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# Gleason Score upgrade in prostate cancer patients after radical prostatectomy.

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**Abstract**
Background/Aim: To evaluate the impact on biochemical relapse of clinically significant GS upgrade.
Materials and Methods: 3403 patients were selected. We considered "clinically significant" any GS change from biopsy to final radical prostatectomy sample.
Biochemical-recurrence-Free Survival (BFS) Kaplan-Meier curves were plotted. The associations of GS change from biopsy to prostatectomy and lymphadenectomy data were investigated.
Results: GS risk classes were confirmed in 66.9% of patients, upgraded in 28.2% and downgraded in 5.0%. Comparing upgraded to unchanged patients, upgraded GS patients have a BCR risk being intermediate between unchanged lower and higher class. GS change is not associated to total number of biopsy cores (p=0.80) nor to positive ones (p=0.98). A higher bGS is related to a more radical surgical approach with a lower incidence of nerve-sparing techniques (from 37.9% to 6.4%) and a higher percentage of lymphadenectomies (from 57.3% to 97.1%).
Conclusion: The study shows clear intermediate behaviour of GS upgraded cases in between lower and higher GS risk classes.

**Keywords:** prostate cancer, Gleason Score, upgrade GS.Abbreviated running title: Gleason Score upgrade. Clinical study;

## Introduction

Prostate cancer (PCa) is the most common cancer in men and the second most common cause of death from tumours in the male population (1). According to stage, grade and PSA level, PCa is stratified into risk categories denoting its aggressiveness (2). PCa grading with the Gleason Score (GS) system is the single strongest prognostic factor for clinical behaviour and treatment response (3), being a predictor of the risk of Bio-Chemical Recurrence (BCR) after radical prostatectomy (RP), which has been estimated up to 40% (4,5). High Gleason Score patients (i.e. GS $\geq$ 8) are at increased risk of PCa failure, metastatic progression and cancer-specific death. In the last years, RP has become a viable option also for this subgroup of patients, demonstrating remarkable long-term survival rates (6). When RP is performed in high-risk patients, though, a less conservative approach must be adopted, together with an extended pelvic lymph nodes dissection (PLND). On the contrary, low-risk and some intermediate-risk PCa are suitable to a nerve-sparing approach, avoiding PLND. Therefore, proper risk stratification is essential in the surgical planning, once a patient has been chosen for RP. Unfortunately, a GS upgrade between prostate biopsy and RP specimen is a common finding, reported in up to 57% of cases (7). The GS upgrade can translate in a dangerous PCa misclassification, meaning that there is a risk of under-treatment in high risk patients surgically managed as if they were lower risk cases. The aim of this retrospective study is to evaluate the oncologic outcomes of clinically significant GS upgrade in a large, multicentric cohort of 3403 RP patients, and to assess whether GS upgrade is a predictor of BCR.

## Materials and Methods

Under institutional review board supervision, data from men who underwent RP between 1999 and 2012 with at least 2-yrs follow-up available (PSA records and clinical visits) at thirteen Urology Divisions located in Piemonte and Valle d'Aosta Italian regions (see Appendix 1) were combined into the Eureka-1 database. Eureka-1 is an observational, multicentric, retrospectively-derived dataset promoted by the CHIC project (sponsored by the European Union, 7th Framework Program, and grant agreement n. 600841). Data collected in Eureka-1 included sociodemographic parameters, clinical tumor characteristics, surgery features, pathology examination, therapies, clinical and PSA follow-up, and clinical outcomes.

Prostate cancer was diagnosed with transrectal or transperineal core needle biopsies with varying biopsy schemes according to the referring urologist. Biopsy cores and RP specimens were examined by the pathologists of each center.

We considered "clinically significant" any GS change translating into an upgrade (or more rarely a downgrade) to a higher (or lower) risk category, being risk categories GS $\leq 6$ (low risk), GS = 7 (intermediate risk) and GS $\geq 8$ (high risk).

Kaplan-Meier curves were plotted for Biochemical recurrence Free Survival (BFS) and were compared with Log-Rank test, and the related BFS tables at 5 yy and 10 years were tabulated both for upgraded and unchanged GS groups. Besides, any change in GS risk class (upgrade or downgrade) was compared to biopsy data, i.e. number of total and positive biopsy cores and maximum percentage of tumor per core through two-sample t tests. Bioptic Gleason Score was compared with prostatectomy extension (radical or monolateral nerve-sparing or bilateral nerve-sparing) and with lymphadenectomy execution through Chi-2 test, and with the number of nodes resected through analysis of variance and Bonferroni t test.

All statistical analyses were performed with Stata SE 13.1 Software (®StataCorp, Texas, USA).

## Results

The baseline characteristics of our patients are shown in Table I.

According to the biopsy findings, 60.1% of the patients had a bGS $\leq 6$, 30.8% a bGS = 7 and 9.1% a bGS $\geq 8$. The percentages change after the definite pathologic exam with 39.3% of pGS $\leq 6$, 47.5% of pGS = 7 and 13.2% of pGS $\geq 8$. In particular, GS risk classes were confirmed in 66.9% of the patients, upgraded in 28.2% and downgraded in 5.0% (see Table II for raw data cross tabulation).

Comparing upgraded patients to unchanged ones, the patients who upgrade from a previous GS risk class to a higher one have a BCR risk being intermediate between unchanged lower class patients and unchanged higher class cases. For example, BFS slope for patients upgrading from $\leq 6$ to 7 is worse than GS $\leq 6$ both at biopsy and post-surgery examination (P = 0.0001) and better than GS 7 in both the pathology evaluations (P 0.0006); the same general behaviour is hold by patients upgrading from bGS $\leq 6$ to pGS $\geq 8$ versus low GS (P < 0.0001) or high GS (P 0.0017) and from bGS = 7 to pGS $\geq 8$ versus GS 7 (P < 0.0001) or GS $\geq 8$ confirmed (P 0.0283). The graphical comparisons and survival tables with confidence intervals between all these GS combinations are shown in Figure 1 and Table III.

Besides, a change in GS (both upgrade and downgrade) is not associated to the total number of biopsy cores (P 0.80), nor to the number of positive ones (P = 0.98) nor to the maximum percentage of tumor per core (P 0.37).

In addition, a higher bGS is clearly associated to a more radical surgical approach with a lower incidence of nerve-sparing techniques (from 37.9% in low bGS to 21.2% in intermediate bGS to 6.4% in high bGS), a higher percentage of lymphadenectomies (from 57.3% to 80.9% to 97.1% respectively) and a modest trend towards a higher number of nodes resected (of 11.8 in bGS $\leq 6$ versus 13.4 in bGS ranging from 7 to 10).

**Appendix 1**

The following centers participated to Eureka-1 study:

| Participating Centers | Number of patients |
|---|---|
| San Giovanni Bosco Hospital, Torino (G Muto) | 513 |
| Città della Salute e della Scienza University Hospital, Torino (P Gontero) | 506 |
| San Luigi Gonzaga University Hospital, Orbassano (F Porpiglia) | 415 |
| Maggiore della Carità University Hospital, Novara (C Terrone) | 376 |
| ASL TO4, Ivrea and Cirié Hospitals (S Annoscia) | 424 |
| Gradenigo Hospital, Torino (D Randone) | 339 |
| Santa Croce Hospital, Cuneo (G Arena) | 311 |
| Aosta Regional Hospital, Aosta (S Benvenuti) | 198 |
| Cardinal Massaia Hospital, Asti (F Bardari) | 140 |
| Mauriziano Hospital, Torino (L Comi) | 129 |
| Maria Vittoria Hospital, Torino (M Moroni) | 122 |
| EDO Tempia Foundation, Biella (G Chiorino) | 65 |
| Total | 3.538 |

**Table I** Baseline patient characteristics

| Variables (N = 3403) | Value |
|---|---|
| Median Age, years (min, max) | 66 (42-79) |
| Median Follow-up, months | 56 |
| Bio-Chemical Relapse | 20.5% |
| Mean PSA level, ng/ml (median) | 9.32 (6.8) |
| Bioptic Gleason Score<br>bGS $\leq 6$<br>bGS = 7 | <br>60.1%<br>30.8% |

| | |
|---|---|
| bGS ≥ 8 | 9.1% |
| Clinical Staging<br>cT1<br>cT2<br>cT3 | <br>66.4%<br>29.4%<br>4.2% |
| Pathologic Gleason Score<br>pGS ≤ 6<br>pGS = 7<br>pGS ≥ 8 | <br>39.3%<br>47.5%<br>13.2% |
| Pathologic Staging<br>pT2<br>pT3-4 | <br>71.2%<br>28.8% |
| Positive margins | 30.1% |
| Lymphadenectomy execution | 68.2% |
| pN+ | 6.5% |
| Number of nodes resected, mean (SD) | 12.6 (7.9) |
| RP extension:<br>Radical<br>Nerve-sparing monolateral<br>Nerve-sparing bilateral | <br>70.2%<br>10.3%<br>19.6% |
| Total number of biopsy cores, mean (SD) | 11.6 (4.3) |
| Positive biopsy cores, mean (SD) | 3.7 (2.6) |
| Max % of tumor per core, mean (SD) | 39.8% (28.7%) |

**Table II** Cross table comparing bioptic Gleason Score and pathologic GS

| | **pGS ≤ 6** | **pGS = 7** | **pGS ≥ 8** | |
|---|---|---|---|---|
| bGS ≤ 6 | 1244 (36, 6%) | 729 (21, 4%) | 73 (2, 1%) | 2046 (60, 1%) |
| bGS = 7 | 79 (2, 3%) | 812 (23, 9%) | 157 (4, 6%) | 1048 (30, 8%) |
| bGS ≥ 8 | 14 (0, 4%) | 76 (2, 2%) | 219 (6, 4%) | 309 (9, 1%) |
| | 1337 (39, 3%) | 1617 (47,5%) | 449 (13, 2%) | 3403 (100%) |

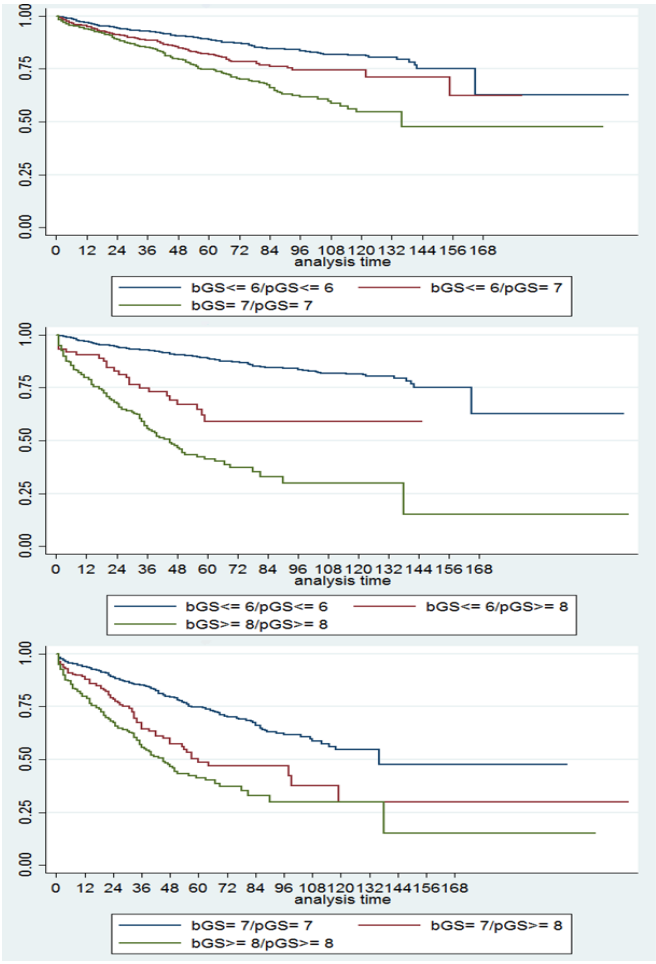


**Fig. 1:** BFS of GS upgraded patients compared to unchanged ones.

**Table III** Biochemical Free Survival tables at 5 y and 10 years

| Group | Time (y) | Survival | 95% CI | |
|---|---|---|---|---|
| bGS ≤ 6to pGS ≤ 6 | 5 | 88.5% | 86.4% | 90.3% |
| | 10 | 80.8% | 77.6% | 83.6% |
| bGS = 7to pGS = 7 | 5 | 75.6% | 72.0% | 78.8% |
| | 10 | 59.6% | 53.9% | 64.9% |
| bGS ≥ 8to pGS ≥ 8 | 5 | 42.0% | 34.8% | 49.1% |
| | 10 | 31.5% | 22.7% | 40.6% |
| bGS ≤ 6to pGS = 7 | 5 | 81.7% | 78.2% | 84.6% |
| | 10 | 72.8% | 67.5% | 77.3% |
| bGS ≤ 6to pGS ≥ 8 | 5 | 59.0% | 45.3% | 70.3% |
| | 10 | 59.0% | 45.3% | 70.3% |
| bGS = 7to pGS ≥ 8 | 5 | 52.9% | 43.7% | 61.2% |
| | 10 | 39.6% | 27.7% | 51.3% |

## Discussion

Gleason score (GS) remains the strongest prognostic factor for clinical behaviour and treatment response of PCa (3), being an essential component of every risk classification system. Unfortunately, GS upgrade between prostate biopsy and RP specimen is a quite common phenomenon, occurring in 28-42% of cases (8–12), up to 57% in one report (7). In a large meta-analysis of 14.839 patients, around 30% of RP patients experienced GS upgrade (13). Similarly, in the present study, GS upgrade was found in 28.2% of patients.

In literature, an association between upgraded GS and a higher risk of BCR was recently suggested by Suer et al (12) in their study on 632 patients. The authors reported that patients with upgraded GS were found to have higher BCR rates than their corresponding low unchanged GS group. Our study confirms such findings, demonstrating for the upgraded patients a risk of relapse in between the ones of the "confirmed" lower and higher groups.

Two main reasons may justify such a trend:

1) The final and more reliable pathologic GS pulls down the BFS curve towards the "original" worse scores;
2) The employ of a sub-optimal surgical strategy, making use of a nerve-sparing approach and/or avoiding a proper, extended PLND may cause a partial under-treatment of the lower grade, but thereafter upgraded patients.

The second factor may be confirmed by the strong association in our data between low bioptic GS and a more conservative surgical approach both at the prostate site and at the lymphatic drainage.

The concept of "clinically relevant" GS upgrade had been introduced by Thomas et al (9), defined as any upgrade into a higher GS PCa risk category. In their analysis of 402 patients, clinically relevant GS upgrade was found in 38.1% of the whole cohort, including a 20% of very low-risk PCa patients increasing to GS ≥ 8 into the high-risk category. These authors suggested that those patients would probably have been under-treated if they had chosen active surveillance or focal therapies, but they did not perform any correlation with survival outcomes.

In the attempt to predict the likelihood of a GS upgrade, several nomograms have been developed (14–17); a recent study evaluated the ability of four nomograms to predict GS upgrades for patients with bioptic GS ≤ 6 PCa undergoing RP, concluding that these prognostic tools have limited predictive ability and are not ready for clinical application (18).

The difficulty to model the probability of GS upgrade with pre-operatory information is confirmed by the absence in our data of any association between GS change from biopsy to definite pathology and the number of total or positive biopsy cores, or the percentage of tumor per core. Therefore, it is possible that, beyond a fair number of cores from 10 to 12, the accuracy of the bioptic GS grading does depend no more on the quantity of organic material (and of tumor) at disposal, being limited by inherent technical shortcomings.

Our study is affected by several limitations, mainly residing in its retrospective nature, in the heterogeneity of biopsy schemes adopted by each center and in the absence of a central pathologic review. In addition, we could not properly evaluate the PLND templates adopted in our patients, being treated up to twenty years ago. Surely, the mean number of nodes removed was not up to current standards, being only 12.6 overall, and 13.4 in intermediate or high risk patients. Furthermore, the therapies sometimes diverged from the current guidelines' advices, as witnessed by the 57.3% of low GS patients who underwent PLND to some extent, whereas 2.9% of high GS cases did not. On the other hand, this is one of the few studies in the literature to address the issue of the clinical relevance of GS upgrade in terms of oncologic outcomes, and the one with the largest cohort and the longest follow-up up-to-date.

## Conclusions

Our study shows a clear intermediate behaviour of GS upgraded cases in between unchanged lower and higher GS risk classes, while it does not evidence any association between GS upgrade probability and the number of biopsy cores.

## Conflicts of interest

Bollito E declares to have participated under fee to scientific meetings for AIOM Servizi srl and Myriad Generic Inc., Salt Lake City, and to have published under fee for Ippocrates Editore, Milano. All other authors have no conflict of interest to declare.

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