Y: 86 10-Y: 61
	Salomon (45)	137	64	17	6-7 : 63% 8-10 : 37%	No	No	No	No	59	5-Y : 34 10-Y : 10	-	-	-
	Freedland (46)	135	63	18	6:25 7:45 8-10: 30	No	No	No	No	44	5-Y : 36	-	-	-

TREATMENT	STUDIES		Age (Y)	PSA (ng/ml)	Gleason score (%)*	N1*	ADT	RT	ADT and RT	Follow-up (months)	DFS (%)	MFS (%)	CSS (%)	OS (%)
EBRT + BT	Koutrouvelis* (41)	37	68	20	6: 19% 7: 56% 8: 25%	No	No	No	No	24	2-Y: 79	-	-	-
	Stone (38)	52	70	-	6: 25% 7: 44% 8-10: 31%	No	All	-	-	56	5-Y: 70 10-Y: 64	-	10-Y: 91	10-Y: 83
	Rades (39)	38	< 70 for 61% of patients	-	6-7: 73% 8-10: 27%	No	All, 5 months	-	-	37	3-Y: 79 and 57 with and without dose escalation in SV	-	-	-
	Tsamura (40)	80	72	47	6: 5% 7: 42% 8: 24% 9-10: 29%	No	All, 36 months	-	-	74	5-Y: 82 10-year: 64	-	5-Y: 95 10-Y: 91	5-Y: 88 10-Y: 84
EBRT only	Our series	276	69	27	6: 7% 7: 51% 8-10: 42%	26%	All	-	-	35	5-Y: 66	-	5-Y: 90	5-Y: 79

Table 4: Review of the literature reporting the treatment (surgery or brachytherapy) of T3b prostate cancer

Selected surgery studies comprises a minimum of 100 patients, with Gleason score and pelvic lymph node involvement analysed on pathological examination. Mean values are given. Y: year; N1: pelvic lymph node involvement; ADT: androgen deprivation therapy; EB-RT: external beam-radiotherapy; BT: brachytherapy; DFS: disease free survival; MFS: metastasis free survival; CSS: cause specific survival; OS: overall survival

*BT only

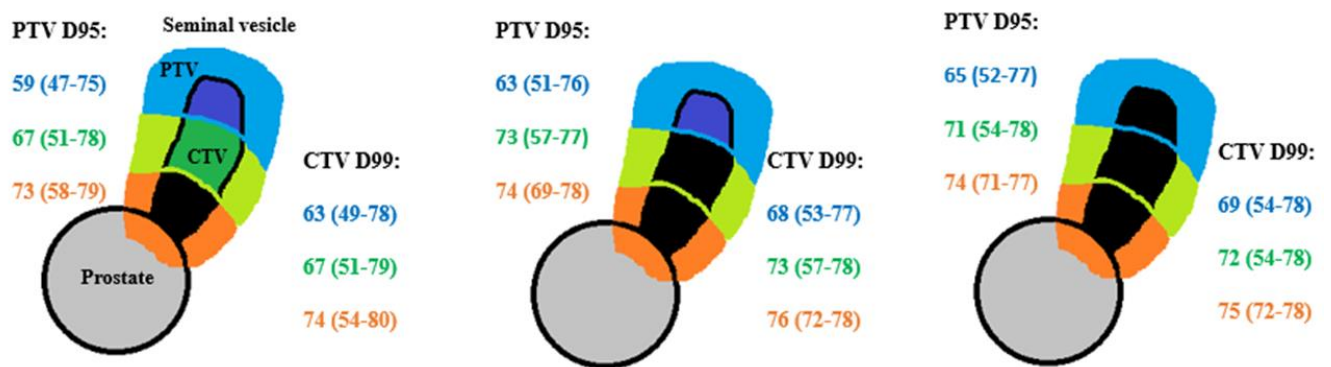


Figure 1: Dosimetric characteristics of each third of the seminal vesicle depending on the length of involved seminal vesicle on MRI (Rennes sub-group only, 106 patients)

Mean value (range) in Gy; Dx: dose received in x% of volume; PTV: planning target volume; CTV: clinical target volume; SV: seminal vesicle; SV PTV = SV CTV + 5 mm in all directions. The proximal third of the seminal vesicle is in orange, the second third in green and the distal third in blue. The involved part of the seminal vesicle is in dark.

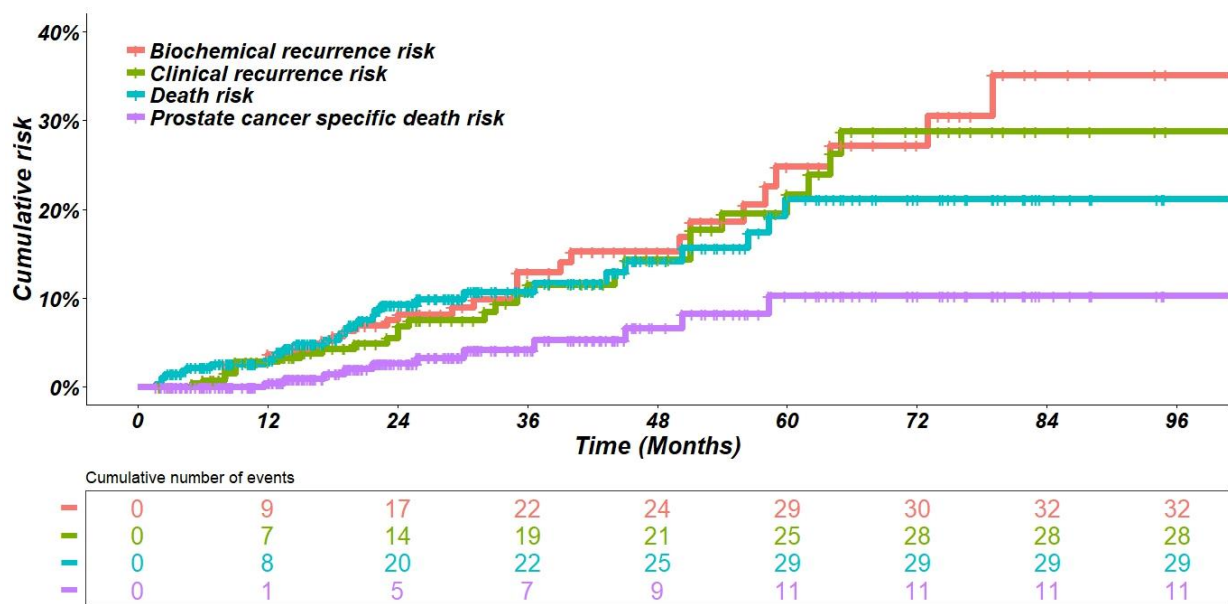


Figure 2: Biochemical and clinical recurrences, prostate cancer specific and overall deaths for T3b prostate cancer patients

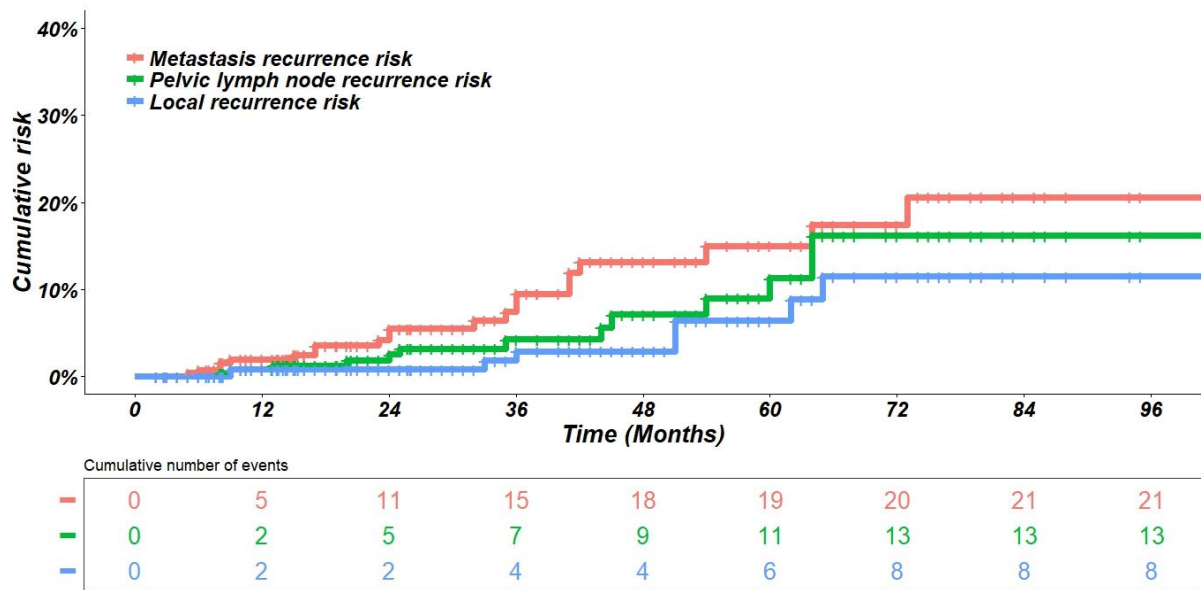


Figure 3: Clinical recurrence risk by recurrence localization (local, pelvic lymph node and metastasis) for T3b prostate cancer patients

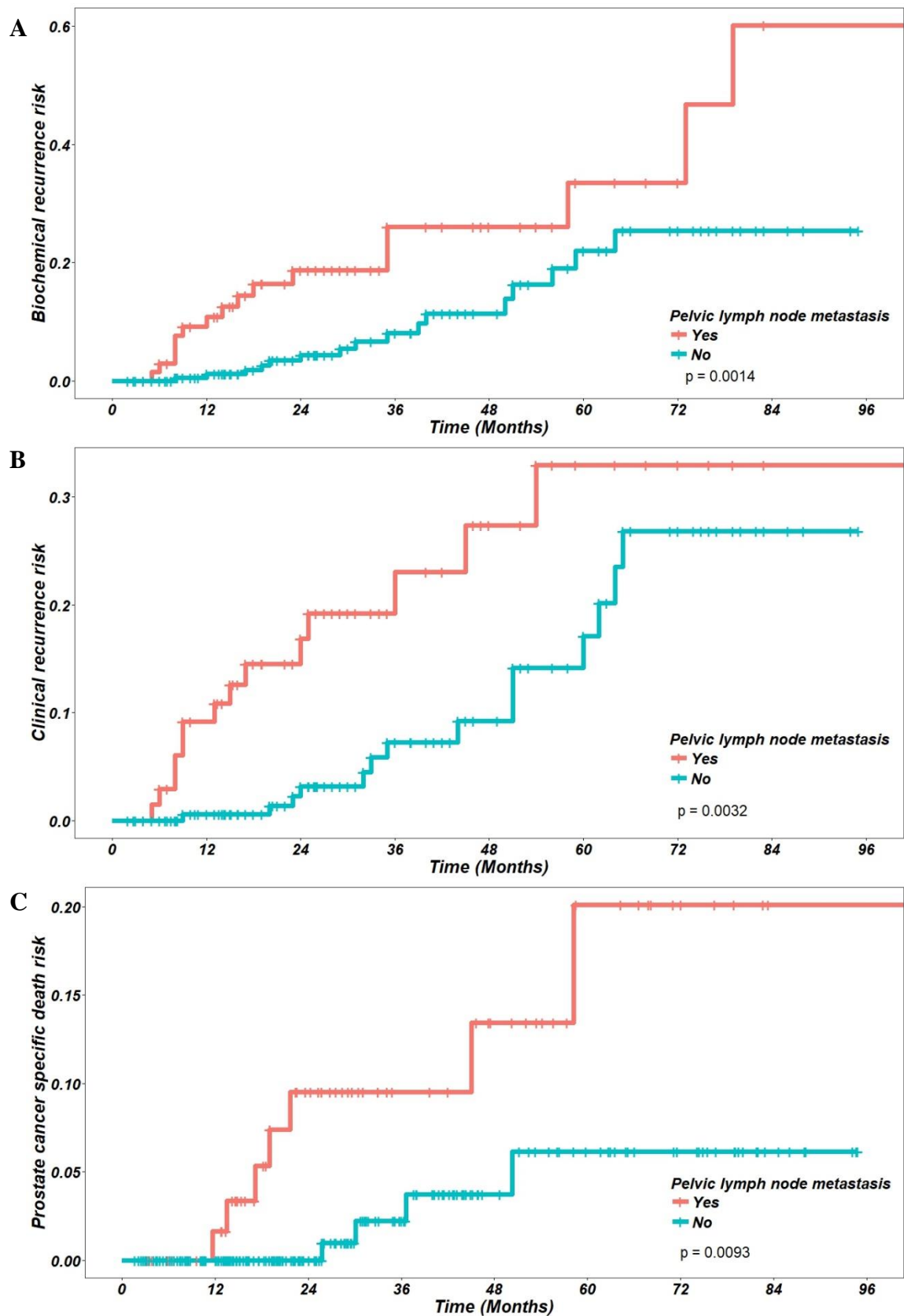


Figure 4: Impact of lymph node involvement on biochemical recurrence (A), clinical recurrence (B) and prostate cancer specific death (C)

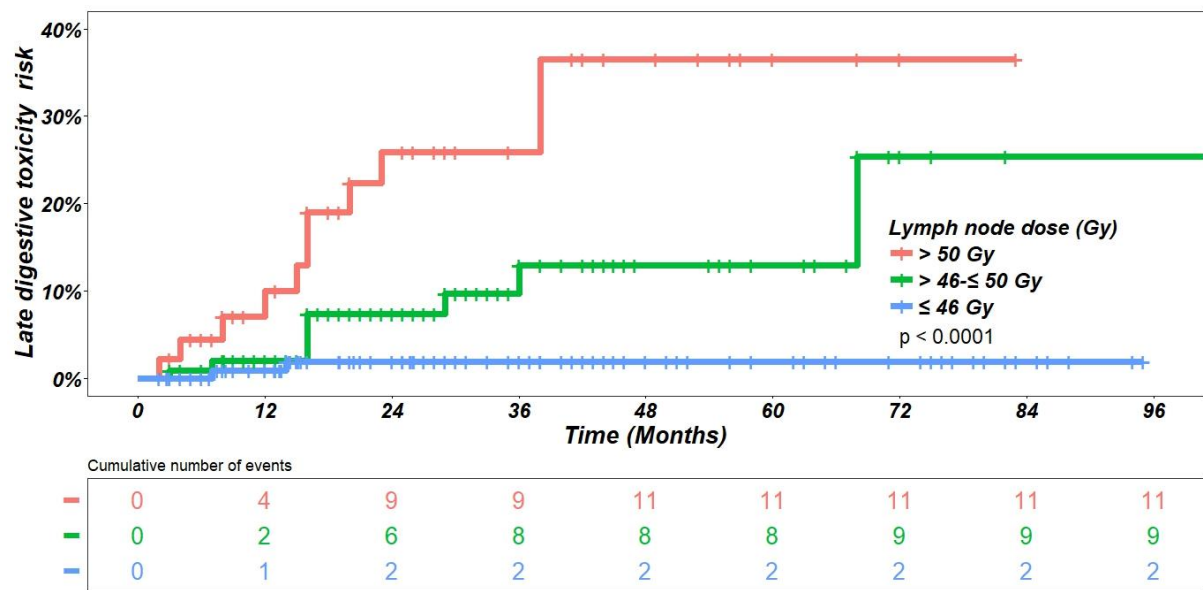


Figure 5: Impact of pelvic node dose on late digestive toxicity (grade ≥ 2)

U.F.R. DE MEDECINE DE RENNES	N°
<p>GOUPY Flora- Radiothérapie avec modulation d'intensité des cancers de prostate avec envahissement des vésicules séminales (T3b): une étude multicentrique rétrospective</p> <p>36 feuilles., 5 graphiques., 4 tableaux., 30 cm.</p> <p>Thèse : Médecine ; Rennes 1; 2018 ; N° .</p>	
<p>Résumé français</p> <p>Objectif: Analyser la distribution de dose et les résultats cliniques chez des patients ayant reçu de l'IMRT pour un cancer de prostate avec envahissement des vésicules séminales (VS), stade T3b.</p> <p>Matériels et méthodes: Analyse rétrospective ayant inclus tous les patients traités par IMRT et hormonothérapie entre 2008 et 2017 dans 6 institutions françaises.</p> <p>Résultats: Un total de 276 patients T3b a été inclus avec un suivi moyen de 35 mois. Les doses prescrites à la prostate et aux VS étaient de 77 et 68 Gy. Les risques à 5 ans de récidives biologique et clinique et de décès par cancer étaient de 24,8%, 21,7% et 10,3%. L'envahissement ganglionnaire pelvien était le seul facteur pronostique significatif de récidives biologique et clinique et de survie spécifique. Les taux de toxicités tardives digestives et urinaires à 5 ans étaient de 12% et 31,5%.</p> <p>Conclusion: L'IMRT pour les cancers de prostate T3b permet de délivrer une dose curative dans les VS envahies dans la majorité des cas, en dépassant rarement les contraintes de dose et sans augmenter les toxicités.</p>	