

# Oncological Outcomes after Radical Prostatectomy in D'Amico Intermediate-risk Prostate Cancer

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## ABSTRACT

**Purpose:** The aim of this study was to analyze the risk factors of recurrence and long-term oncological outcomes in D'Amico intermediate-risk prostate cancer (PCa). **Materials and Methods:** This is a retrospective study focused on 166 intermediate-risk PCa patients who underwent radical prostatectomy between January 2003 and January 2013. **Results:** Median age in the study cohort was 66 years. Mean serum prostate-specific antigen at diagnosis was 15.9 ng/ml. Lower urinary tract symptoms represented 70.3% with suspicious digital rectal examination in 9.7%. Clinical stage was T2b in 9.7% and T1c in 90.3%. All men had Gleason score (GS) 7 and were treated with open radical retropubic prostatectomy. Except for age, there was no difference in the clinical features between men aged 65–69 and  $\geq 70$  years. 100% of cancers were adenocarcinomas. Final pathological review revealed organ-confined disease in 68.1%, extracapsular extension in 20.1%, seminal vesicle invasion in 11.7%, and lymph node involvement in 23.37%. **Conclusion:** D'Amico's intermediate-risk PCa is a heterogeneous neoplasm entity presenting different prognoses based on clinical, biological, and pathological pre-therapeutic findings. Waiting for the development of relevant tools for cancer selection, the GS, and the number of intermediate-risk criteria makes it possible to identify good and poor prognosis subgroups, to optimize the therapeutic approach.

**Key word:** Oncological outcomes, prostate cancer, intermediate risk, radical prostatectomy

## INTRODUCTION

In these late decades, prostate cancer (PCa) remains a public health problem. It is the most common over 50-year-old men's cancer.<sup>[1]</sup> This entity is the leading cancer death cause in over 60-year-old men. Its annual incidence has been increasing steadily since 1982.<sup>[2]</sup>

PCa is localized when there is no clinically detectable capsular extension (stages T1–T2c). Nowadays, it is the most frequently diagnosed form. The diagnosis of localized PCa is mainly based on the digital rectal examination (DRE), the prostate-specific antigen (PSA) assay, and prostate biopsies. Pelvic magnetic resonance imaging (MRI) and bone scan tomography data show the extent of the disease.<sup>[3]</sup>

Screening is based on DRE and the PSA assay, which remains a sensitive but not very specific biological test for the disease and had many false positives. Moreover, the heterogeneity of the genetic and environmental factors that modulate prostatic carcinogenesis leads to a very heterogeneous and variable prognosis. It is of local and general rapid extension in some patients and latent or even indolent in others.

Radical prostatectomy (RP) remains the standard of care for localized PCa; it reduces 10-year mortality by 12–29%, and its effectiveness is proven by cancer control and overall survival rates. It is an aggressive procedure with functional side effects that can permanently affect the patient's quality of life. Therefore, it cannot be practice on latent cancers, low-risk extensive, or for patients with short life expectancy.<sup>[4]</sup>

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The intermediate-risk cancer of D'Amico (T2b or Gleason = 7 or PSA between 10 and 20 ng/ml) is a heterogeneous group of patients that can include a myriad of patients:

- Patients with a good prognosis having a single factor ranking them intermediate D'Amico group.
- Intermediate prognostic patients having 2 factors classifying them intermediate D'Amico group.
- Patients with a poor prognosis including the 3 factors of the intermediate D'Amico group.

Through this study and in light of the literature data, we will try to evaluate the controversies that indicate the management of D'Amico intermediate-risk cancer, as well as the characteristics of the specimen, the biochemical free-survival after RP, overall survival, depending on the presence of one or more pre-therapeutic factors classifying the patient in this heterogeneous D'Amico subgroups.

## MATERIALS AND METHODS

This is a retrospective study of 166 D'Amico intermediate-risk PCa patients, who undergone RP at the Mohammed V Military Teaching Hospital between January 2003 and January 2013.

The main objective of this study was to analyze the risk factors for recurrence and long-term cancer outcomes in intermediate-risk PCa (T2b or PSA tumor node metastasis [TNM] between 10 and 20 ng/ml or Gleason score [GS] = 7).

The study included  $\geq 50$  years' patients, undergone RP in our institution. A subanalysis was performed  $\geq 70$ -year-old men to determine the correlation with age.

The independent variables in this study were age, tumor stage, PSA level, PSA velocity, biopsy Gleason, number of positive prostate biopsies, and core tumor volume.

More than 190 patients selected in our study were over the age of 50 and had intermediate-risk PCa. The extremes of age were 50 and 77 years old.

The pathological and prognostic results (post-operative PSA, whether or not adjuvant treatment) were evaluated.

24 patients were excluded from the study due to some insufficiencies in the clinical records (incomplete data or missing information: Pre-operative PSA isoforms and pathological reports).

The collection of data was done through a comprehensive search in medical records, pre-biopsy PSA kinetics and radiological, operative, and pathological reports.

Pre-operative clinical and paraclinical data included age, clinical TNM stage, pre-operative PSA serum value,

prostatic volume, biopsy GS, pathological GS, extracapsular extension, seminal vesicles invasion, positive margins, and lymphnodestatus.

The paraclinical assessment performed for each patient was as follows: Ultrasound-guided prostatic biopsies, pelvic multiparametric MRI (mpMRI), and bone scan tomography.

A standard operability assessment was performed in all patients. The procedure performed was a radical retropubic open prostatectomy with uretrovesical anastomosis. All patients had bilateral ilio-obturator and hypogastric lymph node dissection.

Early complications were defined by their perioperative occurrence or within 1 month after surgery, whereas late complications were defined by a subsequent onset  $> 3$  months.

The post-operative follow-up consisted of a clinical examination with a DRE and serum PSA measurement at 1 month after surgery, every 3 months for 2 years, every 6 months for 3 years, and then annually.

The biological recurrence was defined by a PSA level higher than 0.2 ng/ml, confirmed by two increases, at two successive assessments of 3 weeks apart.

For statistical analysis, we calculated the statistical significance using the SPSS IBM 20.00 program. A  $P < 0.05$  was considered to be statistically significant.

## RESULTS

The median age at diagnosis was 66 (50–77). The duration of symptoms is the estimated time from the onset of symptoms to hospitalization for radical treatment. This duration had an average of 14 months ( $\pm 12.5$ ). The reason for consultation in 75% was lower urinary tract symptoms, followed by intermittent hematuria in 12.5% and erectile dysfunction in 6.25% [Table 1]. The patients were asymptomatic in 12.5%. The estimated-DRE prostate median volume was 44.6 g. The DRE was suspicious in 9.7%, which corresponds to stage T2b, whereas it was normal in 90.3% that corresponds to stage T1c.

The mean PSA level was 15.9 ng/ml. This rate was 15.1 ng/ml in 50–69 years old patients, and 17 ng/ml in those older than 70 years. The diagnosis was made by series of positive biopsies in 155 men and by transurethral resection of the prostate in 11 cases. All patients had US-guided and randomized biopsies; the number of positive cores was between 1 and 6. Positive biopsies were located at the right apex in 31.3%, the prostatic base and the left middle part in 25%, the left apex in 18.75%, and on suspicious areas in ultrasound in 6%. All patients had a Gleason biopsy score

7, which included them in the intermediate-risk group of D'Amico.

The mpMRI showed a benign prostatic hyperplasia in 18.75% and a heterogeneous image suggestive of malignancy in 89.25%. The detection of a prostatic nodule was possible in 71.3%; the median size of T2 hypointense nodules was 21 mm ( $\pm 3.5$ ). The absence of extracapsular extension (ECE) was noted in 67.2%, and the seminal vesicles and lymph node invasion were present in 21.2%.

The bone scan tomography was normal in 94.63%, while 5.37% of our patients had costal or vertebral hyperfixation areas, and mpMRI target on these areas made it possible to correct the diagnosis and to rule out the metastatic nature of these lesions.

According to 2010 TNM PCa Classification, 5.1% tumors were classified as T1a/b, 85.2% as T1c, and 9.7% T2b.

Before surgery, a standard assessment was performed, including a blood count, ionogram with renal function and protidemia, hemostasis assessment, urinalysis, standard chest X-ray, electrocardiography, and  $\pm$  an echocardiogram. This assessment was normal in 88%, and 11 patients had urinary infections and needed antibiotic treatment before operation.

**Table 1: Characteristics of the cohort study**

Characteristics	Number of patients (%)
Age (years)	
Median age: 66 years (50–77)	92.77
50–69	
>70	7.22
DRE	
Normal	90.3
Suspect	9.7
Symptoms: LUTS	
Present	72.72
Absent	27.28
Total PSA (ng/ml)	
All patients (years)	15.9 (4–20)
60–69	15.1 (4–20)
>70	17 (4–20)
Free PSA/total PSA (%) average:	
19.77%	
<15	60
15–25	30.90
>25	9.1

LUTS: Lower urinary tract symptoms, PSA: Prostate-specific antigen, DRE: Digital rectal examination

The median operating time was 189 ( $\pm 18$ ) min; the operative bleeding ranged between 300 and 550 cc.

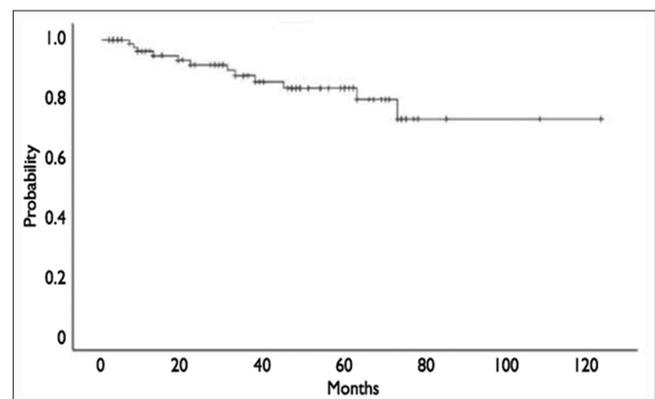
Pathological examination of the specimen showed localized tumors in 68.1%. After RP, 31.9% had locally advanced tumors: pT3a in 20.2% and pT3b in 11.7%. There was no difference in the pathological characteristics between 50 and 69 and over 70-year-old patients. All patients had classical prostate adenocarcinoma. The most common pathological GS was 7(4+3) with 57%, patients with GS 7(3+4) was 27%, GS of 8 or higher was 16%. extracapsular extension was found in 32.8%, seminal vesical invasion in 20.2% and pN+ in 23.37%.

No early post-operative bleeding or lymphorrhea was observed; wound infection occurred in 7.22%. Only 12.5% of patients showed late complications: Anastomotic stenosis in 8.15% and urinary incontinence in 2.68%.

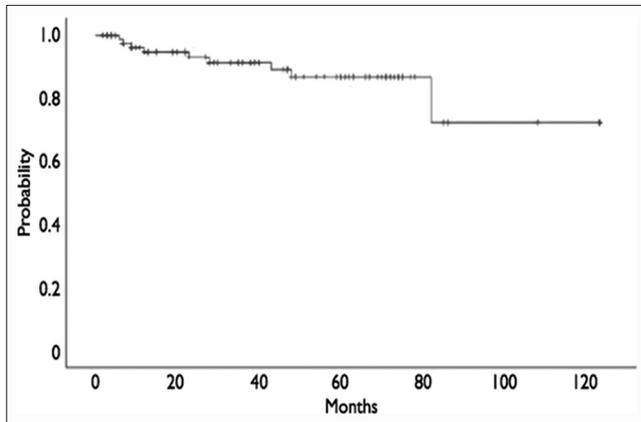
After 9 years' follow-up, the biochemical recurrence rate was 28.06%:

- Local clinical recurrence >2 years with a androgen PSA deprivation therapy (PSADT) >10 months, minority Grade 4 and positive margins at 20.52%.
- The systemic recurrence <6 months: With a PSADT <3 months, a major Grade 4 and lymph node involvement in 7.54%.

Biochemical recurrence-free survival was 71.94% [Figure 1] and overall survival was 88.4% [Figure 2]. There was no significant difference in biochemical recurrence-free survival and PCa-specific survival between 50–69 and over 70-year-old groups ( $P > 0.07$  and  $P > 0.07$ , respectively). According to the PSADT and the specific characteristics of the histological specimen, radiotherapy or adjuvant ADT was performed after surgery in 28.06% of patients: 20.52% had adjuvant radiation therapy on histological or biochemical local recurrence, and 7.54% had adjuvant ADT in case of micrometastasis.



**Figure 1: Kaplan–Meier biochemical progression-free survival after radical prostatectomy**



**Figure 2:** Kaplan–Meier overall survival after radical prostatectomy

## DISCUSSION

The D’Amico intermediate-risk PCa is a myriad of neoplasm, with varying degrees of proliferation and aggression. It may include various volumes of moderately differentiated carcinomas, with rapid growth and high locoregional invasion potential.

Alternatives to surgery in intermediate-risk PCa include radiotherapy with or without ADT, and until now, there is no clear evidence that surgery can compete or surpass these therapeutic procedures. RP is among the mean therapeutic indicated for the treatment of localized PCa, in patients whose life expectancy is equal to 10 years or greater. It may also be considered for tumors with limited ECE (T3a), particularly in young patients, if necessary combined with other physical or molecular therapeutic modalities.<sup>[5]</sup> The main goal of this surgery is to resect the entire cancer as long as it is limited to the prostate gland, which helps the disease control. Lymph node dissection allows the locoregional staging and improves specific cancer survival.

The D’Amico classification based on PSA level, tumor stage, and GS is used for PCa-risk stratification before surgery. This classification is a means of predicting biochemical recurrence after treatment. The estimated evolutionary risk of cancer is based on the biopsy GS, but many studies have shown that this classification is associated with a big risk of under- or over-estimation of the prognostic. Grade assessment can be misleading as a measure of the cancer fatality, especially for the most common grades (GS 3 + 4).<sup>[6,7]</sup> The upgrading rate according to the European Association of Urology and American Urological Association (EAU and AUA) can reach 19–36%.

Due to current risk stratification systems, limitation, and the imperfect prediction of D’Amico’s classification, Asians, Canadians, and Americans introduced various therapeutic

nomograms to facilitate multidisciplinary approach discussions and make conversation with the patient before the pragmatic treatment.<sup>[8]</sup> The challenge of incorporating these nomograms into daily practice is to rationally predict the severity of the disease and the different localized cancer prognostic probabilities.

In history, the first authors to report and alert practitioners about the heterogeneity of this particular group of D’Amico were Asians. jung et al found the same results and showed that there is heterogeneity in the oncological findings in 576 patients treated with RP for intermediate-risk PCa after a median follow-up of 87 months.<sup>[9]</sup>

5 years’ biological progression-free survival was 79.2%. Cancers with two factors were designated as poor prognosis intermediate-risk cancer ( $n = 222$ , 39.9%): biopsy GS 4 + 3 and/or PSA 10–20 ng/ml. Other patients with Gleason 3 + 4 and PSA <10 ng/ml were identified as having a good prognosis intermediate-risk disease ( $n = 334$ , 60.1%). When the intermediate-risk patients were stratified according to the operative specimen’s GS: Gleason 3 + 4, 4 + 3, and 4 + 4 patients had, respectively, 80.4, 70.7, and 53.7% biochemical progression-free survival (BFS) rates (log rank,  $P < 0.001$ ).

The poor prognosis group had significantly higher rates of adverse pathological features: Extracapsular tumor extension (24.6% vs. 38.7%,  $P < 0.001$ ), seminal vesicle invasion (2.4% vs. 8.6%,  $P = 0.001$ ), and lymph node involvement (2% vs. 16.8%,  $P = 0.018$ ). The good prognosis intermediate-risk group had a 5 years’ biochemical progression-survival rate significantly greater compared to the adverse group (87.5% vs. 66.5%) (log rank,  $P < 0.001$ ).

After reporting this statistical reality in 2009 on the, National Comprehensive Cancer Network (NCCN)–AUA–EAU guidelines, other North European teams: The Mayo Clinic, the John’s Hopkins and the MSKCC, retrospectively reviewed their records (open surgery, laparoscopic, and robotic-assisted RP) to evaluate the extent and scale of this particular pathological and heterogeneity of this new D’Amico group.

Zelevsky, Karakwicz, and Stamey were unanimous on the D’Amico intermediate group which included three prognostic subgroups (good, intermediate, and poor prognosis).

The favorable subgroup: The patients had PSA between 10 and 20 ng/ml or T2b at the DRE, but their Gleason biopsy was 3 + 3 or 3 + 4 with <20% primary Grade 4. In this entity, DRE and PSA would be biased by non-neoplastic phenomena; the absence of the primary Grade 4 or its minority character determines the good prognosis.

The intermediate subgroup: In this entity, the tumor volume between 2 and 5 Grade, a correlation between PSA of 10 and

20 ng/ml, and the tumor volume, as well as a primary Grade 4 represent 21–49% of the score 3 + 4.

The poor subgroup: The patients had the 3 indices of the intermediate group: A strong correlation between PSA 10–20 ng/ml and a tumor volume >5 cc. The aggressiveness of this entity is increased by a Grade 4 >50%, transforming an eventual 3 + 4 into a real 4 + 3.

Reese *et al.* found that the BFS was significantly higher in men with clinical intermediate risk than GS or PSA intermediate risk. In addition, no difference was found between low risk and clinical intermediate risk in their series.<sup>[10]</sup> Men with more intermediate-risk criteria had poorer post-operative outcomes.

In our work, the intermediate group had a 48.2% recurrence PSA rate 10 years after RP. These patients, as well as those of the high-risk group, have the same prognostic profile and the same operative specimen histological details. These patients could be assimilated to the poor prognosis intermediate group of Stamey-Eastham and Karakweicz.

Comparing our patients to American and Asian series and subdividing them into three subgroups, we made the following comparative Table 2.

According to the AUA and EAU, the best outcomes were obtained in patients with GS 7 (3 + 4) with 82.7% and BFS rate against 65.1% for men with Gleason 7 (4 + 3). According to this significant difference in prognosis, they proposed that all Gleason grade groups were different prognostic groups and these data justified the reclassification of Gleason 7 into two distinct risk groups, providing additional support for Gleason's new ISUP 2005 stratification.

Stark *et al.* published their research, which was based on studies of pathologists evaluating 693 prostatectomy specimens and 119 biopsy samples to assign primary and secondary Gleason models.<sup>[11]</sup> The researchers collected 20 years of follow-up data on these patients. They found that patients with a GS of 4 + 3 were 3.1 times more likely to develop lethal PCa than patients with a GS of 3 + 4 (95% CI, 1.1–8, 6).

In NCCN intermediate-risk PCa, BFS rates were significantly different, depending on the number of risk factors present. For patients with one intermediate risk factor, the 5 years' BFS was 87.0%, 64.3% for men with two risk factors, and 45.9% for men with three risk factors ( $P < 0.01$ ). There was no significant BFS difference between low-risk men and intermediate-risk group due to clinical stage or between intermediate-risk group and high risk due to clinical stage. The NCCN, AUA, and EAU are unanimous in proposing other less invasive therapeutic approaches for the management of D'Amico intermediate-risk tumors: External beam radiotherapy associated with curative therapy, ablative therapies (cryotherapy), ADT, and combined ADT-radiotherapy. To improve the effectiveness of external beam radiotherapy (EBRT), the combination with ADT has been proposed. The aim of this combination was to potentiate the effect of EBRT in irradiated volumes and to offer an active treatment for metastatic disease in parallel with local radiotherapy treatment.

In a phase III study, conducted by D'Amico *et al.*, 206 patients were randomized between EBRT alone at a dose of 70 Gy (three-dimensional conformational technique) and the same irradiation associated with ADT for 6 months.<sup>[12]</sup> The patients had localized PCa (T1b–T2b), with a GS  $\geq 7$  and/or a PSA level between 10 ng/ml and 40 ng/ml. The majority of patients had intermediate-risk PCa (85% GS <8 and 87% PSA level  $\leq 20$  ng/ml). After 5 years, overall survival increased from 78% to 88% by the combined ADT-radiotherapy ( $P = 0.04$ ).

Salvage ADT free survival was 82% in the ADT-radiotherapy arm versus 57% in the radiotherapy arm alone ( $P = 0.002$ ). In a second analysis, with a median follow up of 7,6 years, the overall survival was 74% with ADT ( $P = 0.05$ ). A more specific analysis showed that this benefit would only exist for patients with little or no comorbidities (heart rate [HR] = 4.2 [2.1–8.5],  $P < 0.001$ ). For patients with moderate-to-severe comorbidities (myocardial infarction, etc.), the combination of ADT-radiotherapy for 6 months would have a deleterious effect, leading to an increased cardiovascular mortality (HR = 0.5 [0.27–1.10],  $P = 0.08$ ).

In RTOG 94–08 trial, 1979 patients were randomized to receive 66.6–68.4 Gy radiotherapy alone or combined with ADT, started 2 months before and continued for 4 months.<sup>[13]</sup>

**Table 2: PSA recidivism rate at 10 years**

Subgroups	Stamey series <i>n</i> =3482 (%)	Eastham series <i>n</i> =5173 (%)	Karakwikcz series <i>n</i> =871 (%)	Our series <i>n</i> =166 (%)
Good prognosis	10.8	12.1	9.2	9.7
Intermediate prognosis	30.2	28.7	24.3	26.1
Poor prognosis	49.7	48.3	45.1	48.2

All patients had PSA  $\leq 20$  ng/ml and T1 or T2 lesion. GS was  $< 7$  for 61% of patients. 10 years overall survival increased from 57% to 62% ( $P = 0.03$ ), by the combination ADT-radiotherapy. Control biopsies were performed in 439 patients in the ADT-radiotherapy arm and 404 in the radiotherapy alone arm. Biopsies were positive, respectively, in 20% and 39% ( $P < 0.001$ ), confirming a benefit in the disease local control. In a subgroup analysis, the 10 years' overall survival with combined ADT-radiotherapy increases from 54% to 61% ( $P = 0.03$ ). This benefit was not found in low risk PCa. The combination of 70 Gy radiotherapy and 6 months of hormonal therapy is considered a reference treatment in intermediate-risk PCa.

Several studies suggested that there might be a dose-response relationship for PCa. In 1988, Hanks *et al.* retrospectively analyzed the effect of the dose on local control in 1516 patients treated with EBRT.<sup>[14]</sup> They observed that an irradiation dose  $> 70$  Gy appeared to provide better local control. In a series of 1127 patients treated at MD Anderson Cancer Center by EBRT between 1987 and 1997, Pollack *et al.* found that an irradiation dose above 77 Gy in intermediate PCa (T1-T2 with PSA between 10 and 20 ng/ml)<sup>[15]</sup> improved biochemical free survival rate. Finally, the long-term (8–12 years) analysis of the dose escalation study results of a Fox Chase Cancer Center including 229 patients also proved the effect of the total radiotherapy dose.<sup>[16]</sup> In the group of patients with PSA between 10 and 20 ng/ml before treatment, the biochemical free survival rates were 19%, 31%, and 84% for total irradiation doses, respectively, lower than 71.5 Gy, between 71.5 Gy and 75.6 Gy, and above 75.6 Gy. These results justified randomized studies to confirm the anticipated dose effect.

Several phase III studies compared 66–70 Gy to 74–80 Gy doses of EBRT. The populations studied were often not very homogeneous, having low-, intermediate-, and high-risk cancers according to the D'Amico classification. All, however, confirmed that a 10 Gy irradiation dose increase was associated with a 5 years' biochemical free survival rate improvement from 50–60% to 70–85%, all stages of the disease combined. This benefit, however, seemed more pronounced in intermediate-risk PCas. Three of these studies proposed an irradiation dose of 78–80 Gy in the experimental arm.

The MD Anderson Cancer Center study compared 78–70 Gy doses.<sup>[17]</sup> 301 patients were included, with intermediate or poor prognosis risk cancers. The main objective was to evaluate the impact of this dose increase on survival without clinical and/or biological recurrence. At 5, 8, and 10 years, respectively, this was increased from 78% to 85%, from 59% to 78%, and from 50% to 73% in the 78Gy arm compared to the 70Gy arm. The increase in irradiation dose was, however, associated with an increase in late grade toxicities  $\geq 2$  rectal (26% vs. 13%) and urinary (13% vs. 8%).

In the Dutch study, 669 patients with intermediate-to-poor prognosis risk cancers were randomized between two doses of irradiation: 68 Gy and 78 Gy.<sup>[18]</sup> 7 years' biochemical free survival was increased from 45% to 56%. The cumulative incidence of digestive toxicities was similarly increased from 25% to 35%.

Finally, the GETUG 6 study, a dose of 80 Gy was compared to a dose of 70 Gy in patients primarily with intermediate-risk PCa.<sup>[19]</sup> 5 years' biochemical free-survival rates were, respectively, 68% and 76.5% in the 70 Gy and 80 Gy arms. In this study, the increase in radiation dose was also associated with an increase in acute and late urinary and rectal toxicity.

If dose irradiation increasing to 78–80 Gy improves the biological control, all of these studies show toxicities increasing which does not allow to consider higher doses in EBRT alone. The 78–80 Gy EBRT, using appropriate irradiation techniques, if possible with modulation of intensity and localization of the prostate before each session, is the standard of care in intermediate-risk PCa. Until now, all randomized studies have been conducted without ADT. The association with dose increase remains to be defined.

Some alternative approaches is the brachytherapy. Iodine 125 LDR-brachytherapy is a PCa treatment technique that implants radioactive iodine 125 or palladium (Pd) sources directly into the prostate. The position of the sources is defined on a 3D reconstruction of the prostate from ultrasound sections. Irradiation is, therefore, delivered directly into the prostate, with great precision, which makes it possible to avoid touching the neighboring organs or to administer higher doses than in EBRT. In France, brachytherapy indications for the prostate are limited to low-risk cancers. In other countries, particularly in the United States, it has also been developed in association with external irradiation and/or in intermediate-risk cancers. The aim is to combine the ability of EBRT to treat a possible extracapsular tumor extension and/or seminal vesicle involvement with the brachytherapy capacity to deliver higher irradiation doses within the prostate than in exclusive EBRT.

In all of these studies, biochemical free-survival rates are particularly high: 86–96% at 5 years, 92% at 8–10 years, and still 80–87% at 14–15 years, which shows a biological control rates much higher than those observed with an exclusive EBRT, and this in a sustainable way as published after 14–15 years of follow-up. A dose-response effect combined to EBRT and brachytherapy has better biological control of PSA than EBRT alone. However, until now, no randomized study has compared the two therapeutic approaches. Only one meta-analysis attempted a comparison between the two treatments without being able to show any difference.<sup>[20]</sup> This analysis was made difficult by variable definitions of biological recurrence from one study to another. The authors encouraged the completion of a randomized phase III study.

For intermediate-risk PCa management evolution, several randomized studies demonstrated that 78–80 Gy dose improves oncological outcomes. The combination ADT-radiotherapy benefit for 70 Gy was observed; however, a 78–80 Gy dose effectiveness remains to be demonstrated. The GETUG 14 study purpose is to evaluate ADT-radiotherapy when the dose is increased from 70 Gy to 80 Gy. 350 patients were randomized between exclusive 80 Gy radiotherapy and the same dose associated with short-term ADT (6 months). The inclusions in this study are complete, and the results are expected. The RTOG Study 0.815 is a randomized study that proposes to compare an irradiation dose increase alone or combined to short 6-month ADT. This irradiation dose increase can be achieved in exclusive radiotherapy (79.2 Gy with 1.8 Gy per fraction) or combined to 125 iodine brachytherapy (110 Gy), palladium 103 (100 Gy), or iridium 192 ( $2 \times 10.5$  Gy). This study is currently being included. Although the results of the EBRT and brachytherapy combination seem encouraging and perhaps superior to exclusive radiotherapy, no randomized study compared the 2 therapeutic modalities. As part of the GETUG, a Phase III study will be started soon. It will compare, in a population of patients with intermediate-risk PCa, external irradiation at 80 Gy in 40 sessions, with combined external radiotherapy at 46 Gy, and brachytherapy achieved either in LDR with iodine 125 or HDR. The main objective will be to determine whether there is a significant improvement in biochemical free survival when brachytherapy is associated with EBRT.

The Scandinavian PCa Group Study 4 (SPCGS-4) randomized 695 men between RP and active surveillance for “localized” cancers that would be predominantly intermediate (80% cT2, median PSA: 12 ng/ml).<sup>[21]</sup> The specific mortality observed for the series was 19% and the overall mortality at 10 years was 45%. With a decline of 23.2 years, the study showed a metastatic free-survival benefit with RP for the entire series, a result, especially, observed for men under 65 ( $P < 0.001$ ) and intermediate-risk tumors. The relative risk reduction (RR) of overall mortality (29%), specific mortality (62%), metastasis (51%), and ADT (55%) was significant with RP.

In the Zumsteg study where 1024 patients received escalated doses of EBRT between 1999 and 2007, it was demonstrated that patients with intermediate-risk PCa belong to heterogeneous group that can be stratified into well and poor prognosis subgroups according to recognized oncological standards.<sup>[22]</sup> They defined men with intermediate-risk PCa as those with a GS of 3 + 4 or less and positive biopsies <50%. All other patients were classified as poor prognosis intermediate-risk subgroup. These had a 2.4 increasing in PSA recurrence, a 4.3 in distant metastases, and a 7.4 in specific mortality.

Other future markers should supplement the D’Amico classification: More predictive molecular and genetic

biomarkers. In our daily practice, in view of the non-availability of new molecular and genetic markers study of the biopsy specimen and the lack of access to MRI-spectroscopy, we prefer to operate our patients, after consent in a well-informed patient through nomograms of AFU, EAU, or AUA.

Since 2010, the AUA, EAU, and NCCN are unanimous on the equality of the oncological outcomes of RP with extensive lymph node dissection versus 3 years ADT-radiotherapy. The only downside is that this combination first makes a perilous RP (vascular lesions and rectosigmoid). Fortunately, the high-intensity focused ultrasound could effectively treat 67% of local recurrences after radiotherapy.

Continuous monitoring is required to confirm these findings with subsequent follow-up. In the meantime, the high scientific level clinical trial results in evidence and our disposal of a histological, genetic, and morphological technical platform, allowing to target real localized cancers; we remain compliant with the recommendations and guidelines of the EAU and AUA regarding the treatment and follow-up of D’Amico intermediate-risk cancer.

The strengths of our work were as follows:

- The intermediate D’Amico group is a heterogeneous entity with three evolutionary modalities (good, intermediate, and poor prognoses);
- The initial PSA and DRE are biased by non-tumor histological changes in the gland, generated by decades and age;
- The only determining factor in univariate and multivariate analysis is the percentage of Grade 4 variable from 1% to 99% on the specimen of the gland;
- Tumoral volume, cancer extent, ECE, and lymph node involvement condition the Grade 4.
- The three subgroups differ by the histological indices mentioned above;
- The three subgroups differ in 5 and 10 years biochemical free-survival rate.
- The three subgroups differ in the need for uni-, bi-, or multi-modal treatment.
- Radiotherapy seems to offer the same long-term oncological results as RP with external and internal iliac lymph node dissection.

## CONCLUSION

D’Amico intermediate-risk PCa is a heterogeneous neoplasms entity that presents different prognoses based on clinical, biological, and pathological pretherapeutic findings.

Considering the data of the literature and the results of our study compared to those of other international institutions, the

best expertise remains the surgical exploration, the detailed analysis of the specimen, and the lymphnode involvement.

Waiting for the development of relevant tools for cancer selection, the biopsy GS and the number of intermediate-risk criteria present make it possible to identify good and poor prognosis subgroups.

Until the incorporation of biomolecular and genetic markers to the standard criteria of D'Amico, only the surgical expertise and/or evolution of PSA for the first 10 years after RP or post-radiotherapy are able to provide accurate information on the subsequent outcome of the disease and the patient survivorship.

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