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Review

# Micro-Focal Prostate Cancer: A Comparison of Biopsy and Radical Prostatectomy Specimen Features

L.M. Boccon-Gibod[a,*], O. Dumonceau[a], M. Toublanc[a], V. Ravery[a], L.A. Boccon-Gibod[b]

[a]*Departments of Urology and Pathology - CHU Bichat, AP HP Assistance Publique – Hôpitaux de Paris – France*
[b]*Department of Pathology - Hopital Armand Trousseau, AP HP Assistance Publique – Hôpitaux de Paris – France*

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**Abstract**

***Objectives:*** To study the pathologic features of radical prostatectomy (RP) specimens of patients operated on the basis of a potentially ''Insignificant'' prostate cancer (Ca P) characterized by one single focus (less than 3 mm) of moderately differentiated adenocarcinoma – Gleason score ≤6, out of 6–10 biopsies and to determine which characteristics, if any, are predictive of the presence of a ''non significant'' prostate cancer in the specimen characterized by a low volume (<0.5 ml) moderately differentiated organ confined, cancer (Gleason score less than 6).

***Patients and methods:*** PSA, biopsy features, and surgical specimens of a series of 56 patients submitted to RP for ''insignificant Ca P'' on TRUS prostate biopsies between 1988 and 2004 were compared regarding the number of tumor foci, Gleason grade and score, tumor volume determined by the cylinder method, as well as extraprostatic extension (EPE) and positive surgical margins (P.SM.).

***Results:*** 70% of the patients had multifocal microfocal cancer apart from the index tumor. The presence of grade 4 was ignored by the biopsy in 50% of the cases, however the primary grade was correctly evaluated in more than 70% of the biopsy sets. 42% of the patients had a cancer volume less than 0.5 ml and 29% met the definition of insignificant/unimportant cancer characterized by a moderately differentiated (Gleason score ≤6) of low volume (less than 0.5 ml) however no feature accurately predictive of insignificant cancer could be individualized. In this whole series, only 8% of the patients had EPE. When the pre-operative PSA was <10 ng/ml, 98% of the patients had an organ confined tumor.

***Conclusion:*** Patients diagnosed with prostate cancer on the basis of one single focus less than 3 mm of moderately differentiated (Gleason ≤6) prostate cancer have 30% of chances of harboring an insignificant tumor in their prostate and are therefore, at risk of being overtreated, however there is at this time no specific feature able to identify these patients pre operatively.



**Keywords:** Micro focal; Prostate cancer; Radical prostatectomy

## 1. Introduction

The widespread use of prostate specific antigen (PSA) testing associated with increasingly extensive transrectal ultrasound (TRUS) prostate biopsy protocols triggered by ever lower PSA thresholds, have led over the recent years to a spectacular stage migration of prostate cancer, exemplified by 2 associated phenomenons:

- a regular increase in the proportion of patients diagnosed with moderately differentiated, low volume (<0.2 to 0.5 ml) potentially insignificant prostate cancers [1],

* Corresponding author. Tel. +33 1 40 25 71 02; Fax: +33 1 42 28 53 20.
*E-mail address:* laurent.boccon-gibod@bch.ap-hop-paris.fr (L.M. Boccon-Gibod).

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- a significant decrease of the volume of the cancers removed at surgery in the frame work of screening and early detection programs where the median tumor volume can be as low as 0.6 or 0.5 ml [2].

These recent changes may explain the renewed interest in observation with delayed therapy at clinical/biological/pathological progression for highly selected patients, particularly those diagnosed with low volume, well differentiated tumors [3–5]. However, it has been known for a long time that the presence of a small volume of cancer on the biopsy may not translate into a small volume of tumor in the prostate, in a significant proportion of cases [6–8].

In the absence of reliable imaging techniques documenting the actual tumor volume, the meticulous analysis of prostate biopsies remains the best tool to ascertain the extension of the cancer whithin and out of the prostate.

Therefore, it may be that a careful evaluation of the pathologic profile of the patients diagnosed with a potentially ''insignificant'' cancer may help to distinguish those with a truely ''insignificant'' well differentiated (Gleason $\leq 6$) of low volume (0.2–0.5 ml) potentially manageable initially by surveillance from those with a potentially life threatening tumor requiring active treatment.

## 2. Patients and methods

From March 88 to March 04, 589 patients with clinically localized (T1 T2) prostate cancer were submitted to a radical retropubic prostatectomy (RRP). All biopsies were performed at our institution, the standard 6 core technique was replaced in 1996 by a 10 core protocol. All RP specimens were handled following the Stanford protocol. Biopsies and specimens were evaluated by 2 experienced uropathologists (L.A. B.G, M.T.) PSA assays were performed at the same laboratory using the Tosoh assay (normal level 3 ng/ml, lower detection limit: 0.05 ng/ml).

From this data base, we extracted the patients operated on the basis of a potentially ''insignificant'' prostate cancer characterized by the presence of 1 single focus measuring 3 mm or less, of well differentiated (Gleason score $\leq 6$) adenocarcinoma. Serum PSA values and PSA density (based on the specimen and not on the ultrasound prostate volume) were recorded for each individual patient. The following features were recorded from the surgical specimen pathology report: number, location, Gleason grade and score of tumor foci, presence or absence of extra-prostatic extension (EPE) and positive surgical margins (PSM); the volume of the largest (index) cancer was evaluated using the cylinder method, i.e.: the largest surface of the tumor multiplied by its height, calculated by the number of sections where it was seen, multiplied by the thickness of each section (3 mm). No shrinkage coefficient was used [9]. This technique tends undoubtedly to over estimate the real cancer volume.

However, the volume of secondary cancer foci was not taken into account as their prognostic impact has been shown to be negligible [10].

## 3. Results

Among the series of 589 consecutive patients submitted to RRP, 107 (18%) had a single positive biopsy. 56 of those met the criteria of potentially ''insignificant'' prostate cancer: one single focus measuring 3 mm less of adenocarcinoma Gleason score less or equal to 6. Their characteristics according to the PSA values (above or below 10 ng/ml) are depicted on Table 1. The stage migration over time is spectacular as the incidence of cancers diagnosed on a basis of a single positive biopsy as well as of ''biopsy insignificant'' prostate cancers as been multiplied by 3 from 1988–1996 when a 6 core protocol was used and biopsy decided for a PSA $\geq 4$ ng/ml to 1996–2004 when the 10 core protocol triggered by a PSA $\geq 3$ ng/ml was implemented. It should also be noted that almost a quarter of the patients were diagnosed on a basis of a repeat prostate biopsy, 3 to 12 months after a prior negative sampling.

The comparisons of biopsy and surgical specimen features allows to identify several salient points:

1. a significant discrepancy appeared between the biopsy and specimen Gleason scores which were identical in only 34% of the whole group and 42% of the 40 patients with a PSA $< 10$ ng/ml. However, a predominant grade 4 was missed in only 24% of the whole group and 15% when the PSA was below 10 (Tables 2 and 3).
2. In 80% of the tumors, irrespective of serum PSA, a number of microscopic tumor foci (1–4, med 2)

**Table 1**
Characteristics of patients with 1 single positive biopsy with 1 focus <3 mm of Gleason $\leq 6$ prostate cancer

| | |
|---|---|
| Number | 56 |
| Age | Med: 63.8 (44–75) |
| PSA ng/ml | Med: 8.5 (11–35) |
| PSA $< 10$ ng/ml | 40 |
| P.S.A.D. | Med: 0.13 (0.03–1.2) |
| T1 C | 42 (75%) |
| Length of cancer | Med: 1 mm (0.1 – 3) |
| Prior biopsy | 13 (23%) |
| Prostate volume | Med: 53 ml (15–165) |

**Table 2**
Biopsy versus specimen Gleason score in the whole series

| Biopsy Gleason score | Specimen Gleason score | | | |
|---|---|---|---|---|
| 6 (3 + 3) | 6 (3 + 3) | 7 (3 + 4) | 7(4 + 3) ≥ | 7 |
| 56 patients | 19 | 25 | 9 | 3 |
| | 44 (75%) | | | |

**Table 3**
Biopsy versus specimen Gleason score in patients with PSA < 10 ng/ml (40 patients)

| Biopsy Gleason score | Specimen Gleason score | | |
|---|---|---|---|
| 6 (3 + 3) | 6 (3 + 3) | 7 (3 + 4) | 7(4 + 3) |
| 40 patients | 17 | 18 | 5 |
| | 35 (87%) | | |

**Table 4**
Tumor volumes

| Tumor volume | Whole series 56 pts | PSA < 10 ng/ml 40 pts |
|---|---|---|
| * Mean | 1.2 ml | 0.83 ml |
| * Median | 0.54 | 0.36 |
| * Range | 0.003–12 | 0.003–3.3 |
| * <0.5 ml | 24 (42%) | 200 (50%) |

were associated with the index cancer measuring 1 to 3 mm in diameter.

The presence of bilateral tumor foci was observed in 78% but it is important to stress that a contralateral cancer focus of grade 4 overlooked at biopsy was detected only in 10% of the radical prostatectomy specimens.

3. The volume of the index cancer was less than 0.5 ml in 42% of the patients of the whole group, and 54% if the PSA was below 10 (Table 4). There was no correlation between the length of the cancer on the biopsy and the volume of the tumor on the specimen.
4. In the whole group of patients, only 8% had EPE and none PSM. When the preoperative PSA was <10 ng/ml, only 2 patients had EPE and none PSM.
5. Finally, in the end, 16 of 56 (29%) of the patients in this series met the criteria of ''insignificant'' prostate cancer: organ confined (Pt2) tumor moderately differentiated – (Gleason score $\leq 6$) of low volume (<0.5 ml). Unfortunately, on the pre-operative criteria, they did not differ from the whole a group as far as prostate volume, PSA and PSA density as well as biopsy features were concerned (Table 5), no predictive criteria of truely ''insignificant'' prostate cancer could be identified from the analysis of these series.

## 4. Discussion

These series may indeed give rise to several critics: it is retrospective; it spans over a 14 years period during which a significant stage migration has occured; the technique used to evaluate the tumor volume was at best simplistic but has been recommended by others [9] secondary foci were not taken into consideration in the measurement of the tumor volume because of the documented lack of their prognostic significance [10]. Nevertheless, the issue of low volume well differentiated prostate cancer is becoming more and more important as the implementation of early diagnosis and screening programs for prostate cancer has led to an over extensive use of PSA testing associated with increasingly aggressive prostate biopsy protocols triggered by lower and lower PSA values from 4 to 3 or even 2.5 ng/ml.

As a consequence, an expanding proportion of prostate cancers are detected on the basis of a small focus of well differentiated tumor present in one single core of the biopsy set [1]. These cancers may indeed cause little harm to the patient during his lifetime hence the emerging issue of over diagnosis leading potentially to over treatment which is estimated to be around 40–50% in the European Screening Program [11]

Insignificant and unimportant prostate cancers in radical prostatectomy specimens have been defined as a low volume (0.2 to 0.5 ml) tumor moderately differentiated without any element of Gleason grade 4 [12].

Several authors have compared specimen and biopsy tumor caracteristics in order to determine the biological and pathological features that would predict with the best accuracy the presence of a low volume ''indolent'' prostate cancer:

**Table 5**
Prostate volume, serum PSA and PSA density (ranges in brackets) in specimen insignificant cancers compared to whole group and to subgroup with PSA < 10 ng/ml

| | Biopsy ≪ insignificant Ca ≫ | | Specimen ≪ insignificant ≫ Ca |
|---|---|---|---|
| | Whole group (56) | PSA < 10 (40) | (16) |
| Med prostate volume | 50 ml (15–165) | 50 (15–90) | 57 (24–90) |
| Med PSA | 7 ng/ml (1.1–35) | 5.6 (1.1–9.9) | 5.9 (1.1–18.5) |
| Med PSAD | 0.13 (0.03–1.2) | 0.10 (0.10–0.13) | 0.11 (0.003–0.65) |

- J Epstein [12] considers that less than 3 positive biopsy cores containing each less than 50% of moderately differentiated prostate cancer (Gleason sum $\leq 6$) with a PSA density 0.15 is highly predictive oF insignificant prostate cancer.
- TA Gardner [13] is more restrictive and considers that to be predictive of insignificant cancer in the specimens there are to be less than 5% of the total length of the biopsy cores invaded by moderately differentiated prostate cancer without any element of Gleason grade 4.
- M. K. Terrris [14] opts for the following definition of biopsy insignificant prostate cancer: one single positive biopsy containing a focus of 3 mm or less of moderately differentiated prostate cancer (Gleason score $\leq 6$), this is the definition we chose as this biopsy profile is increasingly prevalent and the most easy to define.

In this setting 30 to 55% of the patients operated on the basis of a ''biopsy insignificant'' prostate cancer will indeed harbour an ''insignificant'' tumor at pathological evaluation of their specimen. In a recent series, 5% of 1500 consecutive radical prostatectomy specimens contained only a minute focus of cancer sometimes extremely difficult to document [15–17].

Along those lines, it is noteworthy that the problem of ''PT0'' specimens at radical prostatectomy has been recently brought up. The incidence being 0.2, 0.7 or 1% [18–20].

Therefore, it comes to no surprise that the issue of observation with delayed therapy in patients diagnosed on the basis of a potentially insignificant/unimportant prostate cancer has been revisited. On the other hand, it should be stressed that 45 to 70% of the patients with this profile will indeed have a ''significant cancer'' (Gleason score $\geq 7$) volume ($>0.5$ ml) in their prostate warranting active therapy. Unfortunately, as shown in our series, as well as in the experience of others, no clinical, biological, or pathological criteria: PSA, length of biopsies invaded by cancer, prostate volume and PSA density, (contrary to the experience of J.Esptein who like us used the specimen's weight to calculate PSAD [21]) was able to identify on an individual basis the patients harbouring a small volume well differentiated prostate cancer potentially amenable to surveillance with delayed therapy. A nomogram recently devised gives some directions in this respect but it is not reliable on an individual basis and curiously does not take into account the patient's age [22].

Therefore awaiting potential future predictive biomarkers such as genetic biomarkers issued from microarray technology, it may well be that observation over time, using among others, the PSA doubling time [5] will help the clinician to guide the patient's decision regarding treatment options.

However, it should be stressed that 92% of our patients (98% when the PSA was $\leq 10$ ng/ml) had organ confined prostate cancer, a tumor of potentially limited impact on their life expectancy, a finding identical to the Hopkins experience [23,24] underlining the fact that patients with a well differentiated (Gleason score $< 6$) low volume ($\leq 3$ mm) focus of 1 single biopsy out of 10.12 cores have a low risk of unfavourable outcome in the short term and may safely, if they elect to do so, be offered observation with delayed therapy. This of course implies that the patient accepts to disconnect the diagnosis from the treatment of his tumor [25].

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