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# MRI detected extaprostatic extension (EPE) in prostate cancer: Do all T3a patients have the same outcomes?

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ABSTRACT

MRI-detected T3a prostate cancer is a heterogeneous disease. This post-hoc analysis of a prospective trial found that patients with T3a disease presenting obliteration of the recto-prostatic angle, contact-asymmetry of neuro-vascular bundle and periprostatic fat invasion, may be at higher risk of biochemical failure and metastases.



## 1. Introduction

The difference between organ confined disease and extraprostatic disease is crucial on deciding a treatment preference that achieves the best oncologic and functional results for patients with prostate cancer [1]. The role of mpMRI in defining extraprostatic extension (EPE) of prostate cancer has been reported in several studies [2]. In addition, data has shown a firm relationship between the presence of EPE and SVI as predictors of biochemical and metastases failure [3].

We previously described in a prospective study that the presence of EPE (T3a) and seminal vesicles invasion (SVI) were more accurate independent predictors of outcome than most of the traditional clinical variables in patients treated with brachytherapy (BT) and external beam radiotherapy (EBRT) [4].

However, T3a stage may be a very heterogeneous entity. Although some authors have reported higher positive predictive values (PPV) for EPE in patients with periprostatic fat invasion, recto-prostatic angle obliteration and neurovascular bundle asymmetry [5–7], there are no published studies evaluating the risk of failure associated with these radiologic characteristics.

The objective of this post hoc analysis of a prospective trial is to identify different subgroups within MRI-detected T3a patients that could predict biochemical-non-evidence of disease (bNED) and metastases-free survival (MFS) more accurately.

## 2. Materials/methods

In September 2010 we launched a prospective study of mpMRI guided High-Dose-Rate (HDR) BT (15 Gy) and supplemental EBRT (37.5 Gy). Clinical variables included baseline PSA value, clinical T-stage, ISUP grade, percentage of positive cores on prostate biopsy, use of hormonal therapy, MRI T-stage, risk-group based on clinical T-stage and risk-group based on MRI T-stage.

Biochemical failure was defined according to the Phoenix definition [8], the nadir plus 2 ng/ml. Patients with biochemical failure underwent a Choline positron emission tomography (PET)/computed tomography (CT) to rule out the presence of metastatic disease.

Patients with intermediate to high-risk prostate adenocarcinoma using the National Comprehensive Cancer Network practice guidelines were included in the study. Patients with T3b

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disease were only treated with the present radiation schedule if the seminal vesicles involved only the base or less than 1 cm in depth, to assure a good dose coverage with the brachytherapy treatment.

Treatment characteristics and MRI studies characteristics have been describe elsewhere [4,9]. The treatment administered (radiation targets and androgen deprivation duration) was adjusted to the MRI findings.

Two specialists in urologic radiology (A.U, A.G) evaluated retrospectively every MRI study and were blinded to outcome. The factors studied were established by consensus at our urologic oncology tumour board and were defined as tumour burden (number of nodules or intraprostatic mass), lesion laterality, and the presence or lack of EPE, SVI, pelvic lymph node involvement, and/or metastatic bone disease. Specifically, EPE was defined as the presence of any of these: tumor contact with prostate capsule >1 cm, capsule bulging, capsular disruption, irregular prostatic contour, recto-prostatic angle obliteration (RPA), contact or asymmetry of neuro-vascular bundle (NVB) and periprostatic fat invasion.

In the present post-hoc analysis, based on these signs, patients with T3a tumors were divided into two different groups. Patients with tumor contact with prostate capsule, capsule bulging, capsular disruption or irregular prostatic contour were considered minor factors. Conversely, recto-prostatic angle obliteration (RPA), contact or asymmetry of neuro-vascular bundle (NVB) and periprostatic fat invasion were defined as major factors. Finally, patients presenting one of the minor factors were defined as mT3a group, and those patients with any of the major factors were considered MT3a group.

Descriptive analyses were done. Chi-square and Fisher-exact tests were performed to evaluate the influence of different EPE signs on outcomes, and compare between mT3a and MT3a groups. Distributions of bNED survival and MFS times were calculated based on Kaplan-Meier analysis. Cox regression analyses were performed for identification of independent variables associated with time to recurrence and metastases. A $p < 0.05$ considered statistically significant.

## 3. Results

Two hundred and twenty patients were prospectively treated (135 high-risk and 85 intermediate-risk). Fifty seven percent had MR T-stage T1-T2, 31% T3a and 12% T3b. Twenty two percent of patients were ISUP grade 1, 51% ISUP 2–3 and 27% ISUP 4–5 and median baseline PSA was 11.6 ng/mL (2.9–156). Thirty-eight patients presented MT3a characteristics and 28 patients mT3a tumours. Patient and tumour characteristics are presented in Table 1. All patients received combination of HDR BT and EBRT, 160 patients (73%) received androgen deprivation therapy for a median time of 24 months (range 4–36 months).

Median follow-up was 56 months (range 20–98). At the time of the current analysis, 27 (12.4%) patients presented a biochemical failure and 14 (6.5%) had developed distant metastases. Two patients developed local relapse, 4 patients pelvic nodal recurrence, 5 paraortic disease and 5 developed bone metastases.

On univariate analysis higher ISUP grade (ISUP 2–3; $p = 0.045$; ISUP 4–5; $p = 0.049$), androgen deprivation use ($p = 0.046$), MT3a ($p = 0.001$) and T3b disease ($p < 0.001$) predicted for biochemical relapse, and a higher percentage of positive cores on biopsy ($p = 0.004$), MT3a ($p = 0.003$) and T3b disease ($p = 0.002$) predicted for metastases.

A multivariate analysis was performed and after adjusting for all the significant variables of the univariate analysis, only MT3a and T3b disease were independent predictors of outcomes. For biochemical relapse MT3a presented a HR of 5.1 (95% CI 1.9–13.3; $p < 0.001$) and T3b a HR of 7.1, (95% CI 2.4–21.3; $p < 0.001$). For metastatic failure, MT3a presented a HR of 22.780 (95% CI 2.8–185.2; $p = 0.003$) and T3b a HR of 31.5 (95% CI 3.5–282.8; $p = 0.002$).

**Table 1**
Patient and tumour characteristics.

| Characteristics | N (%) |
|---|---|
| cT stage | |
| Tx-T2a | 183 (83.2) |
| T2b-T2c | 23 (10.4) |
| T3a-T4 | 14 (6.4) |
| mrT stage | |
| T1-T2 | 125 (56.6%) |
| T3a | 68 (30.9%) |
| T3b | 23 (10.5%) |
| % of positive cores on biopsy | |
| ≤50% | 131 (59.5%) |
| >50% | 66 (30%) |
| Missing | 23 (10.5%) |
| Clinical risk group | |
| Intermediate | 85 (35.6%) |
| High | 135 (61.4%) |
| ISUP grade | |
| 1 | 47 (21.5) |
| 2 | 57 (25.9) |
| 3 | 54 (24.6) |
| 4 | 35 (15.9) |
| 5 | 26 (11.9) |
| Maximum PSA (ng/mL) | |
| <10 | 92 (41.8) |
| 10–20 | 76 (34.5) |
| >20 | 52 (23.7) |

*Abbreviations:* cT = clinical t; mrT = multiparametric magnetic resonance imaging determined-T stage. PSA = prostate-specific antigen; ISUP = international society of urological pathology. Data in parentheses are percentages.

Mean bNED survival for patients with T1-T2 and mT3a was 86.7 and 83.3 months respectively whereas for patients with MT3a and T3b patients mean survival was 63.7 and 53.4 months respectively ($p < 0.001$) (Fig. 1). Mean MFS for patients with T1-T2 and mT3a was 90.4 and 89.5 months respectively while for patients with MT3a and T3b patients mean survival was 67.4 and 64.2 months respectively ($p < 0.001$) (Fig. 2).

## 4. Discussion

In our study we have found that both MT3a and T3b were the only independent predicting factors for bNED and MFS. Moreover, in the present analysis, we found that patients with MT3a presented similar outcomes to patients with T3b disease. However, patients with minor factors of EPE (mT3a: tumor contact with prostate capsule, capsule bulging, capsular disruption and irregular prostatic contour) presented comparable outcomes as patients with intraprostatic disease.

It is known that predicting EPE with MRI may be challenging with several studies and meta-analysis showing dissimilar results on sensitivity, specificity and accuracy values even in centers with highly experienced radiologists [1,10,11].

Recently, Pesapane et al. found that MRI staging criteria for EPE of prostate cancer can be based on a chronological concept of cancer growth from truly intraprostatic to truly extraprostatic, and they divided the EPE signs into "early" and "late". The "early" signs were: capsular disruption, unsharp prostatic margin and bulging of the prostatic contour, and the "late" signs were: irregular contour, periprostatic fat infiltration, RPA obliteration and periprostatic mass. They found that "late" signs had lower prevalence but higher positive predictive values for EPE after radical prostatectomy [7].

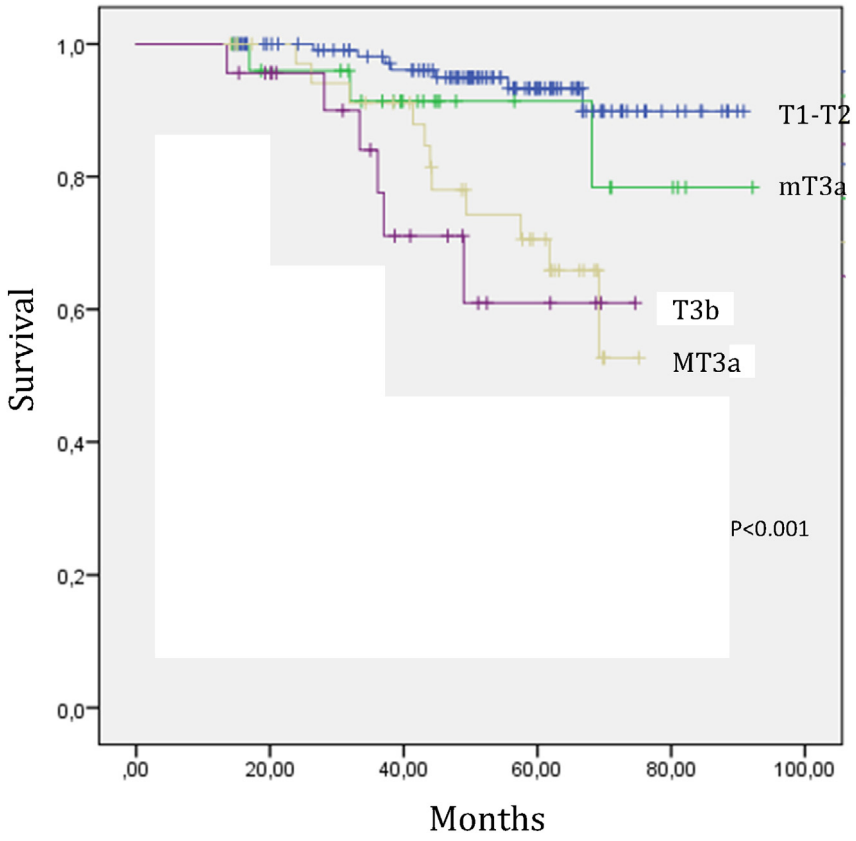


**Fig. 1.** Biochemical non-evidence of disease survival. Kaplan Meier estimates.

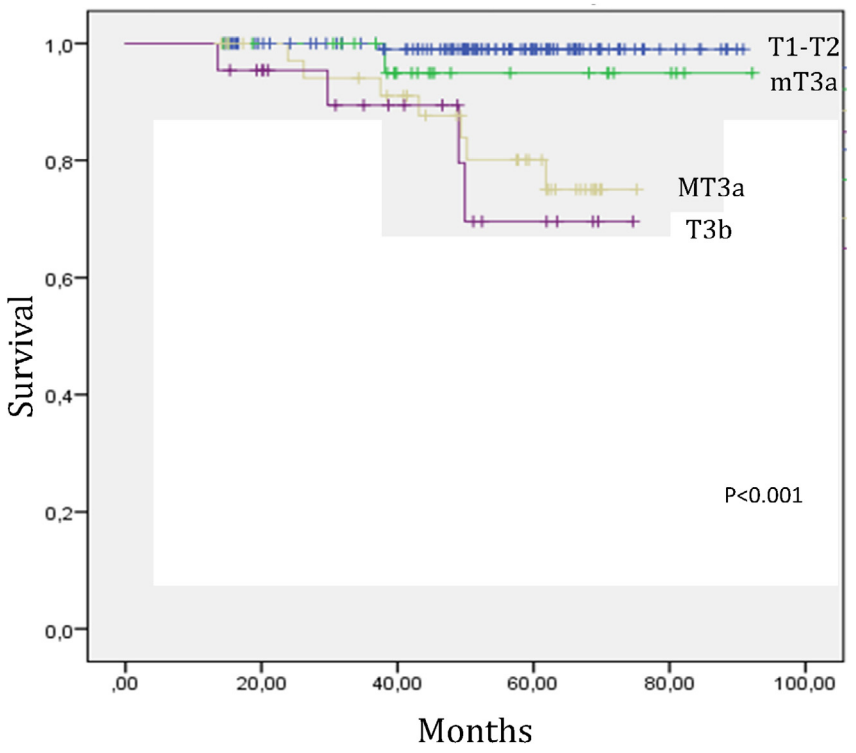


**Fig. 2.** Metastases-free survival. Kaplan Meier estimates.

These results reinforce our own data, since very similar subclassification of T3a disease was used in both studies. Although the results reported by Pesapane et al. are very useful for patients undergoing radical prostatectomy, we believe that our data may add important value to the existing literature, since our subclassification found differences in relevant clinical outcomes such as bNED or MFS.

The evidence on the impact of staging MRI findings on outcome in patients with prostate cancer is limited. Recently, a study of 672 men enrolled in a MRI-based active surveillance protocol found that Gleason score and MRI visible disease were associated with event free survival and treatment free survival [12].

Most of the published data of the impact of MRI staging on outcomes comes from retrospective studies. A recent meta-analysis of twelve studies and 2205 patients showed that EPE, SVI, tumor size, number of cores involved, and tumor infiltration of the prostatic apex were significant factors of biochemical relapse. Likewise, they found that EPE, tumor size and tumor volume, presence of metastatic pelvic lymph nodes, and presence of SVI were significant factors for development of metastasis [3].

A prospective study published by our group demonstrated that the presence of EPE, seminal vesicles invasion and the percentage of positive cores on biopsy were independent predictors for biochemical recurrence and metastases in patients treated with definitive radiotherapy [4].

It is intuitive to think that not all T3a tumors have the same outcomes. Greater tumors with greater EPE may probably be at higher risk of relapse than smaller lesions with minimal EPE on mpMRI. MRI is limited for the detection of focal (microscopic) EPE, which could carry a favorable prognosis compared to more extensive EPE.

Kongnyuy et al. demonstrated that tumor contact length, an indirect sign of EPE, predicts lymph node involvement and biochemical recurrence in patients undergoing radical prostatectomy [13]. Also, in a large single-institution radical prostatectomy cohort, it was found that patients with non focal EPE had worse biochemical outcomes than those with focal EPE [14].

In this regard, Padhani et al. proposed the idea that in this modern era when even patients with extensive EPE undergo successful surgical resections, it should be questioned if it is important to detect the presence of microscopic ECE [15]. The results presented in our study support the idea of Padhani et al., since the clinical outcomes of T3a tumors with minimal EPE are equivalent to T1-T2 tumors. However, our report raises another very important point, which is that T3a tumors with RPA or NVB invasion have a higher risk of biochemical failure and metastases; in fact, in patients with these characteristics this risk is similar to patients with SVI.

Although there are some studies looking at clinical outcomes and their relationship with MRI findings, to our knowledge, this is the first study demonstrating that different EPE characteristics may predict for different outcomes in patients treated with radiotherapy.

In our study, the major factors impacting on bNED and MFS were, periprostatic fat invasion, asymmetry of NVB and recto-prostatic angle obliteration, usually this lesions involve the anatomical site at the prostate fossa containing the vast majority of local nerves and small vessels.

It is well-known that most cases of EPE occur at least in part by extension of cancer along the perineural space [16], on the other hand, in vitro studies, have shown that cells in the perineural space may have an increased ability for proliferation [17]. Lymphovascular invasion (LVI) and perineural invasion (PNI) are independent predictors of poorer prognosis in prostate adenocarcinoma [18]. Initially, they were considered as possible spread paths for cancer cells [19] but recent investigations in animal models show now more complex molecular processes in PNI [20].

In a 2018 metaanalysis, Haoran et al. evaluated the impact of 6 cancer features after prostatectomy. Among them, PNI and LVI shown significant relation with poorer biochemical free survival [21].

Moreover, the 10-year follow-up analysis of the TROG 03.04 RADAR cohort have shown strong association between PNI and bone metastasis after radiation and ADT treatment [22].

Whether the location of these tumors, invading neuromuscular structures, confers them aggressiveness, or the aggressive histological features lead them to invade those anatomical structures, remains uncertain.

We acknowledge several limitations in this study. Our study was conducted within a single, tertiary care, academic institution, with subspecialized multidisciplinary expertise. Thus, the performance of pretreatment mpMRI may not be generalizable to community practice, as EPE staging accuracy may be lower in the community [23]. Second it was a post-hoc analysis of a prospective trial, so conclusions of our study may be considered just as hypothesis generating. Finally, longer follow-up and the presence of more events may clarify the implications of staging mpMRI with respect to the outcome of prostate BT and EBRT.

Based on the results among patients with mrT3a disease with evidence of RPA obliteration, contact or asymmetry of NVB and periprostatic fat invasion, more intensive treatment regimens may be warranted to improve disease control. These regimens could include more intensive dose-escalation regimens, which can be achieved with BT and intensity-modulated radiation therapy, longer courses of ADT, elective nodal pelvic irradiation or the inclusion of second-generation anti-androgen drugs.

## 5. Conclusion

Patients with mrT3a stage may be divided into different risk sub-groups to better predict clinical outcomes. It is important to identify patients with T3a disease on mpMRI presenting obliteration of the recto-prostatic angle, contact-asymmetry of neurovascular bundle and periprostatic fat invasion, since these patients may be at higher risk of biochemical failure and metastases.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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