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# REPEATED MRI SCANS DURING ACTIVE SURVEILLANCE FOR PROSTATE CANCER: NATURAL HISTORY OF PROSTATIC LESIONS AND UPGRADING RATES OVER TIME

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# TABLE OF CONTENTS

*1 SUMMARY ..... 1*

*2 ABBREVIATION LIST ..... 3*

*3 PROSTATE CANCER ..... 4*

**3.1 Epidemiology ..... 4**

3.1.1 Age distribution ..... 4

3.1.2 Geographic Distribution ..... 5

3.1.3 Racial Differences ..... 7

**3.2 Risk Factors and Etiology ..... 8**

**3.3 Prostatic Carcinomas Histotypes ..... 13**

**3.4 Grading of Prostatic Adenocarcinoma ..... 15**

3.4.1 Original Gleason System ..... 16

3.4.2 Modified Gleason System ..... 17

*4 DIAGNOSIS AND STAGING ..... 22*

**4.1 Clinical Presentation ..... 22**

**4.2 Methods of Diagnosis ..... 23**

4.2.1 Digital Rectal Examination ..... 23

4.2.2 Prostate Specific Antigen ..... 23

4.2.3 PCA3 ..... 25

4.2.4 Transrectal Ultrasonography and Prostatic Biopsies ..... 25

4.2.5 Multiparametric magnetic resonance imaging (mpMRI) ..... 27

4.2.6 Other considerations ..... 30

4.2.7 Summary of evidence and practical considerations on pre-biopsy mpMRI ..... 32

**4.3 Screening ..... 33**

**4.4 Clinical and Pathological Staging ..... 34**

4.4.1 T-staging ..... 37

4.4.2 N-staging ..... 38

4.4.3 M-staging ..... 38

**4.5 Prognostic Grouping ..... 39**

*5 CURRENT TREATMENTS FOR PROSTATE CANCER ..... 43*

**5.1 Deferred Treatment: Watchful Waiting/Active Surveillance ..... 43**

**5.2 Radical Prostatectomy ..... 43**
5.2.1 Pelvic Lymphadenectomy ..... 46
**5.3 Androgen Deprivation Therapy ..... 49**
**5.4 Radiation Therapy ..... 51**
5.4.1 External Beam Radiotherapy ..... 51
5.4.2 Radiation Therapy for Non-Metastatic Prostate Cancer ..... 54
5.4.3 Postoperative Radiation Therapy ..... 55
**5.5 Radiation Therapy – Brachytherapy ..... 57**
***6 REPEATED MRI SCANS DURING ACTIVE SURVEILLANCE FOR PROSTATE CANCER: NATURAL HISTORY OF PROSTATIC LESIONS AND UPGRADING RATES OVER TIME ..... 59***
**6.1 Introduction ..... 59**
**6.2 Materials and Methods ..... 63**
6.2.1 Study population ..... 63
6.2.2 mpMRI protocol ..... 64
6.2.3 Variables and outcomes of interest ..... 65
6.2.4 Statistical analyses ..... 68
**6.3 Results ..... 69**
6.3.1 Descriptive analyses ..... 69
6.3.2 Natural history of mpMRI prostatic lesions ..... 70
6.3.3 Diagnostic accuracy of serial mpMRI scans ..... 70
6.3.4 Multivariable logistic regression models ..... 73
6.3.5 Repeated mpMRI scans, PSA-D and baseline PI-RADS score ..... 75
**6.4 Discussion ..... 78**
***7 CONCLUSIONS ..... 82***
***8 BIBLIOGRAPHY ..... 83***

# 1 SUMMARY


**Objectives**

To test upgrading rates in patients on Active Surveillance (AS) for prostate cancer (PCa) after serial multiparametric magnetic resonance imaging (mpMRI) scans.

**Materials and methods**

Retrospective analysis of 558 patients. Five different criteria of mpMRI progression were used: 1) PI-RADS score increase; 2) lesion size increase; 3) EPE score increase; 4) overall mpMRI progression; 5) number of criteria for mpMRI progression (0 vs. 1 vs. 2-3). Moreover, two definitions of PCa upgrading were evaluated:1) ISUP GG≥2 with >10% of pattern 4; 2) ISUP GG≥3. The estimated annual percent changes (EAPC) methodology depicted temporal trends of mpMRI progression criteria. Sensitivity, specificity, positive predictive (PPV) and negative predictive value (NPV) of mpMRI progression criteria were analysed. Multivariable logistic regression models tested PCa upgrading rates.

**Results**

Lower rates over time of all mpMRI progression criteria were observed. The NPV of serial mpMRIs spans from 90.5 to 93.5% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and from 98 to 99% (ISUP GG≥3 PCa upgrading), according to the different mpMRI progression criteria. A PSA-D cut-off of 0.15 ng/ml/ml sub stratified those patients who could skip a prostate biopsy. In multivariable logistic regression models testing PCa upgrading rates, all five mentioned mpMRI progression criteria achieved independent predictor status.

**Conclusions**:

During AS, approximately 27% of patients experience mpMRI progression at first repeated scan. However, the rates of mpMRI progression decrease over time at subsequent mpMRIs. Patients with stable mpMRI findings and with PSA-D<0.15

ng/ml/ml could safely skip surveillance biopsies. Conversely, patients who experience mpMRI progression should undergo a prostate biopsy.

## 2 ABBREVIATION LIST

AS: Active Surveillance

AT: active treatment

PCa: prostate cancer

mpMRI: multiparametric magnetic resonance imaging

PI-RADS: Prostate Imaging Reporting and Data System

EPE: extraprostatic extension

ISUP GG: International Society of Urological Pathology grade group

EAPC: estimated annual percent changes

PPV: positive predictive value

NPV: negative predictive value

PSA: prostate specific antigen

PSA-D: prostate specific antigen density

DRE: Digital Rectal Examination

IQR: interquartile range

cT: clinical T stage

PNBs: previous negative biopsies

CI: confidence interval

OR: Odds Ratio

# 3 PROSTATE CANCER

## 3.1 Epidemiology

Nowadays, prostate cancer (PCa) is considered one of the most important clinical problems facing male population. As a matter of fact, it is the most common solid cancer and the sixth cause of cancer death among men worldwide with 899'000 new estimated cases and 258'000 new deaths in 2008 [1]. According to the American Cancer Society's projections for 2012, 241'740 new cases of PCa and 28'170 deaths linked to the disease are expected in the United States [2,3]. In Europe, the incidence rate is 214 cases per 1'000 men. Furthermore, since 1985 a slight increase in the number of deaths from PCa has been observed in many countries, even in regions where PCa is less common.

### *3.1.1 Age distribution*

The incidence of prostate cancer increases with age. Less than 0,1 % of all patients with PCa are younger than 50 years. About 85% of PCa cases are diagnosed after the age of 65 with the incidence's peak between 70 and 74 years old. The cumulative risk of positive PCa diagnose for a 85 years old man ranges from 0,5 to 20%. However PCa can often remain silent, and for this reason the real incidence of the disease is much higher, as shown in autopsy studies: microscopic PCa lesions are found in approximately 30% of men in the fourth decade, 50% in the sixth decade, and more than 75% in men older than 85 years [4,5]. For these reasons we can assume that the natural history of PCa varies considerably among patients. In some cases PCa can be very aggressive, causing significant morbidity and death. On the other hand, the course of the disease can be indolent in other men. PCa occurs more often in very old man whose life threatening co-morbid conditions are more common, therefore the majority of this cohort of patients suffer of PCa and its symptoms but die for other diseases. With current treatments, survival rate after five years improved from 68% in the 1970s, to 76% in the 1980s and finally moving towards 100% in the last decade.

In addition, mortality increases with age: from 3/100'000 cases of death in patients from 45 to 50 years, going up to 30/100'000 in patients from 60 to 65 years and about

100/100’000 between 70 and 75 years, finishing with a rate of 400-500/100’000 in more than 80 years old patients.

The introduction of the Prostate Specific Antigen (PSA) screening has led to an early PCa diagnosis, increasing the incidence in men aged 50 to 59 years by 50% between 1989 and 1992. However, from 1991, even if the incidence of PCa increased steadily, the rate of mortality started to decrease year by year [6]. This phenomenon can be explained by a gradually increase in the number of elderly people in the world together with the new diagnostic improvement [7,8].

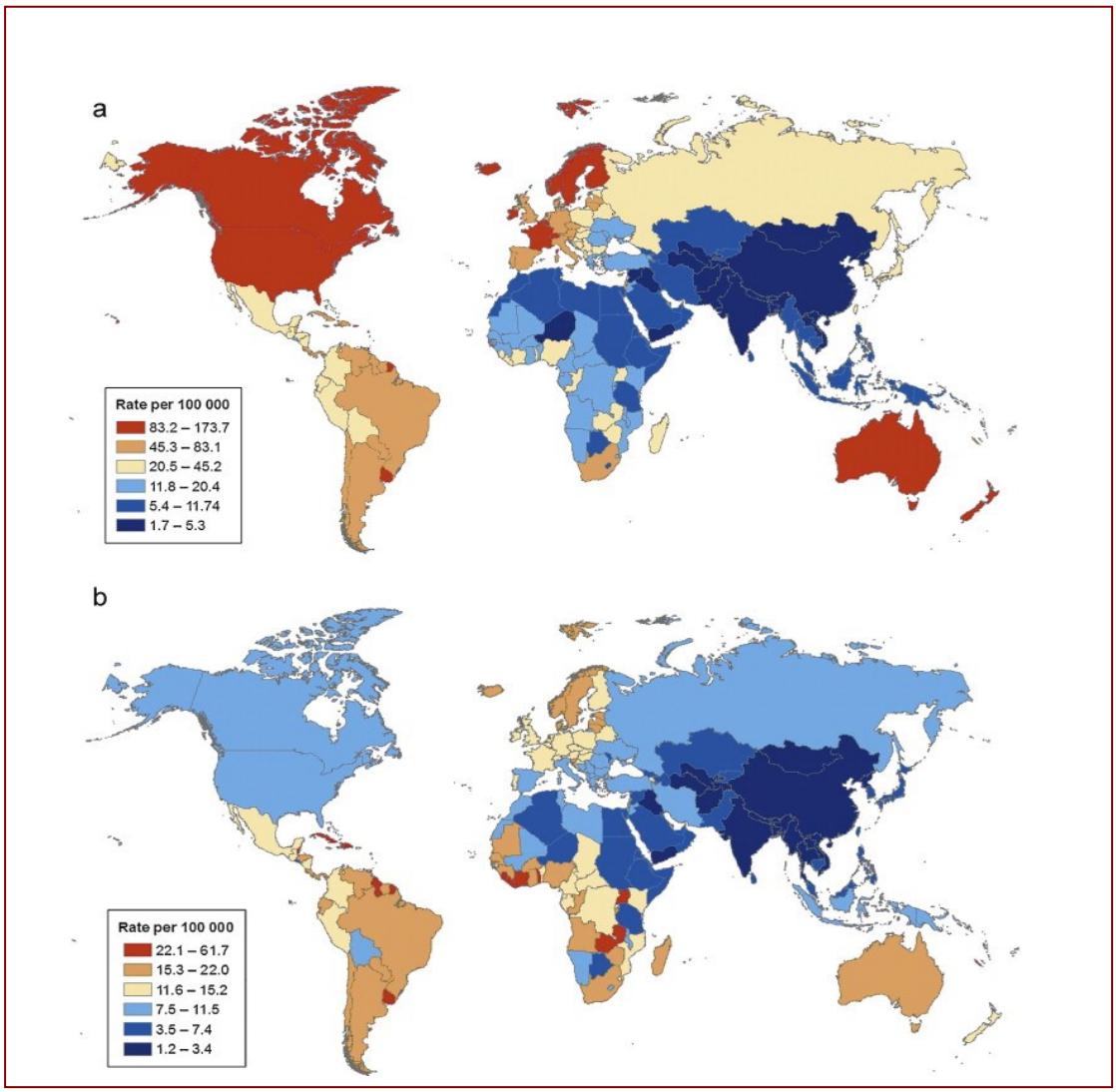
### *3.1.2 Geographic Distribution*

It has been estimated that in 2008 almost 899’000 PCa cases and 258’000 PCa deaths worldwide, with 72% of the cases and 53% of the deaths in developed countries, representing <20% of the world population. Countries with the highest incidence rate of PCa are: Australia/New Zealand, western Europe, North America, and the Caribbean; instead those with the lowest incidence rate are south central Asia, northern Africa, and eastern Asia (Figure 1a). However, estimated PCa mortality rates were highest in the Caribbean and also in a number of countries in southern and western Africa and in South America; while the lowest rates have been observed in most parts of Asia, northern Africa, as well as North America (Figure 1b). Although PCa is the most commonly diagnosed cancer among men in 2008 in many regions of the world (Figure 2a), it is estimated as the most common cause of cancer deaths in only a handful of countries, located primarily in the Caribbean, South America, and sub-Saharan Africa (Figure 2b) [6].

A recent study shows variations in PCa incidence and mortality patterns by examining the most up-to-date incidence rates published for 40 countries. The data are based on 63 population-based cancer registries, as well as mortality rates for 53 selected countries obtained from the World Health Organization (WHO) mortality database [6]. An increase in PCa incidence rates has been observed in 32 of the 40 countries analyzed with the estimated Average Annual Percent Change (AAPC) ranging from 2% to 3% in Sweden, United Kingdom, and Thailand (2 registries) to 12–16% in China (2 registries), the Republic of Korea, and Lithuania; rates are quite steady in any of these countries. Otherwise, PCa mortality rates have decreased in 27 of the 53 countries included in the

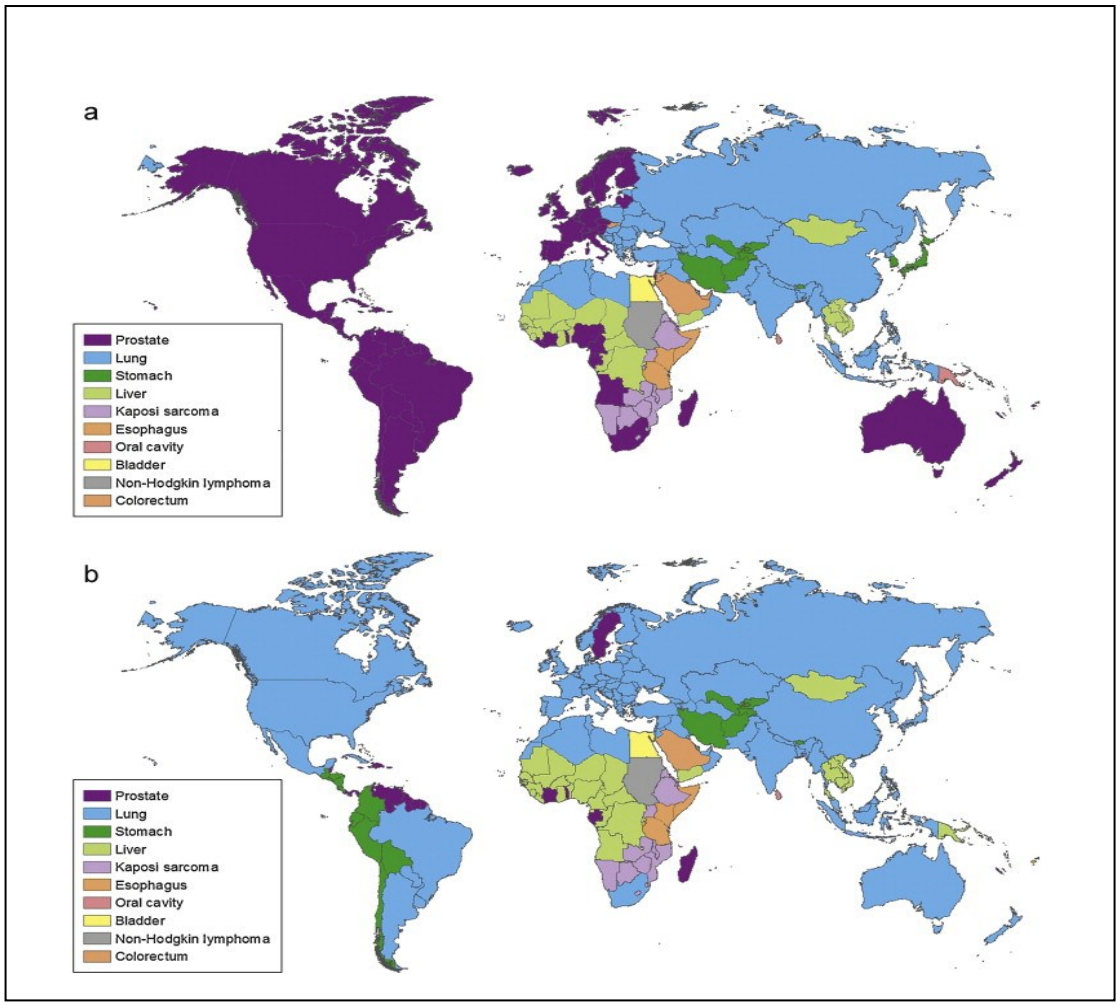
analysis (North America, Oceania, western Europe, and parts of northern Europe), increased in 16 (central and eastern Europe, parts of Asia, and Africa), and remained stable in the other 10 countries [6].

***Figure 1.*** *(a) International variation in age-standardized prostate cancer incidence rates; (b) international variation in age-standardized prostate cancer mortality rates.*




Source: GLOBOCAN 2008 [1]

***Figure 2.*** *(a) Most commonly diagnosed cancer among men worldwide, 2008; (b) leading cause of cancer deaths among men worldwide, 2008.*




Source: GLOBOCAN 2008 [1]

### *3.1.3 Racial Differences*

African American men have the highest reported incidence of PCa among all races, with an incidence rate of 272/100'000, followed by the Caucasian at 169/100'000 and Asian at 101/100'000. Native Americans have a much lower incidence (50/100'000). Mortality rate follows the same pattern: African American men have a mortality rate of around 68/100'000, the Caucasian about 27/100'000 and the Asian about 12/100'000. Many factors have been considered to explain such a high incidence and mortality rate in the African American population relative to the others. Some hypotheses include differences in genetic predisposition; differences in mechanisms of tumor initiation (e.g.

promotion or progression); higher fat diets, higher serum testosterone levels, or higher body mass index relative to other populations. Moreover many social variables have been suggested to have a role such as: structural, financial, and cultural barriers to screening, early detection, aggressive therapy and physician bias. However, there are no data that clearly support any of these hypotheses as explanations for the observed differences in incidence or mortality, probably because many factors and variables interact with each other.

## 3.2 Risk Factors and Etiology

There is little information about the cause of PCa, but like many other solid tumors, it is certainly multi-factorial. Even if the causes of PCa initiation and progression are unknown, there are strong evidences that genetic and environmental factors are mainly involved.

Actually, the most important risk factors are inheritance, advanced age and African American race [6].

Focusing on inheritance, it is noteworthy that 15% of patients have positive family history for PCa. Bratt et al. have shown [9] that the relative risk increases according to the number of affected family members, their degree of relatedness, and the age at which tumors were diagnosed (Table 1).

***Table 1.*** *Family and history and Risk of Prostate Cancer.*

| Family History | Relative Risk | Absolute Risk (%) |
|---|---|---|
| None | 1 | 8 |
| Father or brother | 2 | 15 |
| Father or brother affected <60 yrs | 3 | 20 |
| Father and brother | 4 | 30 |
| Hereditary PCa | 5 | 35-45 |

*Source: adapted from Bratt O, J Urol 2002:168:906-13* [9]

PCa can be divided in: sporadic, familiar, and hereditary tumor. The sporadic ones are defined as cancers occurring in men with no relatives affected by PCa (85% of cases), familiar ones occur in men with one or more relatives affected (6% of cases) and hereditary cancers occur when there are 3 or more affected relatives or at least 2 relatives with early-onset (<55 years old) disease (9% of cases) [10]. If one first-line relative has PCa, the risk of being diagnosed with PCa at least doubles. If two or more first-line relatives are affected, the risk increases 5- to 11-fold [9,10]. Hereditary PCa accounts about 43% among early-onset diseases [10] and is usually diagnosed 6-7 years earlier than spontaneous tumors, but the characteristics of the disease are similar [9].

In the last years many studies focused on familiar and hereditary PCa in order to discover susceptibility genes through segregation analyses. The results of these reports suggest a dominant mode of inheritance for familial PCa cases [11]. Abnormalities of chromosome 1q24-25 have been found in about 30% of the families affected by familiar PCa, while 16% of them have showed abnormalities of the Xq27-28 chromosome [12]. Today, the mayor candidate genes, involved in PCa, are at least eight: RNase L/HPC1 [13], ELAC2/HPC [14], SR-A/MSR1 [15], CHEK2 [16], BRCA2 [17], PON1 [18], OGG1 [19], and MIC1 [20]. Their location on the genome and function is explained in Table 2.

***Table 2.*** *Prostate Cancer Susceptibility Genes*

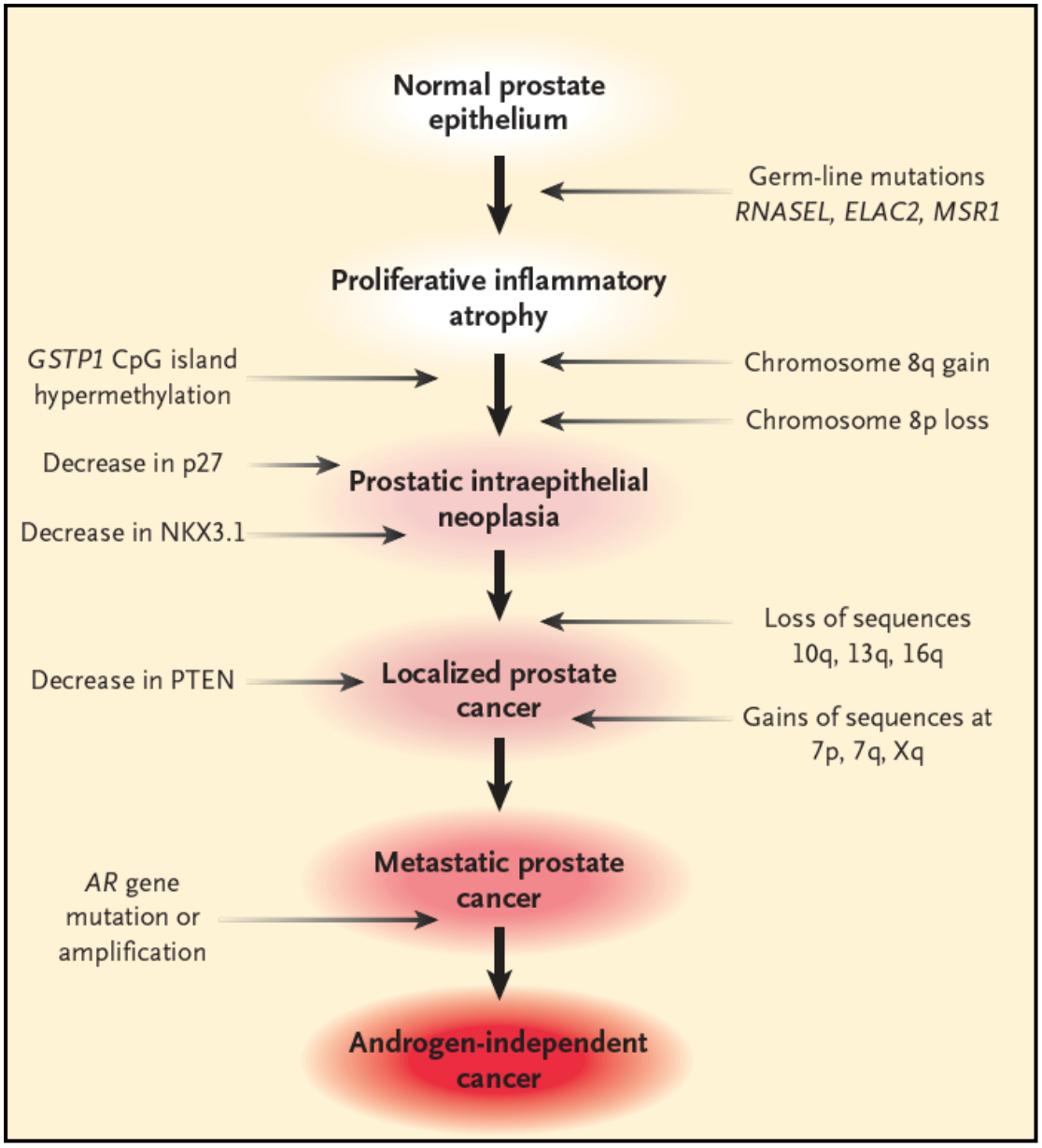
| Gene | Chromosome Location | Year Identified | Function |
|---|---|---|---|
| ELAC2/HPC2 | 17p11 | 2001 | Unknown |
| RNase L/HPC1 | 1q24-25 | 2002 | Apoptosis and susceptibility to infection |
| SR-A/MSR1 | 8p22-23 | 2002 | Inflammation and susceptibility to infection |
| OGG1 | 3p26.2 | 2002 | DNA repair of oxidative damage |
| CHEK2 | 22q12.1 | 2003 | DNA damage signaling and cell cycle control |
| BRCA2 | 13q12.3 | 2003 | DNA repair |
| PON1 | 7q21.3 | 2003 | Antioxidant, free radical scavenger |
| MIC1 | 19p13 | 2004 | Inflammation |

Furthermore, a very important role is played by endocrine and environmental factors. Zaridze et al. have found that the incidence of PCa increases in Japanese men when they move from Japan to Hawaii, and the incidence almost approaches the one of Americans if they move to California [21]. This means that the environment is fundamental in determining the risk of progression from latent PCa to clinical disease. Despite their relevance, environmental factors are very difficult to identify. Actually there are some theories evaluating the role played by changeable factors such as food and alcohol consumption, pattern of sexual behavior, exposure to carcinogens and ultraviolet radiation and finally the occupational exposure [22]. The most studied dietary and nutritional factors that may influence pathogenesis of PCa are: total energy intake, dietary fat, cooked meat, micronutrients and vitamins (such as carotenoids, retinoids, vitamins C, D and E), fruits and vegetables intake, minerals (such as calcium and selenium), and phytoestrogens (such as isoflavonoids, flavonoids and lignans). It seems that an unbalanced diet with a high consumption of fat and an insufficient consumption

of vegetables and fruit contribute to increase the risk of PCa [23]. As a matter of fact, these dietary disorders lead to an increase in BMI and adipose tissue with a possible alteration of the glucydic metabolism, increasing levels of circulating steroids hormones and angiogenic and mitogenic peptides [24]. On the contrary, vegetables and fruits, whose content of isoflavonoids, lignans and vitamins is much higher, seem to prevent the development of such comorbidities. Thus, the low incidence of PCa in Asia might be related also to the poor diet of those countries.

It is also known that chronic or recurrent inflammations are mainly involved in the process of PCa development. The 9% of man between 40 and 79 years report at least one episode of symptomatic prostatitis [25]; even if little is known about its prevalence [26,27]. Sexually Transmitted Diseases (STDs), regardless of the pathogen involved, are associated with PCa. Therefore, this suggests that inflammation, rather than infection, is involved in prostatic carcinogenesis [28,29]. Moreover, it has been hypothesized that oxidant molecules, produced by the immune cells, cause gene alterations in the prostatic epithelial cells, leading firstly to proliferative inflammatory atrophy, secondly to intraepithelial neoplasia and finally to a malignant disease [28,29] (Figure 3).

***Figure 3.*** *The Molecular Pathogenesis of Prostate Cancer.*

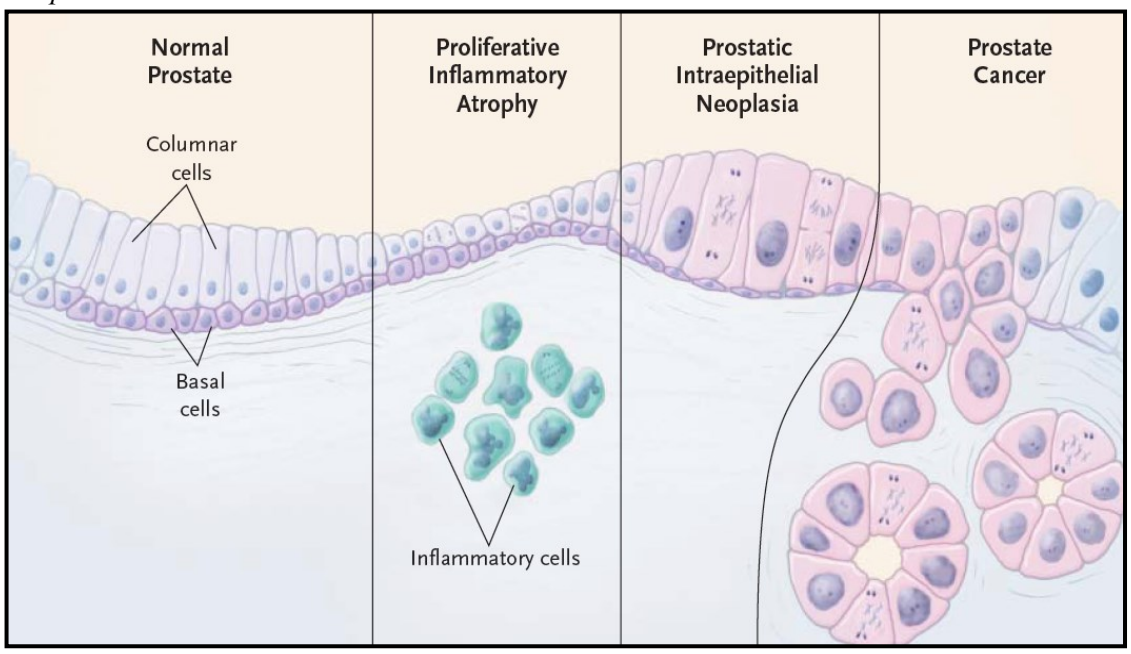



*Source: Nelson WG et al, NEJM 2003: 349:366-81* [30]

The proliferative inflammatory atrophy (Figure 4) is an atrophic lesion containing proliferative epithelial cells, which do not differentiate into columnar secretory cells. These lesions, associated with chronic inflammation, usually occur in the peripheral zone of the prostate, where PCa is most commonly found [31,32]), and they are often directly adjacent to areas of Prostatic Intraepithelial Neoplasia (PIN), PCa or both [31–34]. In the chronological order of prostatic carcinogenesis, firstly occurs chronic

inflammation, secondly the proliferative inflammatory atrophy and finally the intraepithelial neoplasia. Indeed, this process is considered as a consequence of the continuous regeneration of epithelial cells, due to the injury of the reactive oxygen species, which are essential during inflammation. This constant renewal of the cells is often associated with manifest genomic abnormalities, which are similar to those found in malignant cells [34].

***Figure 4.*** *Proliferative Inflammatory Atrophy as a Precursor to Prostatic Intraephitelial Neoplasia and Prostate Cancer.*




*Source: Nelson WG et al, NEJM 2003: 349:366-81.* [30]

In conclusion, both hereditary factors and environmental factors represent a very important feature, in influencing the risk of PCa development.

## 3.3 Prostatic Carcinomas Histotypes

Approximately 85% of tumors are located in the periphery of the prostatic gland, whereas the remaining ones are predominantly located in the transition zone (i.e. peri-urethrally or anteriorly) [35–37]. Tumors, that during digital rectal examination seem to be unilateral, at final pathologic examination are found to be bilateral in approximately 70% of the cases. By definition, PCa is a multifocal disease in more than 85% of the

patients [35]. In many of the multifocal cases, the other foci are small, low grade, and clinically insignificant.

More than 95% of PCa are diagnosed as adenocarcinomas during the histopathological analysis. The remaining 5% of PCa are classified either as transitional cell carcinomas (90%), or as neuroendocrine ("small cell") carcinomas or sarcomas.

The cytological characteristics of prostatic adenocarcinomas include hyperchromatic, enlarged nuclei with prominent nucleoli. Cytoplasm is often abundant; thus, nuclear-cytoplasmic ratios are often useless for a proper diagnosis of prostate cancer, even though it can be important for the diagnosis of other neoplasms. The diagnosis of adenocarcinoma is mainly based on architectural characteristics. The neoplastic glands are typically smaller than benign glands and are lined by a single uniform layer of cuboidal or low columnar epithelium. In contrast to benign glands, PCa glands are more crowded, lacking branching and papillary infolding. One morphologic variant of prostatic adenocarcinoma is mucinous adenocarcinoma [38,39], which has an aggressive biologic behavior.

The second most common histotype is the primary transitional cell carcinoma (i.e. without bladder involvement), and it accounts for 1% to 4% of all prostate carcinomas [40]. These tumors tend to infiltrate the bladder neck and the surrounding soft tissues, so that more than 50% of the patients present a locally advanced disease (i.e. stage T3 or T4) at diagnosis. Furthermore, 20% of men affected by primary transitional cell carcinoma of the prostate have distant metastases: bone, lung and liver are the most common sites. It is important to remember that bone lesions of transitional cell tumors tend to be osteolytitic, in complete opposition to the osteoblastic nature of adenocarcinomas metastases. Survival of these patients is strongly dependent by the stage at presentation of the diagnosis. Patients with localized disease to the prostate (T2 stage) can achieve long-term disease-free survival when treated with radical surgery, while patients with locally invasive disease (T3 stage) have a 5-year survival of 34% when treated with radiation therapy (RT).

More commonly, transitional cell carcinoma of the prostate is found in patients, who had a flat transitional cell carcinoma *in situ* of the bladder and have been treated months to years with a intravescial topical chemotherapy [41–45]. In fact, 35%-45% of cystoprostatectomies performed for bladder cancer show an involvement of the prostate.

These percentages however are dependent on the amount of histologic sampling of the prostatic tissue, and therefore might be higher with more thorough mapping of the specimens [46]. Finally, transitional cell carcinoma may be found in the prostatic stroma as a direct invasion from a primary bladder tumor.

Neuroendocrine carcinomas of the prostate, also known as small cell carcinomas, are identical to small cell carcinomas of the lung [47]. Approximately 50% of these tumors are mixed neuroendocrine carcinomas and adenocarcinomas. It is peculiar that, although most small cell tumors lack evident hormone production, they account for the majority of PCa with clinically evident adrenocorticotropic hormone or antidiuretic hormone production. Unfortunately the prognosis is unmerciful: the average survival of patients diagnosed with small cell carcinoma is less than a year. There is no difference in survival between pure neuroendocrine tumors and those with mixed adenocarcinoma and small cells carcinoma.

Pure primary squamous carcinoma of the prostate is a rare histotype and is associated with poor survival [48]. Sarcomas of the prostatic gland are a rare finding, and they represent 0.1% to 0.2% of all malignant prostatic tumors [49]. Finally, a very small percentage of prostatic tumors are derived from hematological malignances.

In 2016, the World Health Organization (WHO) reviewed the histological classification of prostate cancer adding new variants such as intraductal carcinoma (associated with high grade/stage prostate cancer), microcystic adenocarcinoma (GS 3), pleomorphic giant cell adenocarcinoma (typically highly aggressive), large cell neuroendocrine carcinoma (poor outcome, with mean survival of 7 mo after platinum-based chemotherapy) [50].

## 3.4 Grading of Prostatic Adenocarcinoma

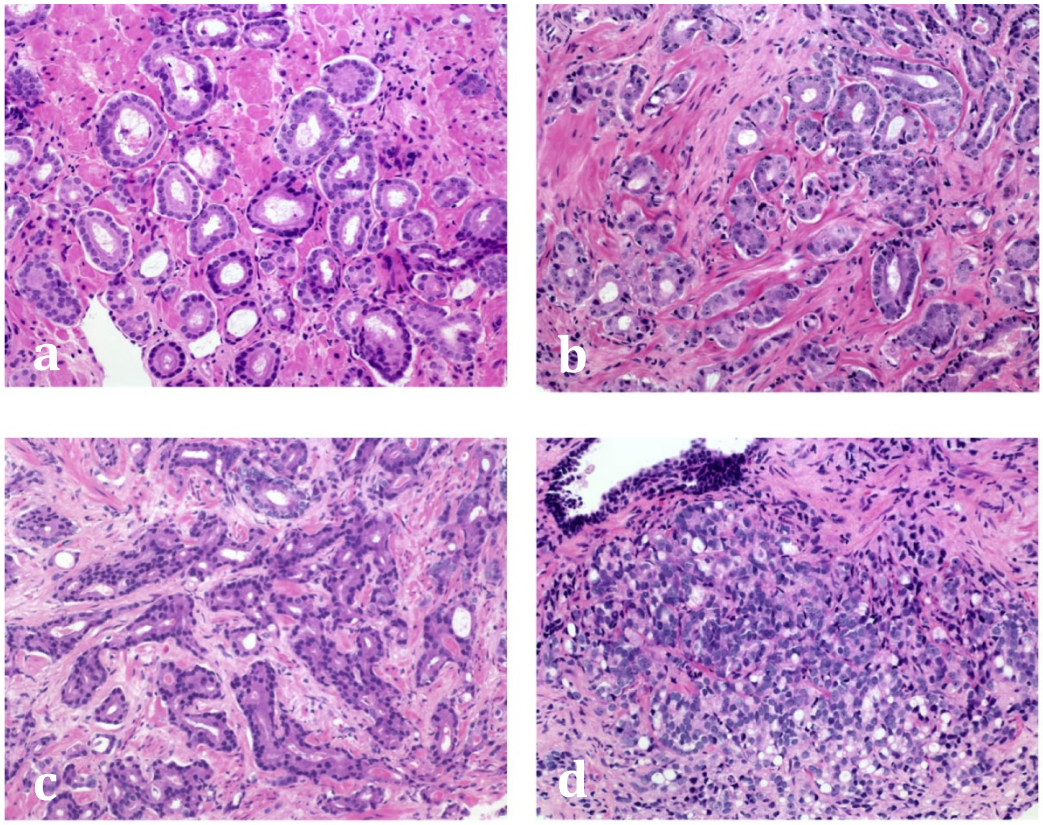
There are many grading systems for PCa, but the most used was developed by Donald F. Gleason in 1966 [51]. Gleason Score (GS) is one of the most accurate grading tool for PCa, in fact it is used in several systems, such as Partin tables and Kattan nomograms, to predict the pathologic stage or the prognosis of patients after Radical Prostatectomy (RP) or RadioTherapy (RT) [52].

### *3.4.1 Original Gleason System*

Differently from other cancers, cytology is not important in grading PCa, indeed GS takes in account only the architectural structure of the neoplasia. The system uses a 5-point scale to define the grade of glandular differentiation, considering 1 as the most differentiated and 5 as the least differentiated, at quite low magnification. The score is composed by the sum of the score of the two most representative areas of the tumor, namely primary (predominant) and secondary (second most prevalent) architectural patterns [52]. This means that GS ranges from 2, which is representative of a well-differentiated lesion, to 10, which is consistent with a totally undifferentiated tumor. In case of presence of only one pattern, this is considered as both primary and secondary pattern.

Gleason pattern 1 and pattern 2 tumors are composed of relatively circumscribed nodules of uniform, single, separate, closely packed, medium-sized glands (Figure 5a). Gleason pattern 3 tumor infiltrates the non-neoplastic prostate and the glands have marked irregularity in size and shape, with smaller glands than in Gleason pattern 1 or pattern 2 (Figure 5b). When glands are no longer single and separate as in patterns 1 to 3, they are considered as Gleason pattern 4. In Gleason pattern 4, it is possible to observe large, irregular, cribriform glands as opposed to the smoothly circumscribed smaller nodules of cribriform Gleason pattern 3 (Figure 5c). A Gleason pattern 4 PCa has a significantly worse prognosis then tumors with only Gleason pattern 3 [53,54]). Lastly, Gleason pattern 5 tumors have little or no differentiation into glands and are composed of solid sheets, cords, single cells, or tumor with central comedonecrosis (Figure 5d).

***Figure 5.*** *(a) Gleason pattern 2, (b) Gleason pattern 3, (c) Gleason pattern 4, (d) Gleason pattern 5.*




### *3.4.2 Modified Gleason System*

In 2005, the Gleason system was modified during the International Society of Urological Pathology conference, which led to the *2005 ISUP Modified Gleason System* [55]). The upgrade was due to several reasons. First of all, in Gleason's era there was no screening for PCa other than DRE (Digital Rectal Examination) because PSA was introduced only in eighties. At that time, most patients had local advanced or metastatic disease [51]. Secondly, at that time, were performed only two-cores biopsies from areas of palpable abnormalities at DRE. Therefore, there was no need for grading of multiple cores from different areas of the prostate. Thirdly, in the sixties, RP was relatively uncommon, therefore the prostate was not often removed and analyzed entirely as they are nowadays. As a matter of fact, grading multiple nodules in the same prostate and dealing with tertiary patterns was not included in the original system. Furthermore, there was no immunochemistry to aid in the diagnosis, therefore it is likely that with

immunostaining for basal cells, many of the original 1-1, or 1-2 carcinomas would nowadays be regarded as adenosis, a benign lesion that mimics cancer.

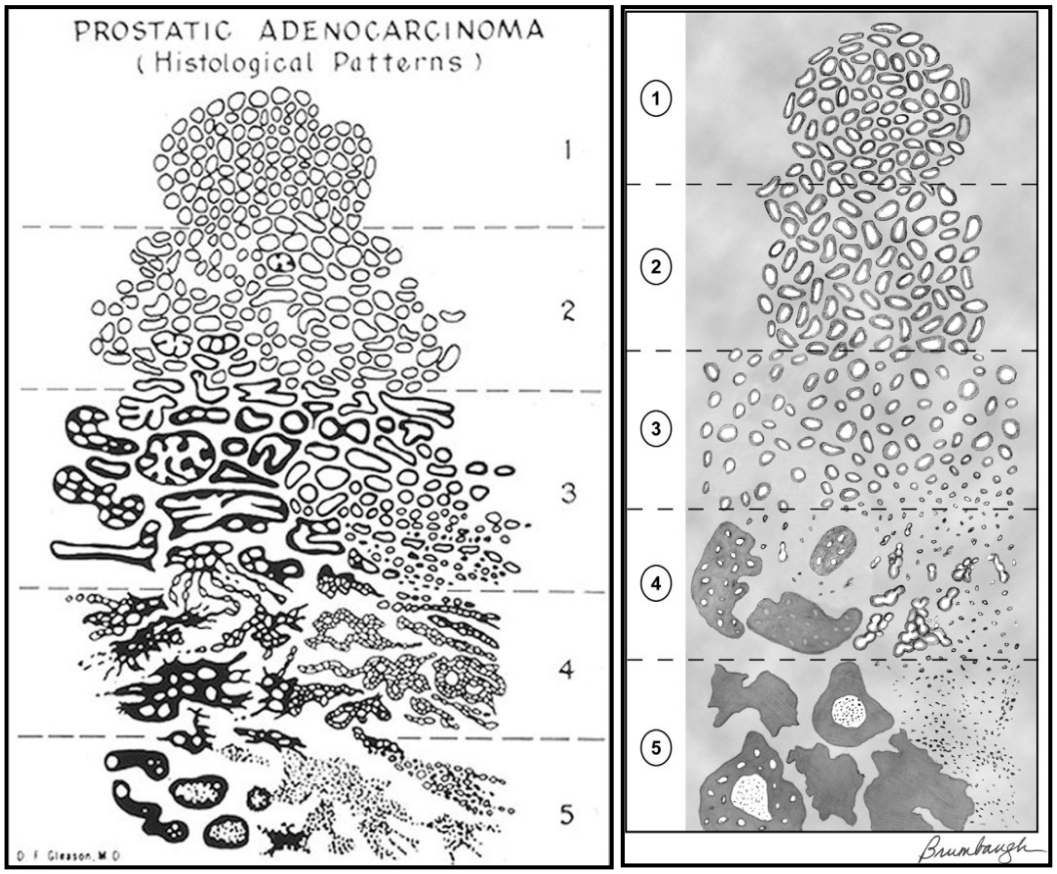
The consensus conference established that a diagnosis of GS 2 to 4 on needle biopsy should be made rarely. These cases represented 2.4% of diagnosis in 2001 [56], but after the statement they decreased to 0% [57]. Besides, there were consequences also about the diagnosis of GS 5 (i.e. 2+3=5 or 3+2=5), which decreased from 12.2% to 0.3%. This phenomenon can be explained considering that low-grade cancers (i.e. Gleason sum 2-5) are rarely found in clinical practice since they often occur in the anterior and transition zones of the prostate, which are very difficult to capture with trans-rectal prostate biopsy. For the purpose of prognosis and treatment, it has been proposed, not to consider anymore GS range from 2 to 10, but only from 6 to 10 [58]. Indeed, patients with GS of 6 usually don't understand that their tumor has the lowest grade, but they commonly assume to have a worse disease compared with 2 to 5 GS PCa.

The conference also established that criteria for assigning cribriform Gleason pattern 3 had to be severely tightened, including only cribriform glands that were rounded, well circumscribed and the same size as normal glands [55]. Later, it was reported that Gleason cribriform pattern 3 carcinoma should never be diagnosed [59]. Cribriform pattern 3 still exists because of the original Gleason schematic diagram, even if Gleason himself never specifically studied the prognostic difference of what he called cribriform pattern 3 and 4. In fact, with the lack of immunohistochemistry techniques, it was impossible to assess if a carcinoma was infiltrating or not in case of cribriform pattern 3. The consensus agreed that glands with poorly formed lumina have to be considered pattern 4 [55].

This change has led to disease upgrading. When comparing the original and modified Gleason systems on biopsies, GS 6 tumors decreased from 48.4% to 22%, while Gleason sum 7 cancers increased from 25.5% to 67.9% [57]. However, the percentage of upgrade deepens on case mix, and upgrading is less when looking at a greater proportion of early stage disease. For example, in another study comparing the two systems on biopsy material, Gleason 6 scores decreased from 68% to 49%, while Gleason 7 increased from 26% to 39% [60]. Therefore, nowadays, cribriform and poorly formed glands are not seen any more in Gleason 6 PCa.

The consensus left the Gleason 5 pattern unchanged in modern practice. The two figures below (Figure 6) graphically compare the two grading systems.

***Figure 6.*** *Original (left) and Modified (right) Gleason systems*




*Source: from Epstein JI, J Urol 2010: 183:433-40* [61]

Another topic in the consensus conference was about the tertiary Gleason patterns. They established that, if there is present a third, less representative and with a lower Gleason pattern focus, this should be ignored. However, it is quite common in biopsies of a Gleason sum 3+4 or 4+3 to find also some areas of Gleason pattern 5. The consensus is that tumors with patterns 3, 4 and 5 should be classified as high grade (GS 8-10) [55]. This is due to the fact that the presence of pattern 4 or 5 on a biopsy specimen is index of a high-grade tumor, and the limited extent of that pattern likely is a result of a sampling issue. In this case, to obtain a GS 8-10, it is advised to sum the primary pattern

with the highest grade. For example, a tumor seen on biopsy as having a GS 3+4 with tertiary pattern 5 should be recorded as a GS 3+5. This approach has been confirmed to be superior with subsequent studies.

With regards to RP specimens, the definition of a tertiary pattern is more controversial, due to the multifocal nature of PCa [62]. The conference recommended assigning a separate GS to each dominant tumor nodule. Some experts define a tertiary pattern in a RP specimen as "the presence of a third component of a Gleason pattern higher than the primary and secondary grades, where the tertiary component is visually estimated to be less than 5% of the whole tumor" [63–65]. Therefore, when the third most common component is the highest grade and occupies more than 5% of the tumor, it is recorded as the secondary pattern.

The only way to compare the old and the new Gleason Score system is to reanalyze samples giving to them first a score according to the original system, then to the new one. It is necessary to proceed in this way because before 2005 most uro-pathologists have already used some of the changes brought by the consensus conference. However, in the few studies carried out, the new system results to be superior. One study demonstrates that the concordance of the GS between biopsy and RP specimen increased from 58% to 72% with the modified system ($p<0.001$) [57]. Another study reports that the reviewed system better predicted biochemical-free progression after surgery [60].

In 2014, it was recognized that there was a need for further modifications to prostate cancer grading based on: (1) the lack of consensus of certain grading issues, many of which were not resolved in the 2005 meeting; (2) a realization that some grading issues were not covered in 2005; (3) since 2005, there has been new pertinent research; and (4) changes in prostate cancer practice has led some clinicians to challenge the existing grading system, necessitating a response by the Pathology community. Thus, a new grading system was proposed dividing patients into 5 different Groups according to histological findings [66].

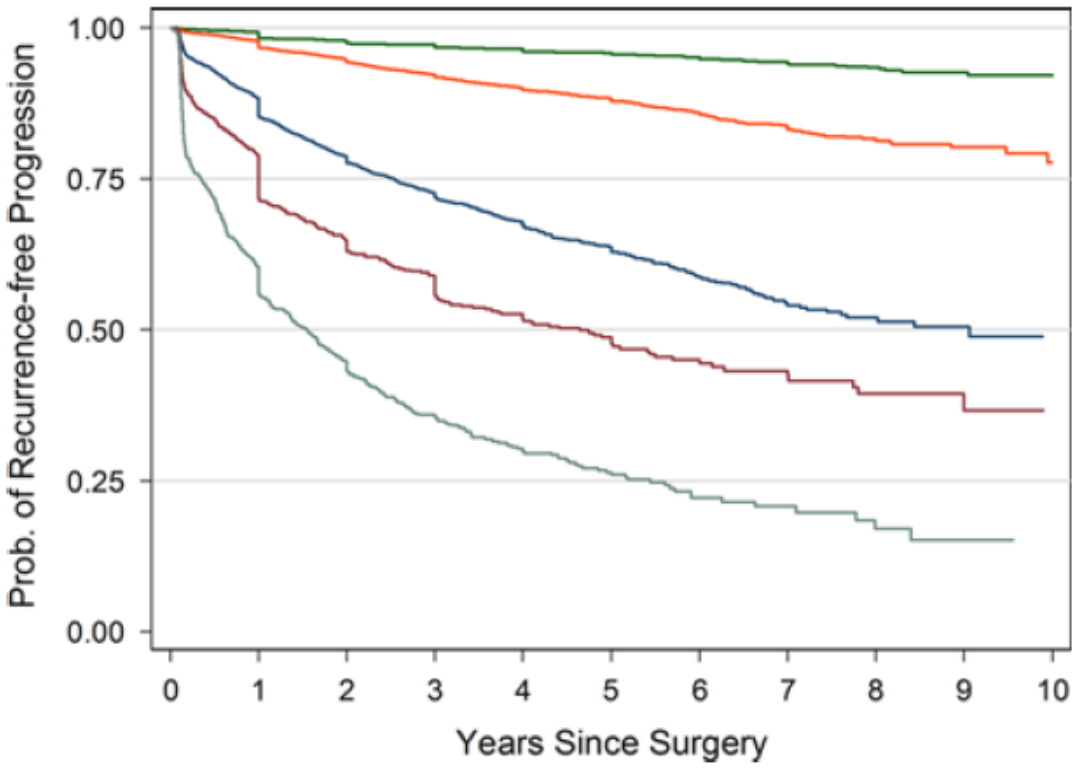
**TABLE 5.** Histological Definition of New Grading System

| |
|---|
| Grade Group 1 (Gleason score $\leq 6$) – Only individual discrete well-formed glands |
| Grade Group 2 (Gleason score $3+4=7$) – Predominantly well-formed glands with lesser component of poorly- formed/fused/cribriform glands |
| Grade Group 3 (Gleason score $4+3=7$) – Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands† |
| Grade Group 4 (Gleason score $4+4=8$; $3+5=8$; $5+3=8$) |
| Only poorly-formed/fused/cribriform glands *or* |
| Predominantly well-formed glands and lesser component lacking glands†† or |
| Predominantly lacking glands and lesser component of well-formed glands†† |
| Grade Group 5 (Gleason scores 9-10) – Lacks gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands† |

†For cases with > 95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of < 5% well-formed glands is not factored into the grade.

††Poorly-formed/fused/cribriform glands can be a more minor component.

The importance of stratifying patients according to this classification in terms of biochemical-free progression was confirmed by a multi-institutional study consucted by Johns Hopkins Hospital, Memorial Sloan-Kettering Cancer Center (MSKCC), University of Pittsburgh, Cleveland Clinic, and the Karolinska Institute [67].




# 4 DIAGNOSIS AND STAGING

## 4.1 Clinical Presentation

Rarely PCa is symptomatic at early stages because in most cases the disease arises from the peripheral area of the gland, far from the urethra. As a matter of fact, systemic symptoms, such as bone pain, renal failure or anemia, are signs of locally advanced or metastatic disease.

Different symptoms are due to the direct invasion of anatomical structures around the prostate. When cancer grows into the urethra or the bladder neck, the patient presents obstructive symptoms, such as hesitancy, reduction in urine stream, intermittency, and/or irritative symptoms, such as frequency, urgency, urge incontinence, nocturia. Otherwise, when tumor invades the trigone of the bladder, it can lead to ureteral obstruction, inducing renal failure if both ureters are involved. Another possibility is when ejaculatory ducts are invaded; this can lead to haematospermia and a decrease of ejaculate volume. In the end, when the cancer spreads into the neurovascular bundles

containing the nerves responsible for erection, it can induce erectile dysfunction. This however is a rare finding in the PSA era.

When the disease becomes metastatic, symptoms are due to the structures invasion. Bone pain, due to microfractures or anemia from replacement of the bone marrow, occurs in case of bone lesions. Lower extremity edema can be a manifestation for the compression of the lymphatic vessels or the iliac veins by metastatic pelvic lymph nodes. Other rare symptoms of systemic involvement include malignant retroperitoneal fibrosis, resulting from dissemination of metastatic cells along the peri-ureteral lymphatics, paraneoplastic syndromes from ectopic hormone synthesis, and disseminated intravascular coagulation (DIC).

However, more than 80% of patients with PCa are asymptomatic, and the diagnosis is usually done by digital rectal examination or an increase of PSA. The introduction of PSA testing in the late 1980s has led to earlier detection of PCa, bringing to a decline of 50-70% in the incidence of distant stage disease at diagnosis between 1986 and 1999 [68].

## 4.2 Methods of Diagnosis

There are mainly four tools to detect PCa: DRE, serum PSA dosing, Trans-Rectal UltraSonography (TRUS) and multiparametric Magnetic Resonance Imaging (mpMRI). However, the confirmation of the diagnosis can only be done through a histological diagnosis on biopsy or operative samples. Furthermore, histopathological examination is fundamental for grading and staging the tumor.

### *4.2.1 Digital Rectal Examination*

As previously explained, PCa often occurs in the peripheral regions of the gland, so DRE is able to detect it when its volume is > 0.2 ml. A positive DRE, that is a detection of a palpable nodule, is an absolute indication for prostate biopsy. About 18% of PCa is detected just with a DRE, regardless PSA value [69]. In a patient with serum PSA level <2 ng/ml, a positive DRE has a Positive Predictive Value (PPV) of 5-30% [70].

### *4.2.2 Prostate Specific Antigen*

Prostate cancer detection has been revolutionized amazingly by the introduction of serum PSA testing [71]. PSA is a kallikrein-like serine protease, produced exclusively by the epithelial cells of the prostate. Unfortunately, it is produced not only by PCa cells,

but also by normal epithelial cells. According to this, PSA levels are usually elevated in case of Benign Prostatic Hyperplasia (BPH), prostatitis and other benign conditions. Nonetheless, if considered as an independent variable, PSA has an higher PPV than DRE or TRUS [72].

A single PSA dosage, even if out of range, cannot give certainty of PCa. Indeed, PSA has no universally accepted cut-off value. Rather PSA is considered as a continuous parameter (Table 3): the higher the value of the serine protease, the higher probability of PCa [73].

As shown in Table 3, also with a low PSA level, there are many men harboring PCa. It should also be considered the value at which a treatment is necessary, because among those men with PCa there will surely be many with not life-threatening cancer [74]. Therefore, the establishment of a proper threshold for PSA is not trivial.

***Table 3.*** *Risk of PCa related to serum PSA in 2950 men* [73]

| **PSA level (ng/mL)** | **Risk of PCa** |
|---|---|
| **0-0.5** | 6.6% |
| **0.6-1** | 10.1% |
| **1.1-2** | 17.0% |
| **2.1-3** | 23.9% |
| **3.1-4** | 26.9% |

Due to limits in specificity for early detection of PCa, there have been several PSA modifications: PSA density, age-specific reference ranges, and PSA molecular isoforms (e.g., cPSA, proPSA). However these are not used in routine clinical setting.

The ratio between free and total PSA (f/t PSA) is widely used to discriminate BPH from PCa. This allows to stratify the risk of PCa in men with total PSA levels between 4 and 10 ng/mL and a negative DRE. In a prospective multicenter trial, PCa was found on biopsy in 56% of men with a f/t PSA < 0.10, and in only 8% of men with f/t PSA >0.25

[75]. However, there are many pre-analytical and clinical factors (for example the instability of free PSA at both 4°C and room temperature), and these should always be taken into consideration. Furthermore, it has been demonstrated that PSA ratio is clinically useless in total PSA levels > 10 ng/mL and in follow-up of patients with already diagnosed PCa.

As explained, PSA should be monitored over time, and there are mainly two methods: (1) PSA velocity (PSAV), defined as an absolute annual increase in serum PSA (ng/mL/year) [76]; (2) PSA doubling time (PSADT), defined as a measure of the exponential increase of serum PSA over time, reflecting a relative change [77]. However, we should not forget the limits of this measurements (variations in PSAV and PSADT, total volume of the gland, etc…), and that several prospective studies demonstrated that this measurements do not to provide further information compared to PSA alone [78–81]. Nonetheless, these variables might have a prognostic role in patients with treated PCa [82].

### *4.2.3 PCA3*

The last years witnessed the introduced of this new marker, PCA3, which is a specific non coding mRNA measured in urine sediment obtained after prostatic massage, with an higher sensibility and specificity than PSA. Its higher specificity is probably due to the fact that PCA3 is not influenced by BPH or inflammation [83–85]. There are also data about a correlation between PCA3 and cancer aggressiveness, but urologists are still debating. In conclusion surely PCA3 may have potential value for identifying PCa in men with initially negative biopsies in spite of an elevated PSA, but its determination remains experimental.

### *4.2.4 Transrectal Ultrasonography and Prostatic Biopsies*

TRUS is mainly used to confirm, through prostate tissue sampling, the presence of PCa in men with high risk of harboring cancer, in consideration of DRE and PSA. Unfortunately, different studies demonstrated the inability of TRUS to localize early PCa [86–88]. Gray-scale TRUS does not detect areas of PCa with adequate reliability. It is therefore useless to replace systematic biopsies with targeted biopsies of suspect

areas. However, additional biopsies of suspect areas may be useful. Even if the transrectal approach is nowadays mainly used, it's possible to use also a perineal approach, with similar cancer detection rates [89,90]. Patient's age, potential co-morbidities, and the therapeutic consequences should also be considered (Table 4).

***Table 4.*** *Percentage given per biopsy session irrespective of the number of cores.*

| **Complications** | **% of biopsies** |
|---|---|
| **Haematospermia** | 37.4 |
| **Haematuria > 1 day** | 14.5 |
| **Rectal bleeding < 2 days** | 2.2 |
| **Prostatitis** | 1.0 |
| **Fever >38.5°C** | 0.8 |
| **Epididymitis** | 0.7 |
| **Rectal bleeding > 2 days ± requiring surgical intervention** | 0.7 |
| **Urinary retention** | 0.2 |
| **Other complications requiring hospitalization** | 0.3 |

*Adapted from NCCN Guidelines Prostate Cancer Early Detection.*

Furthermore, the first elevated PSA level doesn't imply a biopsy. To avoid a false high PSA level due to inflammation or procedures involving the prostate (i.e. catheterization, cystoscopy or TUR), it should be verified after a few weeks by the same assay under standardized conditions in the same diagnostic laboratory, using the same methods [91,92].

When performing a baseline biopsy, the sample sites should be as far posterior and lateral as possible in the peripheral gland. Furthermore, as mentioned above, additional

cores should be obtained from suspect areas by DRE/TRUS. These should be chosen on an individual basis.

Actually, the British Prostate Testing for Cancer and Treatment Study has recommended 10-core biopsies [93]. However, the range usually considered appropriate in prostates of 30-40 ml goes from 8 to 12 cores, because six-core biopsies are no longer considered adequate and many data shows that >12 cores haven't a significant higher sensibility [94].

In case of presence of Atypical Small Acinar Proliferation (ASAP), PSA rising or positive DRE after a first negative baseline biopsy, the biopsy should be repeated. Conversely, the presence of High-Grade Intra-Epitelial Neoplasia (HGPIN) does not indicate the necessity of a re-biopsy [95]. The timing of a second biopsy is not clear yet, even if it has been demonstrated that the later the biopsy is repeated, the higher is the detection rate [96].

### *4.2.5 Multiparametric magnetic resonance imaging (mpMRI)*

Correlation with RP specimens shows that mpMRI, associating T2-weighted imaging with at least one functional imaging technique (DWI, DCE, H1-spectroscopy), has good sensitivity for the detection and localization of ISUP grade > 2 cancers [97–99]. This was further confirmed in patients who underwent template biopsies. In a recent Cochrane meta-analysis which compared mpMRI to template biopsies (> 20 cores) in biopsy-naïve and repeat-biopsy settings, mpMRI had a pooled sensitivity of 0.91 (95% CI: 0.83-0.95) and a pooled specificity of 0.37 (95% CI: 0.29-0.46) for ISUP grade > 2 cancers [100]. For ISUP grade > 3 cancers, mpMRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87-0.99) and 0.35 (95% CI: 0.26-0.46), respectively. As a result, mpMRI is increasingly used to localize suspicious areas that could be targeted by so-called magnetic resonance imaging-targeted biopsies (MRI-TBx).

Multiparametric magnetic resonance imaging is less sensitive in identifying ISUP grade 1 PCa. It identifies less than 30% of ISUP grade 1 cancers smaller than 0.5 cc identified on RP specimens by histopathology analysis [97]. In series using template biopsy findings as the reference standard, mpMRI has a pooled sensitivity of 0.70 (95% CI: 0.59-0.80) and a pooled specificity of 0.27 (95% CI: 0.19-0.37) for identifying ISUP grade 1 cancers [100].

#### *4.2.5.1 The added value of systematic and targeted biopsy*

Magnetic resonance imaging-targeted biopsies can be used in two different diagnostic pathways: 1) the 'combined pathway', in which patients with a positive mpMRI undergo combined systematic and targeted biopsy, and patients with negative mpMRI undergo systematic biopsy; 2) the 'MR pathway', in which patients with a positive mpMRI undergo only MRI-TBx, and patients with negative mpMRI are not biopsied at all. Many studies evaluated combined systematic and targeted biopsy in the same patients and could therefore assess the added value of each technique (i.e. the percentage of patients diagnosed by only one biopsy technique). Data from a Cochrane meta-analysis of these studies and from the MRI-FIRST and 4M trials suggest that the added value of MRI-TBx for detecting ISUP grade > 2 cancers is higher than that of systematic biopsy (see Table 5).

***Table 5***. *Added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 cancer detection*

| | | **ISUP ≥ 2** | | | **ISUP ≥ 3** | | |
|---|---|---|---|---|---|---|---|
| **ISUP grade** | | **Cochrane meta-analysis*** | **MRI-FIRST trial*** | **4M trial** | **Cochrane meta-analysis*** | **MRI-FIRST trial*** | **4M trial** |
| **Biopsy-naïve** | Added value of MRI-TBx | 6.3% (4.8-8.2) | 7.6% (4.6-11.6) | 7.0% (ND) | 4.7% (3.5-6.3) | 6.0% (3.4-9.7) | 3.2% (ND) |
| | Added value of systematic biopsy | 4.3% (2.6-6.9) | 5.2% (2.8-8.7) | 5.0% (ND) | 2.8% (1.7-4.8) | 1.2% (0.2-3.5) | 4.1% (ND) |
| | Overall prevalence | 27.7% (23.7-32.6) | 37.5% (31.4-43.8) | 30% (ND) | 15.5% (12.6-19.5) | 21.1% (16.2-26.7) | 15% (ND) |
| **Prior negative biopsy** | Added value of MRI-TBx | 9.6% (7.7-11.8) | - | - | 6.3% (5.2-7.7) | - | - |
| | Added value of systematic biopsy | 2.3% (1.2-4.5) | - | - | 1.1% (0.5-2.6) | - | - |
| | Overall prevalence | 22.8% (20.0-26.2) | - | - | 12.6% (10.5-15.6) | - | - |

ISUP = International Society for Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

In Table 5, the added values refer to the percentage of patients in the entire cohort; if the cancer prevalence is taken into account, the 'relative' percentage of additional detected PCa can be computed. Adding MRI-TBx to systematic biopsy in biopsy-naïve patients increases the number of ISUP grade > 2 and grade > 3 PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-TBx increases detection of ISUP grade > 2 and grade > 3 PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naïve patients would miss approximately 16% of ISUP grade > 2 PCa and 18% of ISUP grade > 3 PCa. In the

repeat-biopsy setting, approximately 10% of ISUP grade > 2 PCa and 9% of ISUP grade > 3 PCa are missed.

#### *4.2.5.2 Number of biopsy procedures potentially avoided in the 'MR pathway'*

The diagnostic yield and number of biopsy procedures potentially avoided by the 'MR pathway' depends on the Likert/PI-RADS threshold used to define positive mpMRI. In pooled studies on biopsy-naïve patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of > 3 would have avoided 30% (95% CI: 23-38) of all biopsy procedures while missing 11% (95% CI: 6-18) of all detected ISUP grade > 2 cancers (relative percentage) [100]. Increasing the threshold to > 4 would have avoided 59% (95% CI: 43-78) of all biopsy procedures while missing 28% (95% CI: 14-48) of all detected ISUP grade > 2 cancers [100]. Of note, the percentages of negative mpMRI (Likert/PI-RADS score < 2) in MRI-FIRST, PRECISION and 4M were 21.1%, 28.9% and 49%, respectively [101,102].

### ***4.2.6 Other considerations***

#### *4.2.6.1 mpMRI reproducibility*

Despite the use of the PIRADSv2 scoring system [103], mpMRI inter-reader reproducibility remains moderate at best [104–107], which currently limits its broad use by non-dedicated radiologists. In a community hospital that started a prostate mpMRI program in 2010, cancer detection rates improved, and false positives decreased with the implementation of PIRADSv2 scoring and multidisciplinary meetings using pathological correlation and feedback. It is still too early to predict whether quantitative approaches and computer-aided diagnostic systems will improve the characterisation of lesions seen at mpMRI [108–110].

#### *4.2.6.2 Targeted biopsy accuracy and reproducibility*

Magnetic resonance imaging-targeted biopsies can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature does not show a clear superiority of one technique over another [111–115]. However, the

accuracy of most systems have largely been evaluated on phantoms, and data on the accuracy and reproducibility in real-life patients are limited [115]. One study, using an elastic US/MR fusion and intraprostatic fiducials, showed a median 3D registration error of 3.8-5.6 mm depending on the operator's experience. The error tended to be higher at the apex and in the anteroposterior direction [116].

Clinically significant PCa not detected by the 'MR pathway' can be missed because of MRI failure (invisible cancer or reader's misinterpretation) or because of targeting failure (target missed or undersampled by MRI-TBx). The PRECISION trial found a marked difference between targeted and systematic biopsies (detection ratio: 1.46), a finding the MRI-FIRST trial could not reproduce (detection ratio: 1.08). PRECISION allowed four targeted cores per lesion, while MRI-FIRST allowed only three, which might explain these findings. In a retrospective study of 211 patients with a unilateral mpMRI lesion, targeted biopsy alone detected 73.5% of all csPCa (ISUP grade > 2); combining targeted biopsy with systematic biopsy of the lobe with the MRI lesion detected 96% of all csPCas and combined targeted and systematic biopsy of the contralateral lobe only identified 81.6% of csPCas [117]. The difference may reflect targeting errors leading to undersampling of the tumour. Increasing the number of cores taken per target may partially compensate for guiding imprecision, but there is currently no data on the minimum number of targeted cores to be obtained as a function of the prostate volume, lesion size and location. In addition, the inter-operator reproducibility of MRI-TBx is still unclear.

#### *4.2.6.3 Role of risk-stratification*

The negative predictive value (NPV) of a diagnostic test decreases when the disease prevalence increases, i.e. when the a priori risk of the patient increases. Therefore, the excellent NPV reported for mpMRI in the literature may not apply to patients with a risk of disease [118]. Prostate-specific antigen density [119–121] or risk-calculators [122] can select patients with a high risk of csPCa in whom mpMRI NPV is low, and who may still benefit from systematic biopsies even if the mpMRI is negative. Several groups have developed nomograms which combine mpMRI findings with simple clinical data as a tool to predict subsequent biopsy results. These nomograms require

further validation, but in due time they may outperform predictors such as the ERSPC calculator in the selection of patients who may benefit from systematic and/or MRI-TBx [123–128].

#### *4.2.7 Summary of evidence and practical considerations on pre-biopsy mpMRI*

Magnetic resonance imaging-targeted biopsies substantially improve the detection of ISUP grade > 2 PCa. This improvement is most notable in the repeat-biopsy setting, with marginal added value for systematic biopsies. It is less marked in biopsy-naïve patients in whom systematic biopsy retain a higher added value, at least for the detection of ISUP grade 2 cancers. Magnetic resonance imaging-targeted biopsies also detect significantly less ISUP grade 1 cancers than systematic biopsies.

The 'MR pathway' is appealing since it could decrease the number of biopsy procedures, reduce the detection of low-grade PCa while maintaining (or even improving) the detection of csPCa, as compared to systematic biopsy. Limitations of the 'MR pathway' are the moderate inter-reader reproducibility of mpMRI and the lack of standardization of MRI-TBx, as well as the fact that its inter-operator reproducibility has not been evaluated. These caveats also apply to the systematic biopsy procedure. A substantial proportion of csPCa missed by the 'MR pathway' may be due to the imprecision of current targeting methods [117,129]. Therefore, there is a crucial need to improve these methods, or at least to define the minimum number of targeted cores that need to be obtained from each lesion, as a function of its size, location and prostate volume. Without standardization of mpMRI interpretation and of MRI-TBx technique, the 'MR pathway' may lead to suboptimal care outside large-volume (expert) centers.

Finally, it must be emphasized that the 'MR pathway' has only been evaluated in patients in whom the risk of csPCa was judged high enough to deserve biopsy. Pre-biopsy mpMRI must not be used in patients who do not have an indication for prostate biopsy based on their family history and clinical and biochemical data. Because of its low specificity, mpMRI in very low-risk patients would result in an inflation of false-positive findings and subsequent unnecessary biopsies.

## 4.3 Screening

The introduction of serum PSA testing has also developed the concept of screening in PCa. Population screening and early detection are not the same thing: population screening is defined as the examination of asymptomatic men who are at risk, which usually takes place as part of a trial or study and is initiated by the screener. On the other hand, early detection concerns individual case findings, which are initiated by the patients and/or by their physicians. The goals of these two screenings are:

1) Lower mortality rate from PCa
2) Quality of life improvement.

Many studies showed controversial data regarding the reduction in mortality due to PSA screening. For example, a non-randomized screening project in Tyrol (Austria) observed a 33% reduction in PCa mortality rate observed in Tyrol compared to the other region of Austria, where PSA was not tested [130]. On the other hand, a US study have found no difference in the reduction of PCa mortality rate between the Seattle city area (a highly-screened population) and the US state of Connecticut (a seldom-screened population) [131].

Two large prospective randomized trials, one American and one European, have been designed to try to effectively determine the value of PCa screening. The results of both trials were published in 2009.

The American trial, known as the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, randomly assigned 76'693 men at 10 US centers, dividing them into two groups: one received both annual screening with PSA and DRE, the other group received standard of care as the control. After 7 years of follow-up, the incidence of PCa was 116/10'000 people/year (2'820 cancers) in the screening group and 95/10'000 people/year (2'322 cancers) in the control group (rate ratio 1.22) [132]. The mortality rate was 2/10'000 people/year (50 deaths) in the screened group and 1.7/10'000 people/year (44 deaths) in the control group (rate ratio 1.13). Their conclusion was that PCa-related mortality was too low to be significantly different between the two study groups.

The European Randomized Study of Screening for PCa (ERSPC) included a total of 162'243 men between 55 and 69 years old from seven different countries. Patients were randomly assigned either to a group which offered PSA screening at an average of once

every 4 years, or to an unscreened control group. During a median follow-up of 11 years, the cumulative incidence of PCa was 9.6% in the screened group and 6% in the control group [133]. The rate ratio between screened and control group for death from PCa was 0.79. The absolute risk difference was 0.71 deaths per 1'000 men. This means that 936 men would need to be screened and 33 additional cases of PCa would need to be treated to prevent one death from PCa. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from PCa by 20% but was associated with a high risk of over-diagnosis.

Conflicting results among these studies are noticeable. Several aspects can explain the controversies between them. First of all, in the PLCO trial, the rate of contamination in the control arm was about 40% in the first year and increased to 52% in the sixth year for PSA testing, and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40-52% versus 86% in the ERSPC. According to this, the PLCO trial was not able to demonstrate if the screening could influence PCa mortality.

On the other hand, in the ERSCP trial, the real benefit will only be evident after 10-15 years of follow-up, most of all because the 41% reduction of metastasis in the screening arm will have an impact.

These results can explain why some major urological societies consider widespread mass screening for PCa inappropriate. Otherwise, they recommend offering early-detection to well-informed patient.

However, two problems remain unsolved:

1) at what age early detection should begin?
2) what is the timing for PSA and DRE?

Current data suggest a first PSA determination at 40 years of age. Based on this first PSA value, the screening interval may then be adjusted [134]. For example, in a man with a initial PSA level <1 ng/ml may be proposed an 8 year screening interval [135]. Instead, in men older than 75 years and with a baseline PSA of <3 ng/ml, further PSA testing should not be done due to their very low risk of dying from PCa.

## 4.4 Clinical and Pathological Staging

Information obtained from staging are used to define the extent of disease either as localized, as exhibiting spread outside of the organ of origin to regional lymph nodes,

or as metastatic to distant sites. The most widely used system of staging is the TNM (Tumor, Node, Metastases) system codified by the International Union Against Cancer and the American Joint Committee on Cancer (AJCC).

TNM is an anatomically-based classification that defines tumors on the basis of the size of the primary tumor lesion (T1-4, a higher number indicates a tumor of larger size), the presence of nodal invasion (N0 and N1 for the absence and presence, respectively, of involved nodes), and the presence of metastatic disease (M0 and M1 for the absence and presence, respectively, of metastases). The various combinations of T, N, and M scores (including tumor histologic grade G) are used to define stages, usually indicated by the roman numerals I-IV. The 2009 TNM classification for PCa is shown in Table 6.

Cancer clinical staging uses pre-treatment parameters to predict the true extent of the disease. The endpoints of staging are the assessment of prognosis and the choice of the best treatment option for the patient. An accurate assessment of disease extent is crucial for men with newly-diagnosed PCa, because pathologic stage is one of the most reliable means of predicting the outcome of definitive treatment in men with clinically-localized cancer [136].

The primary extension assessment of PCa is usually made by DRE, PSA measurement and bone scan, supplemented with computed tomography (CT) or magnetic resonance imaging (MRI), and chest X-ray in specific situations.

***Table 6.*** *The 2017 TNM (Tumor Node Metastasis) classification for PCa*

| **T - Primary tumor** | | |
|---|---|---|
| Tx | | Primary tumor cannot be assessed |
| T0 | | No evidence of primary tumor |
| T1 | | |
| | T1a | Tumor incidental histological finding in 5% or less of tissue resected |
| | T1b | Tumor incidental histological finding in more than 5% of tissue resected |
| | T1c | Tumor identified by needle biopsy (e.g. because of elevated PSA level) |
| T2 | | Tumor confined within the prostate[1] |
| | T2a | Tumor involves one half of one lobe or less |
| | T2b | Tumor involves more than half of one lobe, but not both lobes |
| | T2c | Tumor involves both lobes |
| T3 | | Tumor extends through the prostatic capsule[2] |
| | T3a | Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement |
| | T3b | Tumor invades seminal vesicle(s) |
| T4 | | Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall |
| **N - Regional lymph nodes[3]** | | |
| NX | | Regional lymph nodes cannot be assessed |
| N0 | | No regional lymph node metastasis |
| N1 | | Regional lymph node metastasis |
| **M - Distant metastasis[4]** | | |
| MX | | Distant metastasis cannot be assessed |
| M0 | | No distant metastasis |
| M1 | | Distant metastasis |
| | M1a | Non-regional lymph node(s) |
| | M1b | Bone(s) |
| | M1c | Other site(s) |

*[1]Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*
*[2]Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.*
*[3]Metastasis no larger than 0.2 cm can be designated pN1 mi.*
*[4]When more than one site of metastasis is present, the most advanced category should be used.*

### *4.4.1 T-staging*

This parameter regards primary tumor dimensions and local invasion. The distinction between intracapsular (T1-T2) and extracapsular (T3-T4) disease has the most important implication about treatment decisions. DRE often cannot correctly evaluate tumor extension; a positive correlation between DRE and final pathological tumor stage was found in fewer than 50% of cases [137]. However, further examinations for adequate T-staging, are only recommended in selected cases where a more precise staging may change treatment decision, i.e. when curative treatment is an option.

It is known that serum PSA levels increase with stages. However, since PSA is produced by both healthy and malignant prostatic tissue, there is no direct relationship between serum PSA concentration and the clinical and pathological staging [138–140]. It is possible to have a more precise staging with a combination of serum PSA level, GS on prostate biopsy and clinical T-stage [141].

TRUS is the most widely used method to get images of prostate, however, only 60% of lesions are detectable with TRUS. In order to increase sensibility it's possible to combine DRE with TRUS, this combination can detect T3a PCa more accurately than either method alone [142]. Besides, TRUS is not able to determine tumor extension with sufficient accuracy, so it shouldn't be recommended as routine for staging. About 60% of pT3 tumors will not be detected pre-operatively by TRUS.

There are also two large multi-institutional studies, which observed that TRUS had the same accuracy of DRE in predicting organ-confined PCa [143,144].

Another pathological characteristic that impacts on local relapse and distant failure is seminal vesicle invasion (SVI). It has been showed that seminal vesicle biopsies, which are not a first-line examination, may be used to increase the accuracy of pre-operative staging [145]. They should be done in patients with high risk of SVI in which a positive seminal vesicle biopsy would change treatment decisions. It has been suggested that patients with a clinical stage higher than T2a and a serum PSA level higher than 10 ng/ml are good candidates for seminal vesicle biopsies [146,147]. Also, all patients with any of the basal biopsies positive for cancer have an elevated risk of positive seminal vesicle biopsies [148]. It is known that biopsy GS, serum PSA level and clinical stage are independent predictors of adverse pathological characteristics after Radical Prostatectomy (RP).

### *4.4.2 N-staging*

The measurement of PSA level alone is unhelpful in predicting the presence of Lymph Node Invasion (LNI) for an individual patient. High PSA values combined with stages T2b-T3 disease, poor tumor differentiation and peri-neural tumor invasion have been associated with a higher risk of the presence of nodal metastases [141,149,150]. Nomograms can be used to integrate all these variables together and give a better prediction of the probability of LNI [151].

Another variable which defines the risk of LNI is the presence of the Gleason 4 pattern in six-core biopsies. Specifically, if any core had a predominant Gleason 4 pattern, or > three cores had any Gleason 4 pattern, the risk of LNI is about 20-45%. For the remaining patients, the risk was 2.5%. So it is noticeable that lymph node staging is not necessary for all patients [152].

Several studies show that CT and MRI have no difference in pelvic LNI detection, although CT seems to be slightly better [153]. However, in both CT and MRI imaging, have a poor accuracy in predicting pathological LNI. This may stem from the fact that the only sign of LNI on CT and MRI is their enlargement, which might not be so accurate. Specifically, a threshold of 1 cm in the short axis for the oval nodes, and 0.8 cm for the round nodes, has been recommended as the criteria for the diagnosis of LNI [154].

Fine-Needle Aspiration Biopsy (FNAB) can surely confirm positive imaging results. Unfortunately, pelvic lymph nodes are not so easy to be reached, remembering that sensitivity of FNAB is not so high, with a false-negative rate of 40% [154].

### *4.4.3 M-staging*

Skeletal lesions are present in about 85% of men who die from PCa [155]. The presence and the extent of bone lesions are important prognostic factors.

An indicator of bone metastases is the skeletal alkaline phosphatase, that has been found elevated in 70% of patients with skeletal metastatic PCa [156]. This assay can be evaluated together with PSA increasing the clinical effectiveness to approximately 98% [157]. In a prospective study, multiple regression analysis showed the extent of bone disease to be the only variable influencing the serum levels of skeletal alkaline

phosphatase and PSA, even if only the skeletal alkaline phosphatase demonstrated a statistical correlation with the extent of bone disease [158].

Bone scintigraphy represents the most sensitive technique in detecting skeletal lesions, its superiority to other tests (clinical evaluation, bone radiographs, serum alkaline phosphatase measurement and prostatic acid phosphatase (PAP) determination) has been demonstrated in several studies [159,160]. Technetium diphosphonates are the optimum radiopharmaceuticals currently available because of their extremely high bone-to-soft tissue ratio [161].

However bones are not the only metastatic target of PCa, it commonly affects distant lymph nodes, lung, liver, brain and skin. To study these other sites, clinical examination, chest X-ray, ultrasound, CT and MRI scans are considered appropriate methods of investigation, but only if in presence of clinical evidence of soft-tissue metastasis.

The need for reliable serum markers to improve the pre-treatment staging of patients with PCa has long been recognized, especially because patients should undergo more meticulous imaging. Nowadays the only most important marker of metastatic disease is a PSA level higher than 100 ng/ml, with a positive predictive value of 100% [162]. Furthermore, it helps to reduce the number of patients with newly diagnosed PCa who requires a bone scan. Indeed, patients with a low serum PSA concentration have only rarely been found to harbor detectable skeletal metastases. The correlation between serum PSA and bone scintigraphy in patients with newly diagnosed untreated PCa has been further investigated [163–167]. Results showed that a staging bone scan is not necessary in asymptomatic patients with well or moderately differentiated PCa and serum PSA concentration lower than 20 ng/mL. On the other hand, in patients with poorly differentiated tumors and locally-advanced disease, a staging bone scan should be done regardless the serum PSA value [168,169].

## 4.5 Prognostic Grouping

Pathologic staging has a more important impact on the prognosis compared to clinical staging. Information given by pathological examination are tumor volume and grade, ECE, SVI, LNI and Surgical Margins (SM) status. All of them are important predictors of prognosis. Furthermore, the higher the pathological stage, the worse the outcome,

which translates into lower rates of biochemical-free survival and Cancer-Specific Survival (CSS).

In the past, positive DRE patients had a higher risk of disease recurrence and higher rates of CSS mortality. However, the introduction of PSA has caused a stage migration increasing the number of PCa diagnosis in men with non-palpable cancers (cT1c). Therefore, apart from cT3 or cT4 stage patients, further methods of risk assessment were identified in case of advanced disease, high risk or failure after surgical therapy.

Several risk classification systems have been created, using easy-to-obtain variables, such as PSA and biopsy GS, in order to be able to use them in the routine clinical practice.

One of these systems was initially set up in the 1990s and updated in 2001 by Partin et al. [141,170]. The so-called "Partin tables" are used in the pre-operative prediction of final pathological stage in men undergoing RP. However, these tables were set up on patients with localized PCa at the initial clinical evaluation, and it should be used only in this population. Starting from the point that clinical-stage, serum PSA level and GS individually predict pathological stage and prognosis, Partin and colleagues combined these variables to increase the accuracy of the prediction. Tables showed that a significant number of men with clinically-localized disease actually harbor more advanced disease at final pathological examination. Therefore, the possibility of predicting pathological stage allows better pre-treatment counseling of patients as well as better therapeutic planning.

More complex models have been created based on biopsy information. The endpoint of these tools is not only the prediction of the pathological stage, but also cancer outcomes such as biochemical-free survival after treatment. In fact, even if biochemical-free survival is used as a frequent endpoint in clinical studies, it's just a surrogate outcome variable. Further, there are not so many trials assessing the biochemical-free survival as a marker of CSS. Nonetheless, the most widely used tools to predict biochemical-recurrence after local therapy are the nomograms developed by Kattan and colleagues [171,172]. These nomograms are based on clinical stage, biopsy Gleason grade, and pre-treatment serum PSA level. There are specific models set up for different therapies, for example nomograms for RT also include data regarding androgen deprivation (AD), total radiation dose, and combination treatment (such as external beam and permanent

brachytherapy). The RP nomogram, on the other hand, was created on a population of nearly 1000 patients with clinically localized disease (T1c-T3a NX M0). Unfortunately, this model cannot be used in those patients with evidence of seminal vesicle invasion or regional spread.

It is possible to make easier risk stratification, maintaining the possibility to predict disease behavior and response to intervention, dividing patients into fewer groups. The most commonly used risk stratification is the one implemented by D'Amico et al. [173]. The "D'Amico risk stratification" groups patients in low, intermediate, and high risk for biochemical failure, starting from pre-treatment disease characteristics, namely clinical stage, PSA value and GS.

This model divides patients into low, intermediate and high-risk of biochemical progression after local treatment. Low risk correspond to patients with a clinical T1c or T2a stage, a PSA level at diagnosis ≤ 10 ng/mL and a biopsy GS ≤6. High-risk patients, on the other hand, are those with either stage T2c, a PSA level >20 ng/mL or a biopsy GS of 8-10. All patients not included in these criteria are grouped in the intermediate group. To stratify patients, D'Amico et al studied a total of 1872 men that underwent primary local therapy with either RP, external beam radiotherapy (EBRT) or brachytherapy.

The European Association of Urology (EAU) uses a variation of the D'Amico risk groups carried out by the National Comprehensive Cancer Network (NCCN). According to the NCCN, patients can be stratified into 4 prognostic groups:

- Very low risk: cT1c, PSA <10ng/mL, biopsy GS ≤6, fewer than 3 positive biopsy cores, ≤50% of cancer in each core, PSA density <0.15 ng/mL/g;
- Low risk: cT1c, PSA <10ng/mL, biopsy GS ≤6;
- Intermediate risk: cT2b-T2c, or PSA 10-20 ng/mL or biopsy GS 7;
- High risk: cT3a, or PSA >20 ng/mL or biopsy GS 8-10:
- Very high risk: cT3b-T4.

This stratification is very accurate only for low-risk patients, because they generally do well and are unlikely to have biochemical recurrence, men in the other two groups may have widely discrepant outcomes. For this reason, more modern and accurate risk prediction models and nomograms should be set up for these patients [174].

**Table 7.** *Prognostic grouping*

| | | | | |
|---|---|---|---|---|
| **Group I** | T1a-c | N0 | M0 PSA < 10 | Gleason ≤ 6 |
| | T2a | N0 | M0 PSA < 10 | Gleason ≤ 6 |
| **Group IIA** | T1a-c | N0 | M0 PSA < 20 | Gleason 7 |
| | T1a-c | N0 | M0 PSA ≥ 10 < 20 | Gleason ≤ 6 |
| | T2a, b | N0 | M0 PSA < 20 | Gleason ≤ 7 |
| **Group IIB** | T2c | N0 | M0 Any PSA | Any Gleason |
| | T1-2 | N0 | M0 PSA ≥ 20 | Any Gleason |
| | T1-2 | N0 | M0 Any PSA | Gleason ≥ 8 |
| **Group III** | T3a, b | N0 | M0 Any PSA | Any Gleason |
| **Group IV** | T4 | N0 | M0 Any PSA | Any Gleason |
| | Any T | N1 | M0 Any PSA | Any Gleason |
| | Any T | Any N | M1 Any PSA | Any Gleason |
| *Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA of Gleason is available. When neither is available prognostic grouping is not possible, use stage grouping.* | | | | |

# 5 CURRENT TREATMENTS FOR PROSTATE CANCER

Currently, treatment decisions are based on the grade and stage of the tumor, the life expectancy of each patient, the ability of each therapy to ensure disease-free survival, its associated morbidity, and patient and physician preference.

## 5.1 Deferred Treatment: Watchful Waiting/Active Surveillance

The incidence of small, localized, well-differentiated PCa is increasing, mainly as a result of PSA screening and 'multicore' schemes of prostate biopsy. These data suggest that many men with localized PCa would not actually benefit from definitive treatment.

With the aim of reducing the risk of overtreatment in this subgroup of patients, two conservative management strategies of "watchful waiting" and "active surveillance" have been proposed.

The term "watchful waiting" was coined in the pre-PSA screening era (before 1990) and referred to the conservative management of PCa until the development of local or systemic progression. At this point, the patient would then be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction, and hormonal therapy (HT) or RT for the palliation of metastatic lesions.

A more modern concept of watchful waiting is better termed "active surveillance", also known as "active monitoring". It includes an active decision not to treat the patient immediately. Instead, the patients are followed up under close surveillance and treated at pre-defined thresholds that classify progression (i.e. short PSA doubling time and deteriorating histopathology factors on repeat biopsy). Treatment options are intended to be curative.

## 5.2 Radical Prostatectomy

Radical prostatectomy is the surgical treatment of PCa. It involves the removal of the entire prostate gland, and resection of both seminal vesicles along with sufficient

surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by a bilateral pelvic lymph node dissection.

Radical prostatectomy was first applied at the beginning of the 20th century by Young [175] using a perineal approach, while Memmelaar and Millin were the first to perform retropubic radical prostatectomy (RRP) [176]. In 1982, Walsh and Donker described the anatomy of the dorsal venous complex and this resulted in a significant reduction in blood loss [177].

Furthermore they described the anatomy of the neurovascular bundles [177].

So, depending on the characteristics of the tumor and patient sexual function, this may involve sparing of the neurovascular bundle, which increases the likelihood of preserving potency and improved continence [178].

Men most suitable for RRP are those with a life expectancy of at least 10 years with disease that does not extend beyond the prostate capsule [178]. In these patients the goal of RP by any approach should be eradication of disease, while preserving continence and whenever possible potency [179]. There is no age threshold for RRP and a patient should not be denied this procedure on the grounds of age alone [180].

Rather, increasing co-morbidity that greatly increases the risk of dying from non-PCa-related causes [181] may contraindicate RRP. An estimation of life expectancy is thus paramount in counseling a patient about surgery [182].

Currently, RRP is the only treatment for localized PCa to show a benefit for cancer-specific survival (CSS) compared with conservative management, as shown in a prospective, randomized trial [183]. In fact according to EAU guidelines, in patients with low and intermediate risk localized PCa and life expectancy > 10 years, RP is indicated. In addition, RRP is a reasonable treatment option for selected PCa patients with low-volume, high-risk, localized PCa (cT3a disease or GS 8-10 or PSA > 20 ng/ml).

Moreover, RP can be an optional in highly selected patients with very high risk PCa: clinical stage T3b-T4 N0 or any TN1 PCa in the context of a multimodality approach.

Surgical expertise has decreased the complication rates of RP and improved cancer cure [184–187]. Radical retropubic prostatectomy and perineal prostatectomy are performed through open incisions, while more recently minimally invasive laparoscopic (LRP) and robot-assisted RRP (RARP) have been developed (Figures 7,8).

The retropubic approach is more commonly performed over the perineal procedure, as it enables simultaneous pelvic lymph node assessment. It has been suggested that perineal RRP might result in positive surgical margins (PSMs) more often than the retropubic approach [188]. Robotic radical prostatectomy is displacing RRP as the gold standard surgical approach for clinically localized PCa in the United States and is also being increasingly used in Europe. A recent systematic review of the literature compared the results of RRP versus LRP/RALP. It has been concluded that LRP and RALP are followed by a significantly lower blood loss and transfusion rate, but the available data were not sufficient to prove the superiority of any surgical approach in terms of functional and oncological outcomes [189–191].

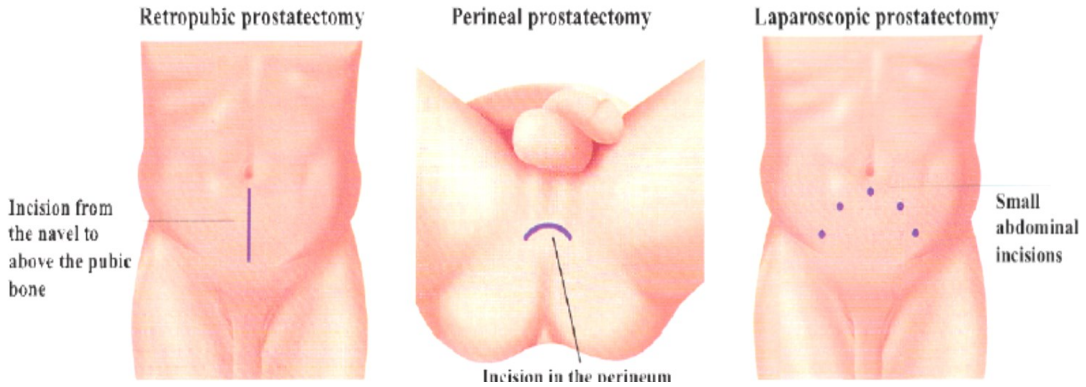



***Figure 7.*** *Radical prostatectomy by retropubic (left), perineal (center) and laparoscopic (right) approach.*

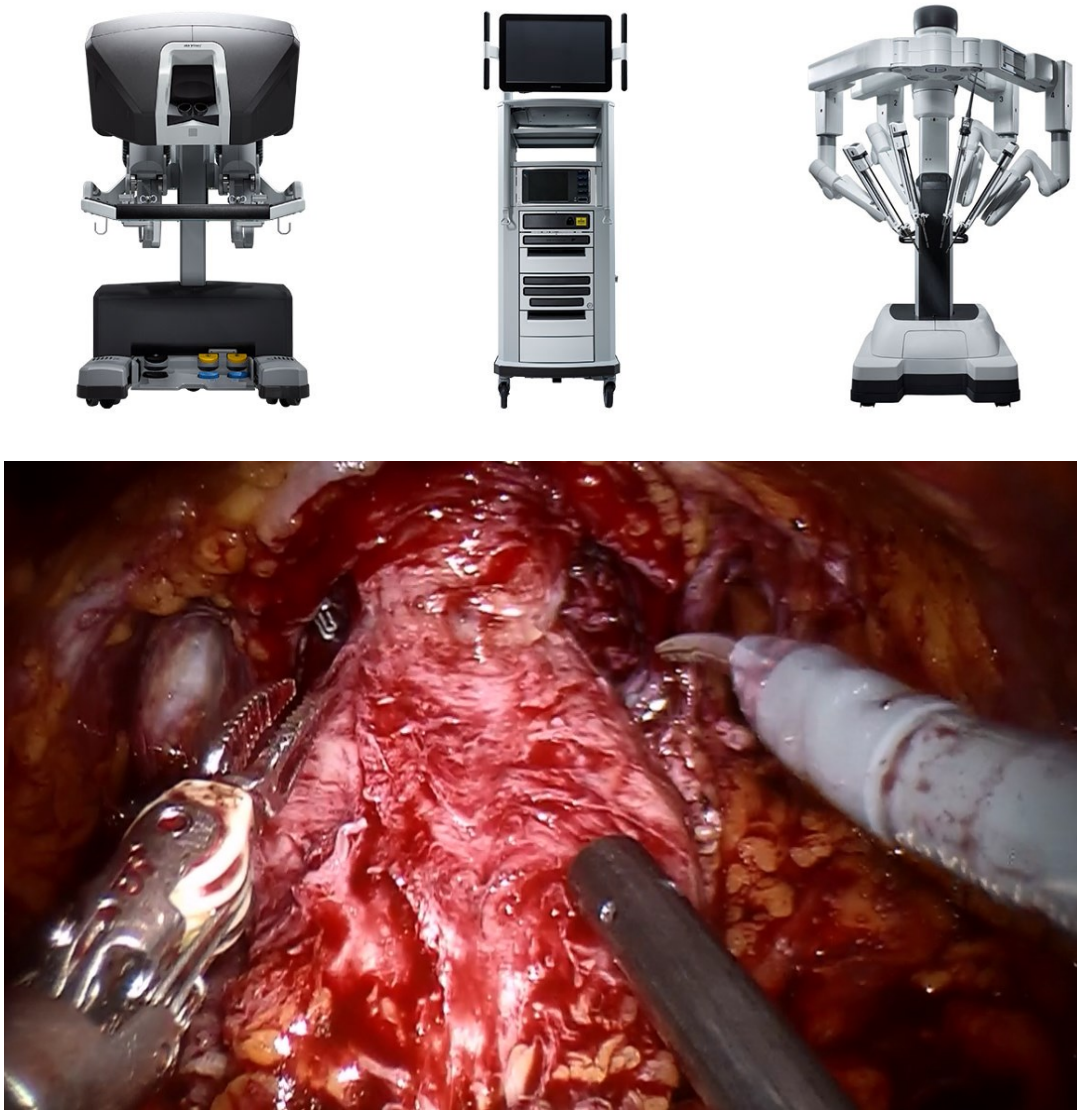


***Figure 8.*** *Robot-assisted radical prostatectomy (RALP).*

### *5.2.1 Pelvic Lymphadenectomy*

Pelvic lymphadenectomy (PLND) represents the gold standard for lymph node staging of PCa [192,193]. Two principal variants of PLND are commonly used: limited pelvic lymph node dissection (lPLND) and extended pelvic lymph node dissection (ePLND).

Consensus has not yet been reached that whenever PLND is indicated, this should be extended. Indeed, several studies have shown that the rate of LNI in PCa patients almost linearly increases with the extent of PLND [194,195]. Extended PLND includes the removal of the nodes overlying the external iliac vessels, the nodes within the obturator

fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery, given that the internal lymph nodes represent the primary landing zone of lymphatic drainage [196–198] (Figure 9).

Some authors sustain that ePLND must also include the removal of the presacral lymph nodes [199,200] and of the common iliac lymph nodes that are present up to the ureter crossing with the iliac vessels [201,202]. More specifically Mattei et al. studied the primary lymphatic landing sites in patients undergoing RP and ePLND [202].

In this study, the Authors described a multimodality imaging technique using single-photon emission computed tomography, combined with computed tomography or magnetic resonance imaging and compared the results with patients undergoing limited or extended PLND [202]. From their data, the Authors concluded that PLND for PCa should include not only the external and obturator regions and the areas lateral and medial to the internal iliac vessels, but also the common iliac lymph nodes up to the ureteric crossing; this technique may lead to the removal of approximately 75% of all nodes potentially harboring metastatic spread [202].

The true value of ePLND is based on a well-defined field of resection, which means that more lymph nodes will be removed, and the primary landing sites of potential metastases should be included. Supporting the idea of extending the field of resection, Heidenreich et al. emphasized the value of extended compared to standard PLND during RRP [199]. They found that ePLND was associated with a high rate of lymph node metastases outside the fields of standard lymphadenectomy in cases of clinically localized PCa [199]. Indeed, up to 50% of lymph node metastases were localized on the internal iliac lymph nodes [200,201,203,204], which are not included in lPLND. An ePLND might not only be important for PCa staging but also might be curative in a sub-set of patients with limited amount of nodal invasion [205]. More recently, the pathological extent of nodal metastases was investigated and it was found that both the diameter of any individual lymph node metastasis and its extra-nodal extension have a significant prognostic impact [206,207]. It has also been shown that the number of positive nodes and lymph node density are of significant importance [193,208,209].

In order to guarantee correct lymph node staging, the average number of lymph nodes that should be removed is around 20 [210]. Current European Association of Urology (EAU) guidelines suggest that if PLND is indicated, extended PLND should be performed to include obturator, external iliac, hypogastric with or without presacral and common iliac nodes. This procedure guarantees removal of an average of 20 nodes per patient, whereas PLND would allow the removal of an average of only 8-10 lymph nodes [192].

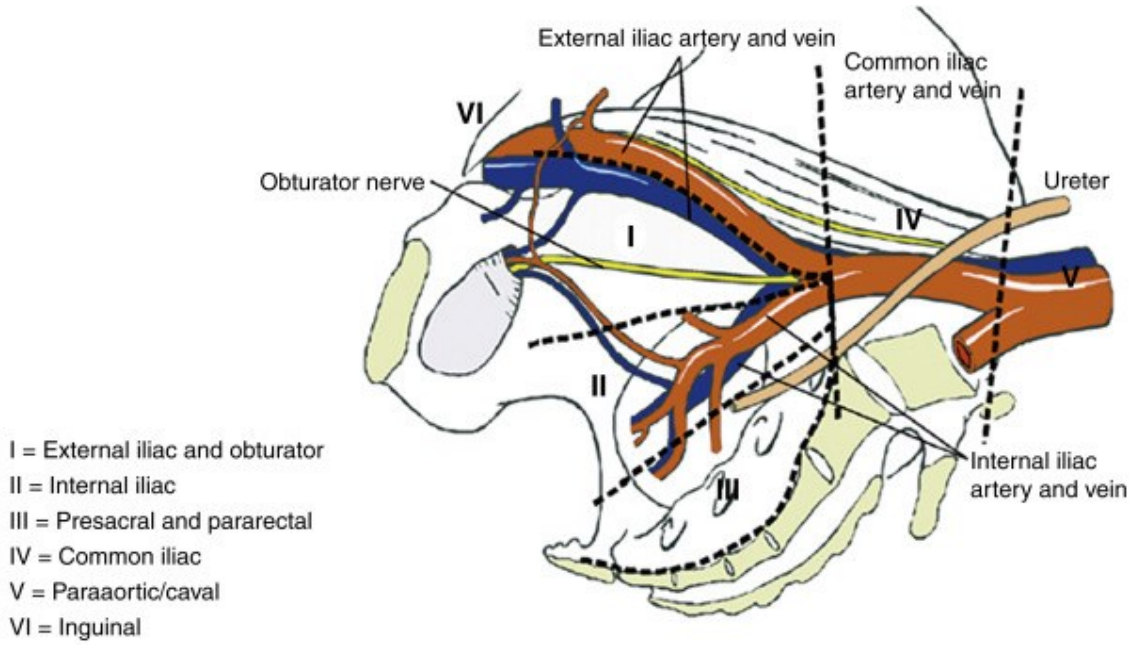



***Figure 9.*** *Limited pelvic lymphadenectomy (lPLND) refers to pelvic lymph node dissection on the I region; extended pelvic lymphadenectomy (ePLND) refers to pelvic lymph node dissection on the I and II region, and to III and IV region according to other authors.*

Even in experienced hands, it is certain that the complication rate of ePLND, such as lymphocoeles and lymphedema is increased and it is to be considered when planning treatment strategies [211]. According to the EAU guidelines, ePLND is not necessary in low-risk, localized PCa because the nomogram predicted risk of positive lymph nodes does not exceed 5% [212]. ePLND should be performed in intermediate-risk, localized PCa if the estimated risk for positive lymph nodes exceeds 5%, as well as in high-risk

cases [212]. In conclusion, this extended dissection removes more lymph nodes than in a more limited dissection, improving staging and providing potential therapeutic benefit in some patients.

## 5.3 Androgen Deprivation Therapy

The pivotal studies of Huggins and Hodges in 1941 [213,214] showed that the development and growth of PCa cells are dependent on androgens and demonstrated that either medically or surgically AD is an effective treatment for PCa.

Since then, androgen deprivation therapy (ADT) has been increasingly utilized for the treatment of PCa. Paul Niehans et al. reported similar results in 1940 [214]. Androgen deprivation therapy has been mostly considered as a palliative treatment used to slow down disease progression and used as the treatment of choice for advanced or metastatic PCa. Currently, <5% of men with newly diagnosed PCa have distant metastases at first presentation [215]. In the last years, ADT has become often considered also for locally advanced disease. Androgen deprivation therapy is now the second most common approach, after surgery, for the treatment of clinically organ-confined PCa in the United States [216,217].

Androgen deprivation therapy is based on the reduction of circulating androgens and/or on the blocking of androgen receptors. There are different types of ADT:

1) Surgical and medical castration: bilateral orchiectomy causes rapid and sustained suppression of testicular androgens with resulting circulating testosterone levels <20 ng/ml in most patients [218]. Bilateral orchiectomy has been largely replaced by luteinizing hormone-releasing hormone (LHRH) agonists (busereline, gosereline, leuproreline, triptoreline), because of better patient and physician acceptance. LHRH agonist represents the most commonly used ADT [218]. Initially, they stimulate pituitary LHRH receptors, inducing a transient rise in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. This elevates testosterone production (‘flare-up’ phenomenon), which begins about 2-3 days after the first injection and lasts for about one week [219]. Chronic exposure to LHRH agonists eventually results in down regulation of LHRH-receptors. This then suppresses pituitary LH and FSH

secretion and testosterone production, so that testosterone levels decrease to castration levels usually within 2-4 weeks [220]. To avoid the flare-up phenomenon a concomitant therapy with an anti-androgen is used, but does not completely remove the possibility of its occurrence.

2) Steroidal and non-steroidal anti-androgens that compete with testosterone and dihydrotestosterone hormone (DHT) at the receptor level in the prostate cell nucleus, thus promoting apoptosis and inhibiting PCa growth [221].

3) LHRH antagonists (Abarelix and Degarelix): Unlike the LHRH agonists, LHRH antagonists cause an immediate and reversible suppression of LH and FSH secretion, subsequently, testosterone [222,223].

4) Cytochrome P450c17 inhibitors of steroidogenesis: they block the synthesis of androgens in the testes, adrenal glands, and prostate by inhibition of cytochrome P450c17, a rate-limiting enzyme in androgen biosynthesis.

Nowadays there are three main indications for the use of ADT:

(1) to support EBRT in high-risk patients, which showed prolonged overall survival [224,225];

(2) to downsize the prostate gland prior to brachytherapy (although in this setting ADT does not prolong patient survival) [226,227];

(3) to minimize the risk of fatal cancer-related complications and palliation of symptomatic disease in patients with advanced metastatic disease [228,229]. Another indication of the EAU guidelines is immediate ADT in case of LNI at ePLND [229].

Androgen deprivation therapy may lead to numerous side effects, such as osteoporosis, obesity, sarcopenia, lipid alterations, insulin resistance, anemia, decreased cognitive function, loss of libido, erectile dysfunction, fatigue, hot flushes, arterial stiffness and increased risk for diabetes and cardiovascular morbidity. This toxicity profile may reduce quality of life and/or overall survival [230,231]. Consequently, these issues should be discussed in detail with patients and their families before initiation of ADT

[229]. These risks do not exclusively apply to long-term use of ADT; even short-term use of ADT may induce some of these conditions [232–234].

## 5.4 Radiation Therapy

In 1895 Roentgen described x-rays; by 1899 a patient with skin cancer was cured with radiation; and within 10 years, radiation was used to treat PCa.

Although aggressive surgery and other treatments have supplanted some of the uses of RT, radiation continues to play a major role in the management of PCa.

The effects of radiation on tumor and surrounding normal tissues seem to be mediated primarily through the induction of unrepaired double-strand breaks in DNA. Excited electron species generated in the presence of oxygen form peroxide radicals, which fix chemical lesions and result in the generation of either repairable or non-repairable DNA double-strand breaks. High linear energy transfer radiation is associated with less repairable DNA damage. Classically, the expression of radiation damage is not seen until the target cells enter mitosis. Differentiated normal tissues with low mitotic activity, such as the heart and the spinal cord, tend to express the effects of radiation much later than cells from more kinetically active tissues, such as the epithelial cells lining the rectum, bladder or urethra. However, differentiated normal tissues with low mitotic activity are more sensitive to the use of high dose per fraction or high linear energy transfer RT. In organs in which the functional stromal cells are postmitotic, such as muscle cells and neurons, the damage is expressed by slowly dividing support cells such as endothelial cells. In addition to the classic mechanism described above, radiation has been shown to induce programmed cell death (apoptosis). Androgen-independent human PCa cells activate a genetic program of apoptotic cell death in response to exposure to ionizing radiation, in a dose- dependent fashion [235].

### *5.4.1 External Beam Radiotherapy*

In external beam radiotherapy high-energy external beam radiation is focused on the prostate gland (Figure 10). It is an outpatient procedure that requires no anesthesia.

Conventional EBRT has been used in the United States for treating PCa for more than 35 years. Conventional techniques generally involve the use of open square or rectangular fields with minimal to no blocking and are characterized by the use of relatively small boost fields. These standard EBRT techniques depend upon bony landmarks to define treatment borders or a single CT slice to define the target volume. Often these traditional techniques were associated with inadequate coverage of the target volume in 20-41% of patients treated. In addiction total dose used was 65-70 Gy because it was believed that this dose was sufficient and close to the maximum dose allowable by the surrounding normal tissues. All these factors contributed to risk of local failure following external-beam irradiation. These technical problems are partially resolved with the improving imaging and using of novel treatment planning (three-dimensional conformal and intensity modulated RT: 3DCRT, IMRT). Beginning in the early 1990s, 3DCRT began to be established as the new standard of care for treating clinically localized PCa.

Anatomical data, acquired by scanning the patient in a treatment position, are transferred to the 3D treatment planning system, which visualizes the clinical target volume and then adds a (surrounding) safety margin. At the time of irradiation, a multi-leaf collimator automatically and, in the case of IMRT, continuously, adapts to the contours of the target volume seen by each beam. Real-time verification of the irradiation field by means of portal imaging allows for comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. 3D-CRT allows high dose radiation to conform to the target volume with greater sparing of the surrounding normal tissues. IMRT is a more sophisticated form of 3DCRT that allows higher doses of radiation (up to as much as 86 Gy within the target volume) to be given with less toxicity [236].

To date, no randomized trials have been published comparing dose escalation using IMRT and 3D-CRT. With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumor control and treatment toxicity.

Evolving techniques will therefore combine IMRT with some form of image guided RT (IGRT), in which organ movement can be visualized and corrected for in real time, although the optimum means of achieving this is still unclear.

Another evolving technique for the delivery of IMRT is tomotherapy, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the center of the ring, analogous to spiral computed tomography (CT) scanning. Preliminary data suggest that this technique is feasible in PCa treatment [237].

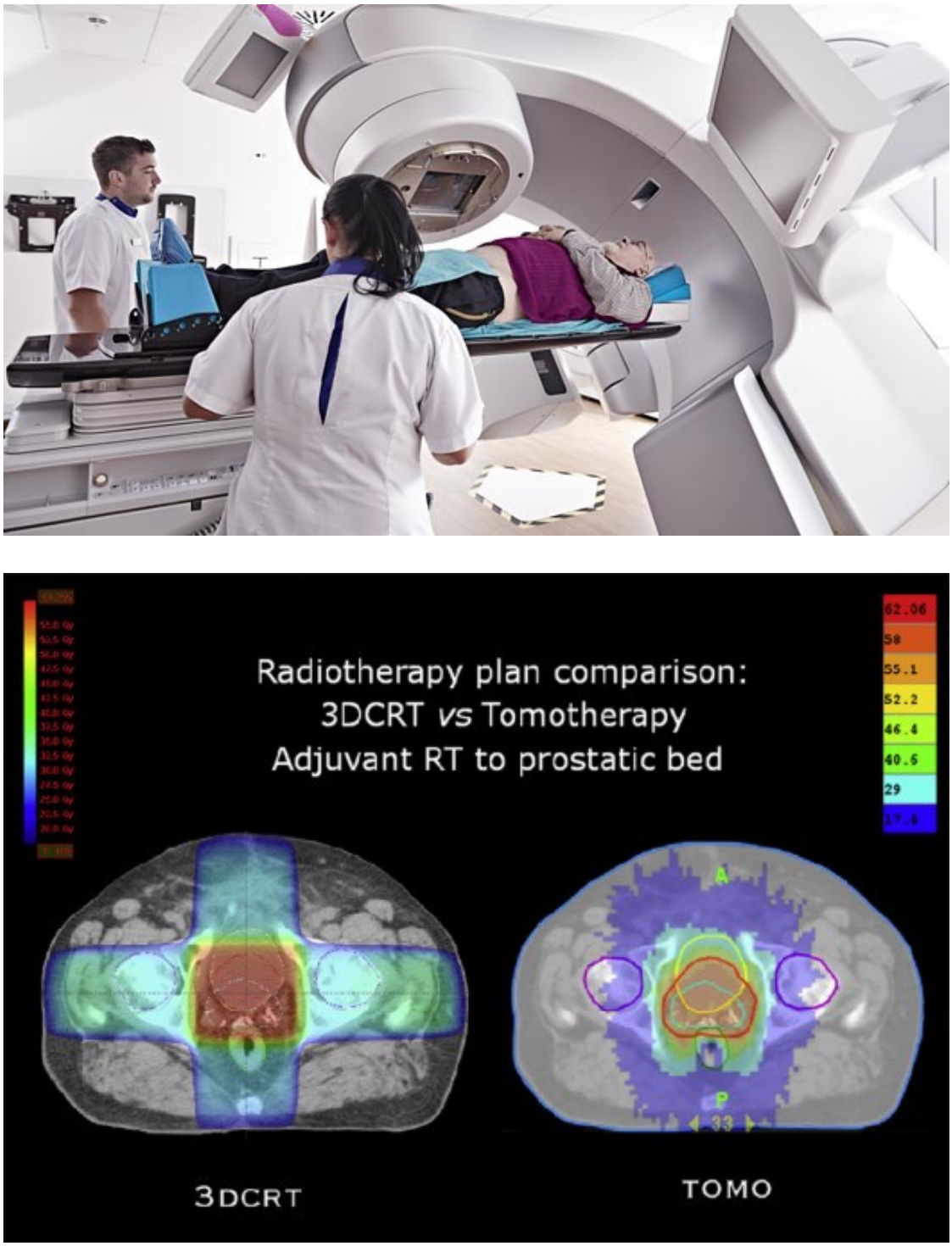



***Figure 10.*** *External Beam Radiotherapy*

In summary, these new treatments allow for better targeting, conforming or shaping radiation volume more closely around the prostate, and the use of higher doses without exceeding tolerance of surrounding normal tissues. Such radiotherapy has resulted in dramatic reduction in acute and late genitourinary or gastrointestinal toxicity of radiation treatment and improved tumor control compared with conventional dose RT. So patients must be informed about this potential toxicity, as well as the impact of irradiation on erectile function.

Nowadays there are no randomized studies comparing RP with EBRT or brachytherapy for localized PCa. However, the National Institutes of Health (NIH) consensus set up in 1988 remains available: external irradiation offers the same long-term survival results as surgery; moreover, EBRT provides a QoL at least as good as that provided by surgery [238].

### *5.4.2 Radiation Therapy for Non-Metastatic Prostate Cancer*

Radiation therapy is recommended in localized PCa T1c-T2c N0 M0 even for young patients who refuse surgical intervention. Several randomized and non-randomized studies have shown that dose escalation (range, 76-80 Gy) has a significant impact on 5- year survival without biochemical relapse [239,240]. Furthermore, several investigators have shown that the results of RT may be improved with the use of neo-adjuvant, concurrent and adjuvant ADT. On the basis of several randomized trials and nonrandomized trials, ADT improves the outcome of radiation in those with intermediate or high-risk disease. A combination of external irradiation with short-term ADT improves overall survival, based on the results of a phase III randomized trial which included 206 patients with a PSA level of at least 10 ng/mL (maximum 40 ng/ mL), a GS of at least 7 (range 5-10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with 6 months of ADT. After a median follow-up of 7.6 years, intermediate- or high-risk patients without moderate or severe co-morbidity, who had been randomized to receive 3D-CRT + ADT, showed a 13% improvement in overall survival rate ($p < 0.001$). In contrast, data from the EORTC-22961 randomized phase III trial, comparing 36 months of hormonal treatment plus RT

with 6 months of hormonal treatment plus RT, showed that increased hormonal treatment improved overall survival in patients with high-risk PCa at 5 years [241].

In summary, according to the EAU 2012 guidelines, the use of long-term ADT prior to and during RT is recommended for high-risk, being associated with increased overall survival. EAU recommends that patients with locally advanced PCa (cT3-4 N0 M0) treated with EBRT and with WHO 0-2-performance status should be treated with concomitant and adjuvant HT for a total duration of 3 years. Finally, a subset of intermediate risk patients with T2c-T3 N0-X and a GS of 2-6 should instead receive short-term (3-4 months) neoadjuvant and concurrent ADT, because it may favorably influence overall survival.

### *5.4.3 Postoperative Radiation Therapy*

Postoperative RT is given as adjuvant therapy to men with high-risk pathologic features or as salvage therapy for those patients previously treated with RP who further developed biochemical recurrence (BCR).

Adjuvant radiotherapy is given in the immediate postoperative period in men with an undetectable PSA level at 6 weeks postoperatively. These patients do not have macroscopic residual or recurrent disease, but deemed at high risk of microscopic residual disease. There is no specific time course for administering aRT, although common practice is to wait until post-prostatectomy stress urinary incontinence has resolved, due to concerns that it may adversely affect recovery. Adjuvant RT is usually given within 4 months after surgery [242].

Adjuvant RT is a local intervention. The rationale for aRT is based on several factors. First, the pattern of treatment failure suggests local failure is the most common site of recurrence in men without lymph node metastasis. Second, aRT is likely to be more effective than salvage RT (SRT). In fact the aim of aRT is sterilization of residual tumor cells in the prostate bed following surgery, eradicating microscopic residual tumor in the periprostatic tissues. If left untreated, it is believed that these residual cells may disseminate outside the pelvis. By this logic, delaying RT until the time of BCR may

decrease the probability of secondary cure. Therefore, the ultimate aim of aRT is improvement in overall survival [243,244].

Regarding salvage RT, it refers to treatment of patients with detectable or rising postoperative PSA beyond 6 weeks with or without palpable local disease, and may occur at any stage following RP. The optimal salvage treatment is controversial.

Although other treatment modalities, including HT or chemotherapy, may be used when relapse is identified, RT is the only modality currently known to have the potential to cure men with residual or recurrent disease localized to the RT treatment volume. The rationale for SRT is based on several factors.

First, it restricts therapy- and treatment-related complications to those patients who have evidence of BCR.

Second, the risk of competing causes of mortality far exceeds the risk of PCa-specific mortality for the majority of men who are candidates for postoperative RT.

Third, the ability of RT to cure patients with residual pelvic disease after RP may not be compromised if it is deferred until the earliest evidence of PSA recurrence levels.

Fourth, the majority of patients candidate for aRT are cured by RP alone and their long-term risk of PCa-specific mortality is low [242].

All these concepts have been recently summarized by the EAU guidelines as follows:

1. Immediate postoperative external irradiation after RP can be offered to patients with pT3N0M0 PCa since it may improve overall survival and biochemical and clinical disease-free survival [245], with the highest impact in patients with positive margins [246].

2. Salvage irradiation is indicated in patients with pathological tumor stage T2- 3N0M0, in case of persisting PSA or biochemical failure, but before the PSA level rises above 0.5 ng/mL [247,248].

With regards to very high-risk PCa, c-p N1 M0, with no severe co-morbidity few studies showed that pelvic external irradiation and immediate long-term ADT can improve overall survival, disease-specific failure and biochemical control [249,250].

However, further prospective studies are needed to clarify these issues.

## 5.5 Radiation Therapy – Brachytherapy

An alternative form of radiation for the treatment of PCa is brachytherapy (Figure 7).

The term brachytherapy refers to a treatment technique that places radioactive source directly into the prostate in close proximity to or directly into the tumor.

The major theoretic advantage of this form of radiation is the ability to deliver a very high dose of radiation to a localized area with a decreased number of treatment visits. The use of modern-era imaging techniques for visualizing the placement of radioactive seeds has obviated the need for open surgical procedures. Transrectal ultrasound-guided closed techniques are currently considered the standard. Implantation is taken under general anesthesia or spinal block.

There is consensus on the following eligibility criteria for brachitherapy:

• Stage cT1b- T2a N0, M0;

• A GS ≤ 6 assessed on a sufficient number of random biopsies;

• An initial PSA level of < 10 ng/mL;

• Less than 50% of biopsy cores involved with cancer;

• A prostate volume of < 50 cm3;

• An International Prostatic Symptom Score < 12 (IPSS) [251].

Patients with low-risk PCa are the most suitable candidates for low-dose rate (LDR) brachytherapy.

There are no randomized trials comparing brachytherapy with other curative treatment modalities, and outcomes are based on non-randomized case series.

Recurrence-free survival after 5 and 10 years was reported to range from 71% to 93% and from 65% to 85%, respectively [252].

A significant correlation has been shown between the implanted dose and recurrence rates [253]. Patients receiving a D90 of > 140 Gy demonstrated a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at 4 years than patients receiving less than 140 Gy (92% vs 68%). There is no benefit from adding neoadjuvant or adjuvant ADT to LDR brachytherapy [254].

In cases of intermediate- or high-risk localized PCa, brachytherapy in combination with supplemental external irradiation or neoadjuvant hormonal treatment [255] may be considered.

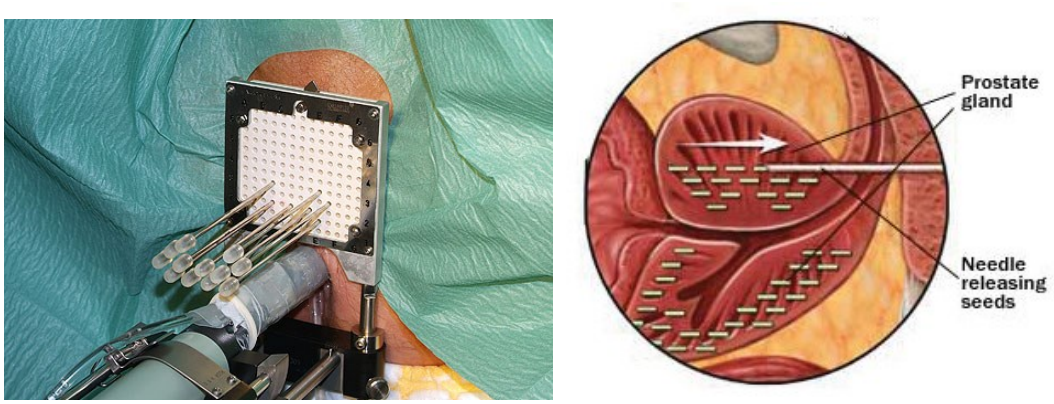



***Figure 11.*** *Brachytherapy*

# 6 REPEATED MRI SCANS DURING ACTIVE SURVEILLANCE FOR PROSTATE CANCER: NATURAL HISTORY OF PROSTATIC LESIONS AND UPGRADING RATES OVER TIME

## 6.1 Introduction

Active Surveillance (AS) protocols rely on repeated prostate biopsies to assess and monitor prostate cancer (PCa) progression [256]. However, excessive and invasive surveillance testing may unnecessarily decrease compliance to AS, leading patients to switch to active treatment (AT) [257,258].

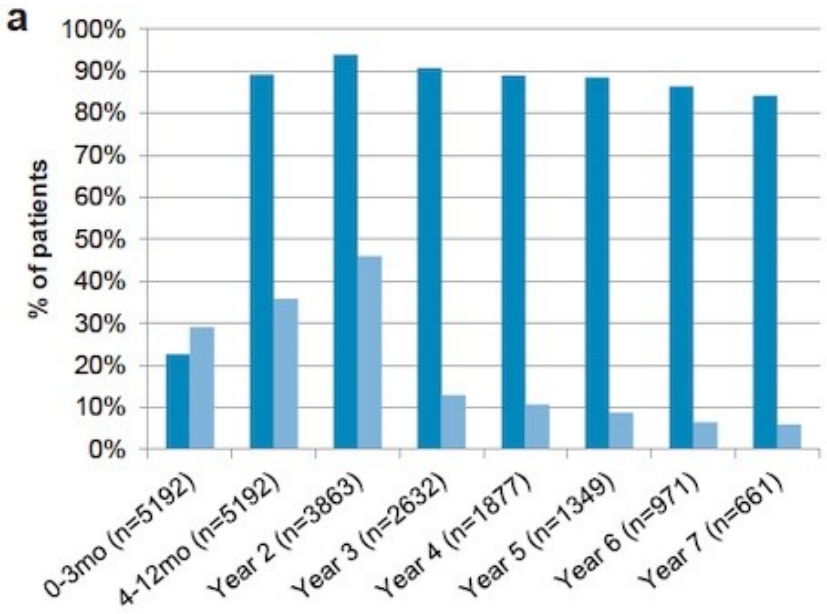



***Figure 12.*** *Proportion of men who underwent PSA test (dark blue bars) and biopsy (light blue bars) during each AS year* [258]**.**

To reduce the frequency of prostate samplings while simultaneously increase patient compliance, multiparametric magnetic resonance imaging (mpMRI) has been implemented in several AS series [259]. However, it remains unclear whether mpMRI can safely replace repeated biopsies during follow-up [260,261]. To date, conflicting results have been reported in previous analyses that tested the diagnostic accuracy of serial mpMRI scans in men on AS [262–272].

Table 3 – Diagnostic performance of MRI progression in included studies

| Author [reference] | Serial MRI assessment | TP | FP | FN | TN | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| Amin [17] | Institution specific | 13 | 16 | 8 | 63 | 0.62 | 0.80 | 0.45 | 0.89 |
| Caglic [25] | PRECISE | 31 | 29 | 10 | 225 | 0.76 | 0.89 | 0.52 | 0.96 |
| Chesnut [26] | Institution specific | 20 | 28 | 46 | 113 | 0.30 | 0.80 | 0.42 | 0.71 |
| Fujihara [27] | Institution specific | 8 | 17 | 5 | 38 | 0.62 | 0.69 | 0.32 | 0.88 |
| Giganti [20] | PRECISE | 109 | 62 | 19 | 116 | 0.85 | 0.65 | 0.64 | 0.86 |
| O'Connor [a] [28] | PRECISE | 64 | 204 | 58 | 295 | 0.53 | 0.59 | 0.24 | 0.84 |
| Osses [29] | PRECISE | 7 | 10 | 28 | 66 | 0.20 | 0.87 | 0.41 | 0.70 |
| Ullrich [30] | PRECISE | 29 | 15 | 0 | 11 | 1.00 | 0.42 | 0.66 | 1.00 |
| Dieffenbacher [31] | PRECISE | 17 | 13 | 12 | 116 | 0.59 | 0.90 | 0.57 | 0.91 |
| Hsiang [32] | Institution specific | 12 | 42 | 17 | 51 | 0.41 | 0.55 | 0.22 | 0.75 |
| Elkjaer [33] | Institution specific | 7 | 0 | 3 | 40 | 0.70 | 1.00 | 1.00 | 0.93 |
| Thurtle [34] | Institution specific | 10 | 10 | 10 | 74 | 0.50 | 0.88 | 0.50 | 0.88 |
| Frye [35] | Institution specific | 39 | 68 | 10 | 49 | 0.80 | 0.42 | 0.36 | 0.83 |
| Felker [36] | Institution specific | 7 | 3 | 12 | 27 | 0.37 | 0.90 | 0.70 | 0.69 |
| Walton Diaz [37] | Institution specific | 9 | 8 | 8 | 33 | 0.53 | 0.80 | 0.53 | 0.80 |

FN = false negative; FP = false positive; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; TN = true negative; TP = true positive.
[a] Data provided for MRI intervals.

***Figure 13.*** *Diagnostic performance of MRI progression in previous studies* [260]**.**

However, most of these studies were limited by the low number of patients enrolled [262,263,269,271,272] or by the short follow-up time [264,265,271,272]. Moreover, only few previous analyses focused on the natural history of mpMRI prostatic lesions over time and found a small annual growth rate in most of the cases [273,274].

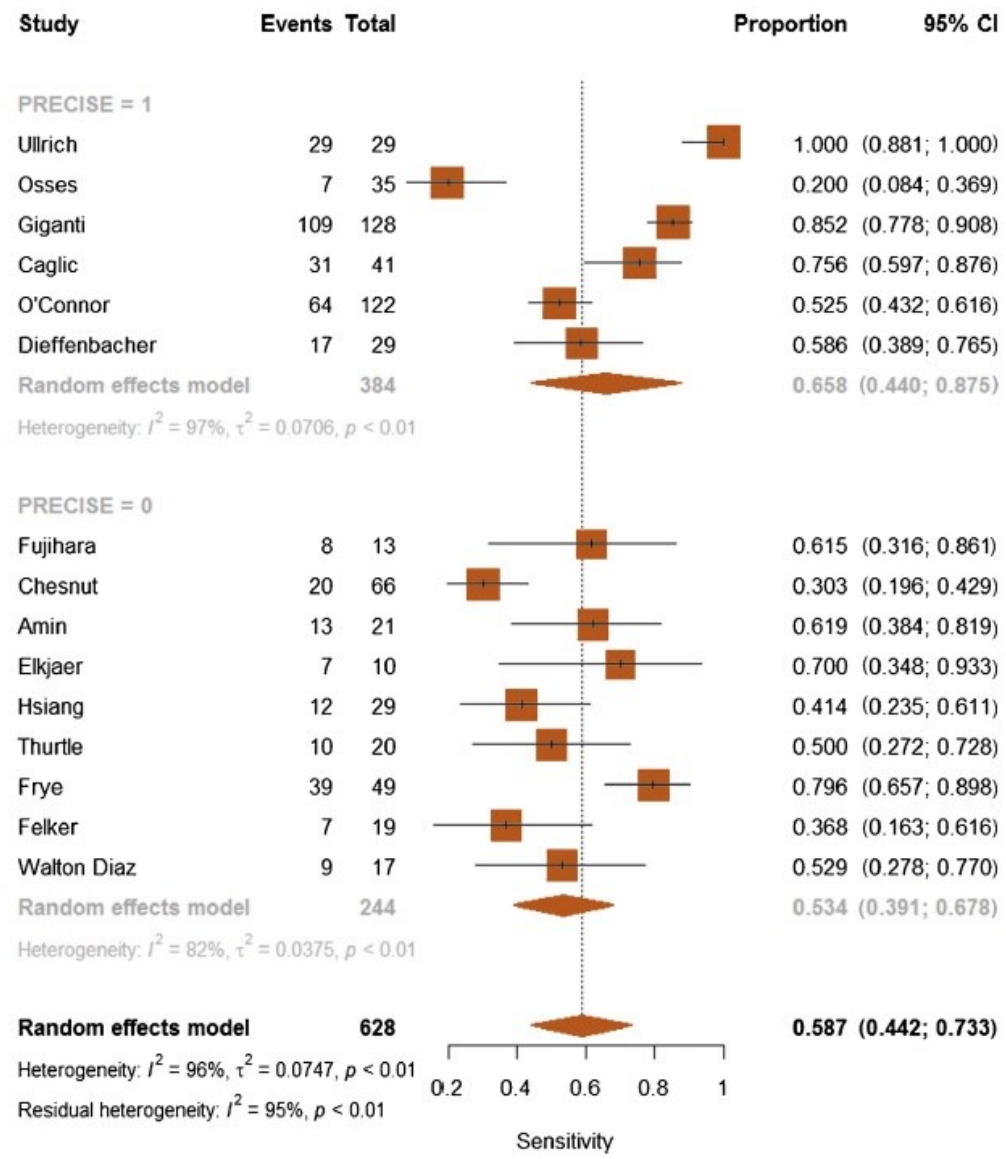



**Fig. 3 – Forest plots for pooled sensitivity or all studies, stratified by serial MRI assessment reporting scheme type. PRECISE = 1 indicates studies using PRECISE recommendations for MRI progression, and PRECISE = 0 indicates studies using institution-specific definitions of MRI progression. CI = confidence interval; MRI = magnetic resonance imaging; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.**

***Figure 14.*** *Pooled sensitivity of MRI progression in previous studies* [260].

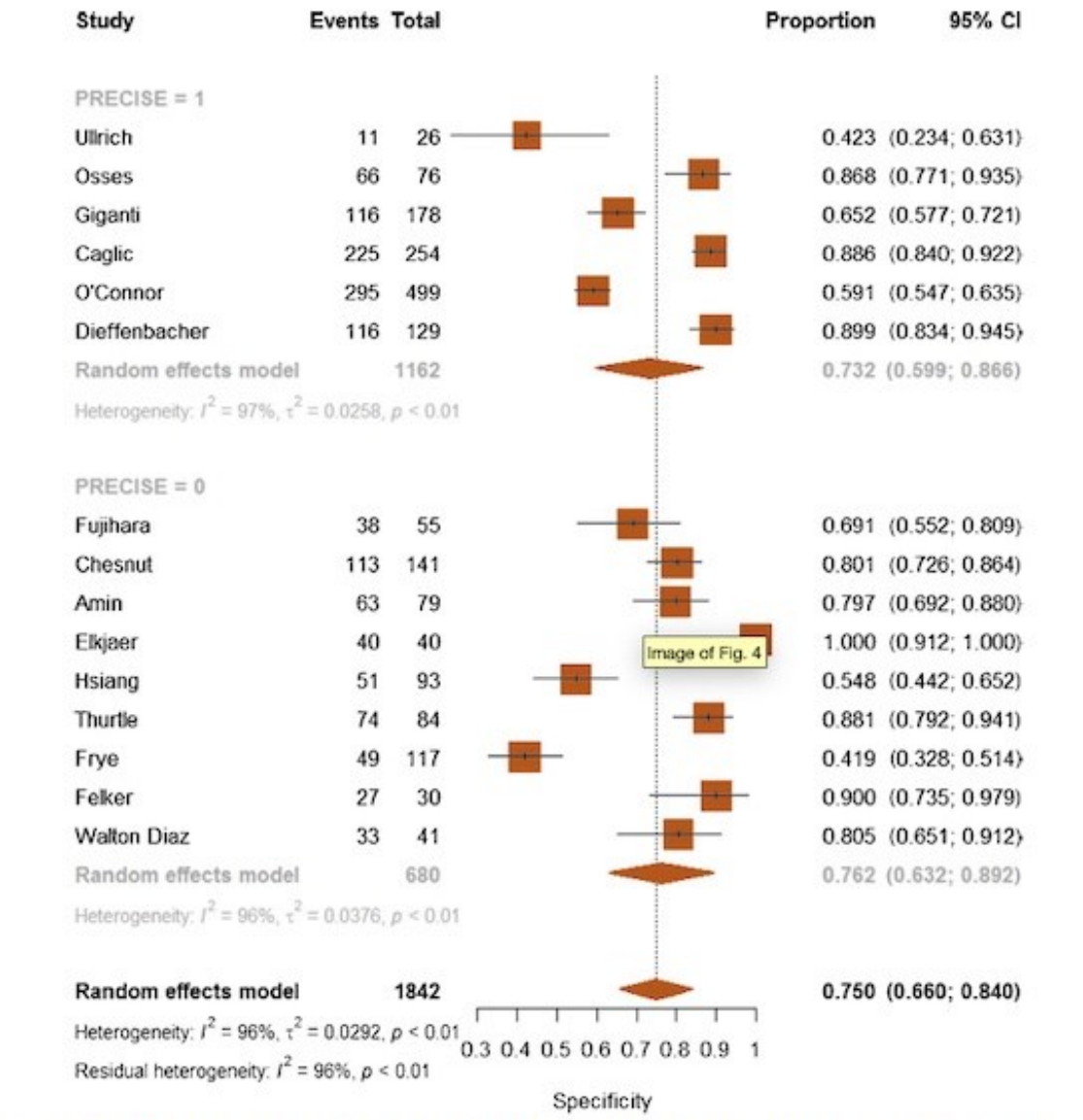



Fig. 4 – Forest plots for pooled specificity or all studies, stratified by serial MRI assessment reporting scheme type. PRECISE = 1 indicates studies using PRECISE recommendations for MRI progression, and PRECISE = 0 indicates studies using institution-specific definitions of MRI progression. CI = confidence interval; MRI = magnetic resonance imaging; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

***Figure 15.*** *Pooled specificity of MRI progression in previous studies* [260].

This said, robust data from large, contemporary and homogeneous cohorts of AS patients followed with repeated mpMRI scans are urgently needed. We tried to give a first answer to fill this gap.

## 6.2 Materials and Methods

### *6.2.1 Study population*

This retrospective data analysis was approved by the Institutional Review Board of the European Institute of Oncology.

Overall, 961 patients with PCa were enrolled in AS between 2008 and 2020. AS inclusion criteria were the following: prostate specific antigen (PSA) ≤10 ng/ml; clinical stage cT1c/cT2a; International Society of Urological Pathology Grade Group (ISUP GG) 1 PCa with ≤3 positive cores or ISUP GG2 PCa with pattern 4≤10% in a single core. AS protocol consisted of: repeated PSA testing every 6 months; clinical assessment every 12 months and repeated surveillance biopsies at 12, 36 and 84 months. From 2013, all patients underwent confirmatory mpMRI at AS begin and, eventually, targeted biopsies of all Prostate Imaging Reporting and Data System (PI-RADS) score ≥3 lesions [103,275–277]. Moreover, repeated mpMRIs were performed before all surveillance targeted (PI-RADS≥3 lesions) or systematic (PI-RADS≤2 lesions) prostate biopsies. Additional prostate samplings or mpMRI scans were taken at any time according to clinician preference.

Patients were switched to AT due to: 1) ISUP GG upgrading (ISUP GG≥2 with >10% of pattern 4); 2) volume upstaging (>3 positive cores); 3) rising PSA; 4) patient preference.

For final analyses, we excluded all patients that did not undergo confirmatory mpMRI at AS begin (n=268). Then, we selected only patients submitted to at least two consecutive mpMRI scans (n=558). This patient subgroup was used to study the natural history of mpMRI prostatic lesions over time. Finally, we excluded all patients that were lost at follow-up (n=101) or that were not submitted to surveillance prostate biopsies (n=93). Overall, 364 patients were used to test PCa upgrading rates.

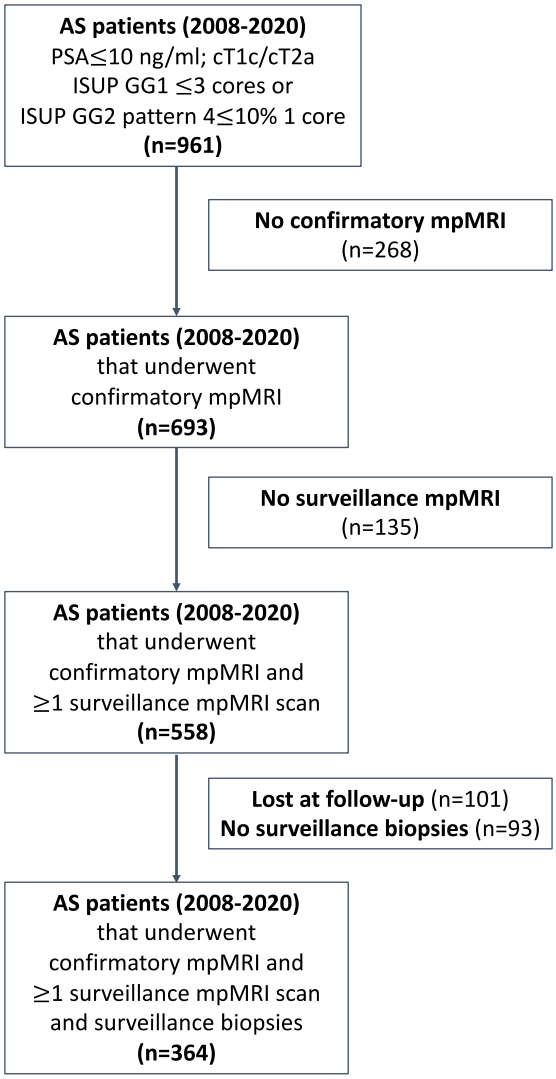



***Figure 16**. Consort Diagram with inclusion and exclusion criteria.*

### *6.2.2 mpMRI protocol*

All mpMRI scans were performed on a 1.5-T scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) with a phased-array coil. MpMRI protocol was compliant with the ESUR guidelines [277]. Specifically, sagittal, coronal and axial T2-weighted images, axial diffusion weighted and dynamic axial T1-weighted images were obtained after injection of contrast agent. All images were analysed by three dedicated radiologists (GP, SA, PP) with, respectively, 6, 3 and 2 years of experience at study beginning. Suspicious lesions were scored according to PI-RADS v1 (2013-2015) [277] and PI-RADS v2 (2015-thereafter) guidelines [103]. All mpMRIs performed at other

centres were reviewed by our radiologists and, in case of low quality images, were repeated at our hospital.

### *6.2.3 Variables and outcomes of interest*

Five different definitions of mpMRI progression were used:

-PI-RADS score increase: 1) novel PI-RADS≥4 lesion in patients with PI-RADS≤3 lesions; 2) novel PI-RADS 5 lesion in patients with PI-RADS 4 lesions.

-Lesion size increase: enlargement of ≥3 mm (largest dimension).

-Extraprostatic extension (EPE) score, defined according to 2012 ESUR prostate MR Guidelines [277], increase: 1) novel EPE≥3 lesion in patients with EPE≤2 lesions; 2) novel EPE≥4 lesion in patients with EPE 3 lesions; 3) novel EPE 5 lesion in patients with EPE 4 lesions.

-Overall mpMRI progression (NO vs. YES): at least one criterion among PI-RADS score vs. Lesion size vs. EPE score increase.

-Number of mpMRI progression criteria (among PI-RADS score vs. Lesion size vs. EPE score increase): 0 vs. 1 vs. 2-3 criteria.

We focused on PCa upgrading rates on repeated surveillance biopsies. Two different definitions of PCa upgrading were used [278]: 1) ISUP GG≥2 with >10% of pattern 4; 2) ISUP GG≥3.

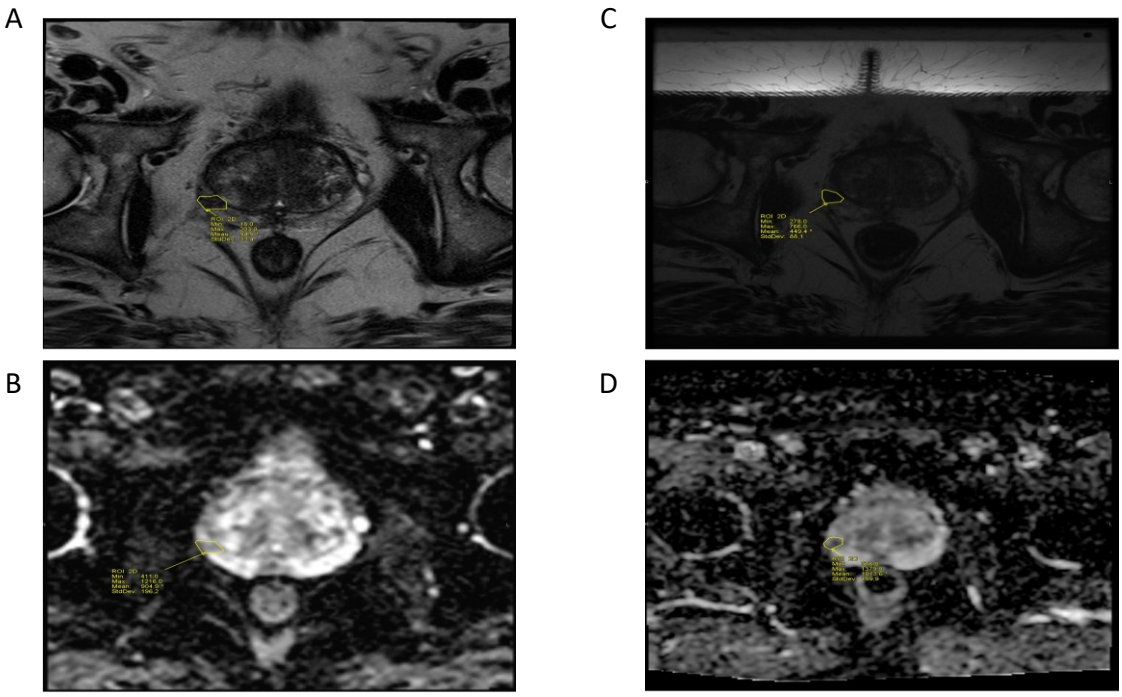



***Figure 17.*** *A 63 years old patient that was diagnosed with single core positive for ISUP GG1 prostate cancer. Baseline mpMRI showed a 6 mm PI-RADS score 4, EPE score 2 lesion in the PZ of the prostate, right side, at the level of the base. This lesion remained stable at a second mpRMI that was perfomed after 1 year of AS.*

*A) T2- weighted images of baseline mpMRI*

*B) ADC map of baseline mpMRI*

*C) T2- weighted images of repeated mpMRI*

*D) ADC map of repeated mpMRI*

*AS: Active Surveillance; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension; PZ: peripheral zone; ADC: apparent diffusion coefficient*

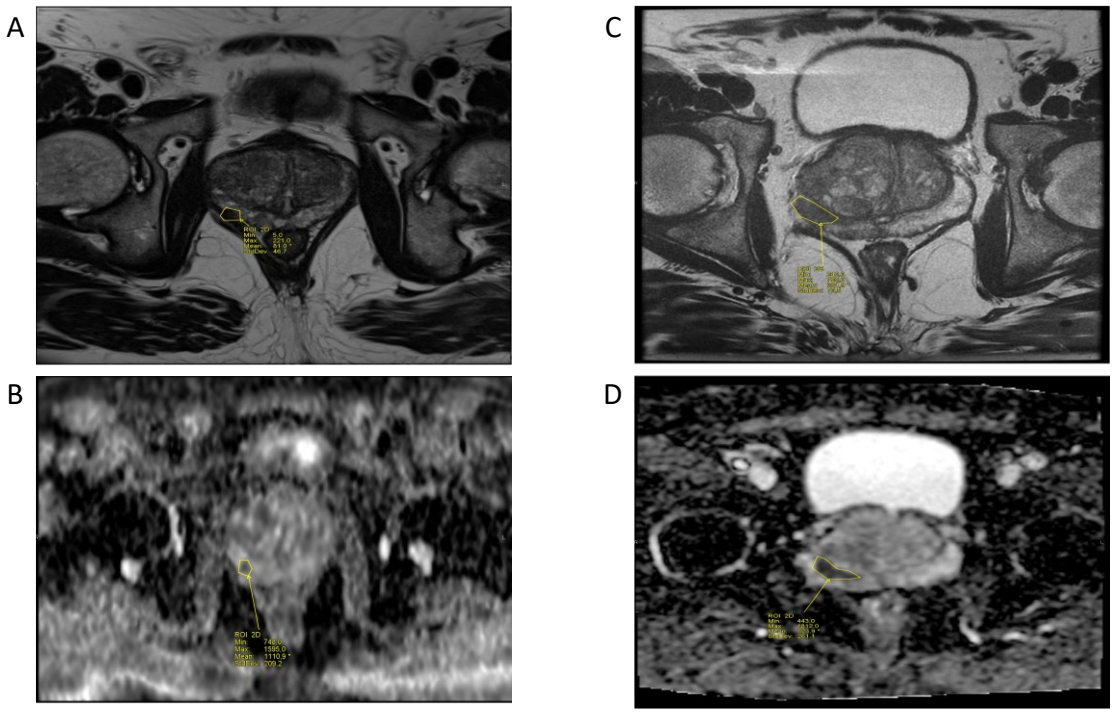



***Figure 18.*** *A 66 years old patient that was diagnosed with 3 cores positive for ISUP GG1 prostate cancer. Baseline mpMRI showed a 5 mm PI-RADS score 4, EPE score 1 lesion in the PZ of the prostate, right side, medium/base level. This lesion experienced radiological progression at a second mpMRI that was perfomed after 1 year of AS (23 mm, PI-RADS score 5, EPE score 4).*

*A) T2- weighted images of baseline mpMRI*

*B) ADC map of baseline mpMRI*

*C) T2- weighted images of repeated mpMRI*

*D) ADC map of repeated mpMRI*

*AS: Active Surveillance; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension; PZ: peripheral zone; ADC: apparent diffusion coefficient*

### *6.2.4 Statistical analyses*

Differences in medians and proportions were evaluated by, respectively, the Kruskal-Wallis and chi-square tests. First, temporal trends of mpMRI progression criteria after repeated mpMRI scans were evaluated with the estimated annual percent changes (EAPC) methodology. Second, we tested sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the five mentioned mpMRI progression criteria. Third, multivariable logistic regression models tested PCa upgrading rates at surveillance biopsies.

R software environment was used in all statistical analyses and graphics (version 3.4.3). All tests were two sided with a level of significance set at $p<0.05$.

## 6.3 Results

### *6.3.1 Descriptive analyses*

At AS begin, 250 (44.8%) vs. 176 (31.5%) vs. 125 (22.4%) vs. 7 (1.3%) men had PI-RADS score ≤2 vs. 3 vs. 4 vs. 5 lesions, respectively. Moreover, 534 (95.7%) vs. 22 (3.9%) vs. 2 (0.4%) mpMRI lesions were EPE score ≤2 vs. 3 vs. 4. Median (IQR: interquartile range) mpMRI lesion size was 8.5 (7-11) mm.

| | | Overall (n = 558) |
|---|---|---|
| Age (years) | Median (IQR) | 63 (58-69) |
| PSA (ng/ml) | Median (IQR) | 5.9 (4.5-7.8) |
| PSAD (ng/ml/ml) | Median (IQR) | 0.1 (0.1-0.2) |
| cT | cT1c<br>cT2a | 518 (92.8)<br>40 (7.2) |
| Diagnostic biopsy cores | Median (IQR) | 14 (12-16) |
| Diagnostic biopsy positive cores | 1<br>2<br>3 | 331 (59.3)<br>144 (25.8)<br>83 (14.9) |
| ISUP GG | 1<br>2 | 537 (96.2)<br>21 (3.8) |
| Number of PNBs | 0<br>1<br>≥2 | 452 (81)<br>72 (12.9)<br>34 (6.1) |
| Prostate volume (ml) | Median (IQR) | 50 (37-68) |
| PI-RADS score | ≤2<br>3<br>4<br>5 | 250 (44.8)<br>176 (31.5)<br>125 (22.4)<br>7 (1.3) |
| Lesion size (mm) | Median (IQR) | 8.5 (7-11) |
| EPE score | ≤2<br>3<br>4<br>5 | 534 (95.7)<br>22 (3.9)<br>2 (0.4)<br>0 (0) |

***Table 8.*** *Clinical characteristics and mpMRI findings at AS begin of 558 patients enrolled between 2008 and 2020. Data are shown as medians for continuous variables or as counts and percentages (%) for categorical variables.*

*AS: active surveillance; IQR: interquartile range; PSA: prostate specific antigen; PSAD: prostate specific antigen density; cT: clinical T stage; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PNBs: previous negative biopsies; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension.*

### *6.3.2 Natural history of mpMRI prostatic lesions*

Median (IQR) follow-up time was 36 (23-52) months. Overall, 245 (43.9%) vs. 179 (32.1%) vs. 87 (15.6%) vs. 47 (8.4%) patients underwent 1 vs. 2 vs. 3 vs. 4 repeated mpMRI scans, respectively.

Lower rates over time of PI-RADS score increase (EAPC:-22.5%; p=0.03; Figure 19a), lesion size increase (EAPC:-33.5%; p=0.003; Figure 19b) and EPE score increase (EAPC:-35.5%; p=0.1; Figure 19c) were observed after serial (from 1 to 4) mpMRI scans. Moreover, lower rates of overall mpMRI progression (EAPC:-31.3%; p=0.004; Figure 19d) were recorded. Last, the percentage of 1 (EAPC:-35.7%; p=0.04) and 2-3 criteria (EAPC:-27%; p=0.02) for mpMRI progression decreased over time (Figure 19e).

### *6.3.3 Diagnostic accuracy of serial mpMRI scans*

Of all 364 patients, 268 (73.6%) vs. 78 (21.4%) vs. 18 (4.9%) underwent 1 vs. 2 vs. ≥3 surveillance biopsies, respectively. Overall, 91 (25%) and 21 (5.8%) patients experienced ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading.

Rates of ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading according to the five different definitions of mpMRI progression are reported in Figure 20.

Sensitivity, specificity, PPV, NPV for PI-RADS score increase in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 42%, 88%, 33%, 91.5% and 52%, 85.5%, 9.5%, 98% (Table 9). Sensitivity, specificity, PPV, NPV for lesion size increase in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 46%, 82.5%, 37%, 91.5% and 62%, 80%, 8.5%, 98.5%. Sensitivity, specificity, PPV, NPV for EPE score increase in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 27.5%, 96%, 50%, 90.5% and 33.5%, 94%, 14%, 98%. Last, sensitivity, specificity, PPV, NPV for overall mpMRI progression in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 61.5%, 78.5%, 28.5%, 93.5% and 66.5%, 74.5%, 7%, 99%.

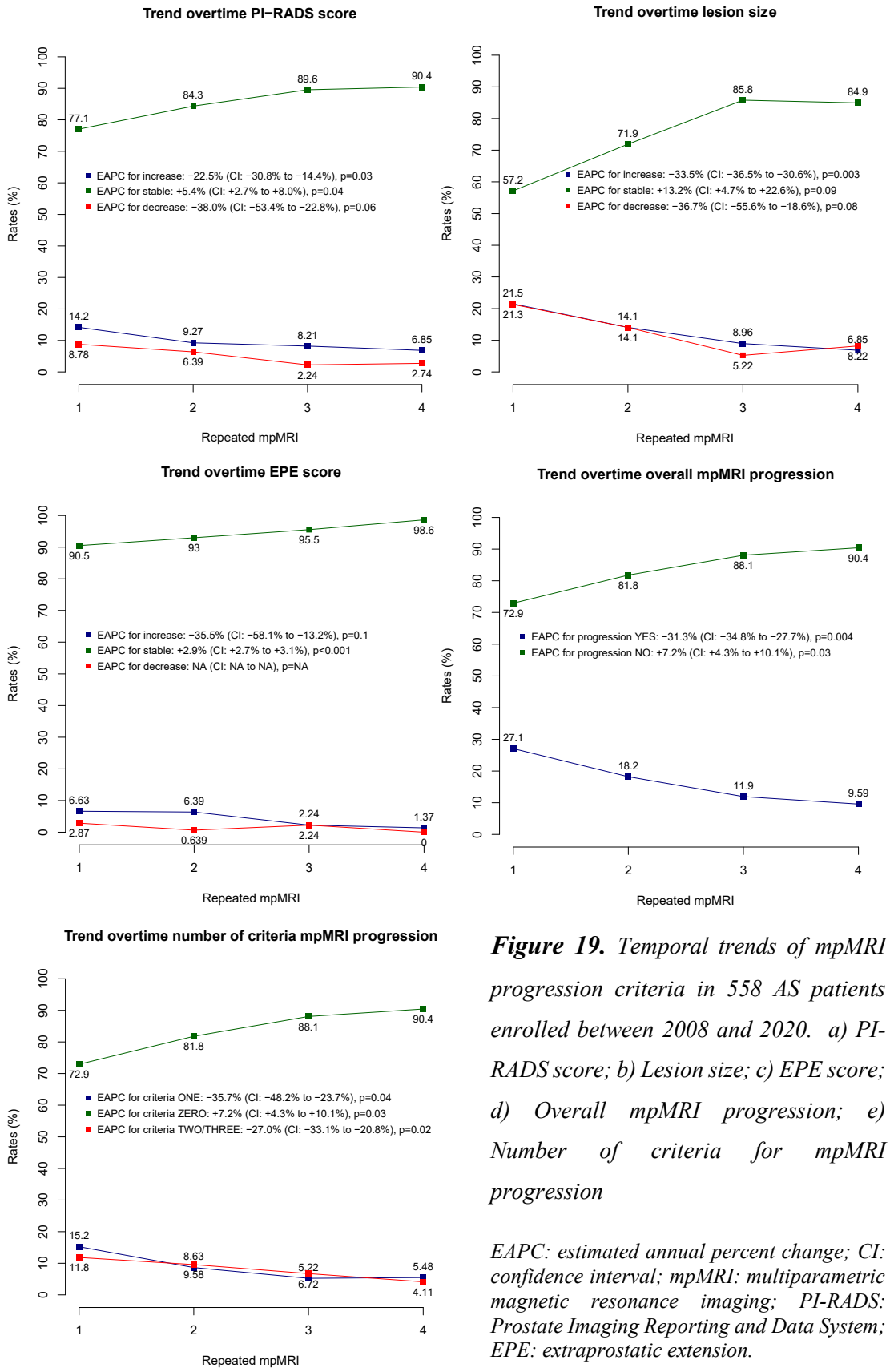



***Figure 19.*** *Temporal trends of mpMRI progression criteria in 558 AS patients enrolled between 2008 and 2020. a) PI-RADS score; b) Lesion size; c) EPE score; d) Overall mpMRI progression; e) Number of criteria for mpMRI progression*

*EAPC: estimated annual percent change; CI: confidence interval; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension.*

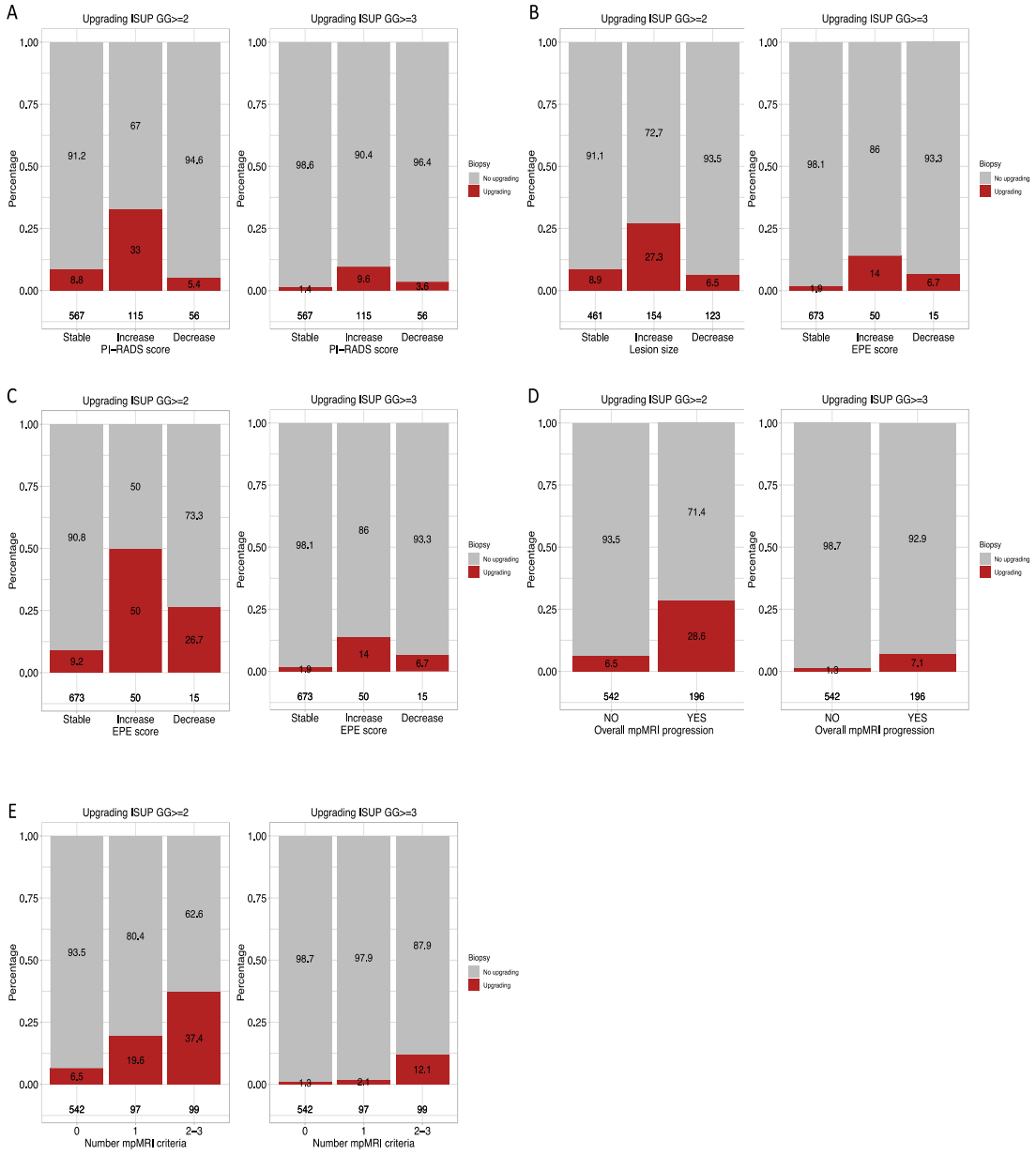



***Figure 20.*** *Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to mpMRI progression criteria, in 364 AS patients enrolled between 2008 and 2020. a) PI-RADS score; b) Lesion size; c) EPE score; d) Overall mpMRI progression; e) Number of criteria for mpMRI progression*

*mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension.*

| | PI-RADS score increase | Lesion size increase | EPE score increase | Overall mpMRI progression |
|---|---|---|---|---|
| **ISUP GG≥2 with pattern 4>10%** | | | | |
| **Sensitivity** | 42% | 46% | 27.5% | 61.5% |
| **Specificity** | 88% | 82.5% | 96% | 78.5% |
| **PPV** | 33% | 37% | 50% | 28.5% |
| **NPV** | 91.5% | 91.5% | 90.5% | 93.5% |
| **ISUP GG≥3** | | | | |
| **Sensitivity** | 52% | 62% | 33.5% | 66.5% |
| **Specificity** | 85.5% | 80% | 94% | 74.5% |
| **PPV** | 9.5% | 8.5% | 14% | 7% |
| **NPV** | 98% | 98.5% | 98% | 99% |

***Table 9.*** *Diagnostic accuracy (sensitivity, specificity, PPV and NPV) of repeated mpMRI scans during follow-up in 364 AS patients enrolled between 2008 and 2020.*

*AS: active surveillance; mpMRI: multiparametric magnetic resonance imaging; PPV: positive predictive value; NPV: negative predictive value; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extra-prostatic extension.*

### *6.3.4 Multivariable logistic regression models*

In multivariable logistic regression models (Table 10) predicting ISUP GG≥2 with >10% of pattern 4 PCa upgrading, PI-RADS score increase (Odds Ratio [OR]:1.12; p=0.002), lesion size increase (OR:1.06; p=0.04), EPE score increase (OR:1.34; p<0.001) and overall mpMRI progression (OR:1.22; p<0.001) achieved independent predictor status. Moreover, compared to 0 criteria, 1 (OR:1.12; p<0.001) and 2-3 (OR:1.34; p<0.001) criteria for mpMRI progression were associated with higher rates of PCa upgrading.

In multivariable logistic regression models (Table 10) predicting ISUP GG≥3 PCa upgrading, PI-RADS score increase (Odds Ratio [OR]:1.04; p=0.04), lesion size increase (OR:1.03; p=0.03), EPE score increase (OR:1.07; p=0.004) and overall mpMRI progression (OR:1.05; p<0.001) achieved independent predictor status. Moreover, compared to 0 criteria, 2-3 (OR:1.11; p<0.001) criteria for mpMRI progression were associated with higher rates of PCa upgrading.

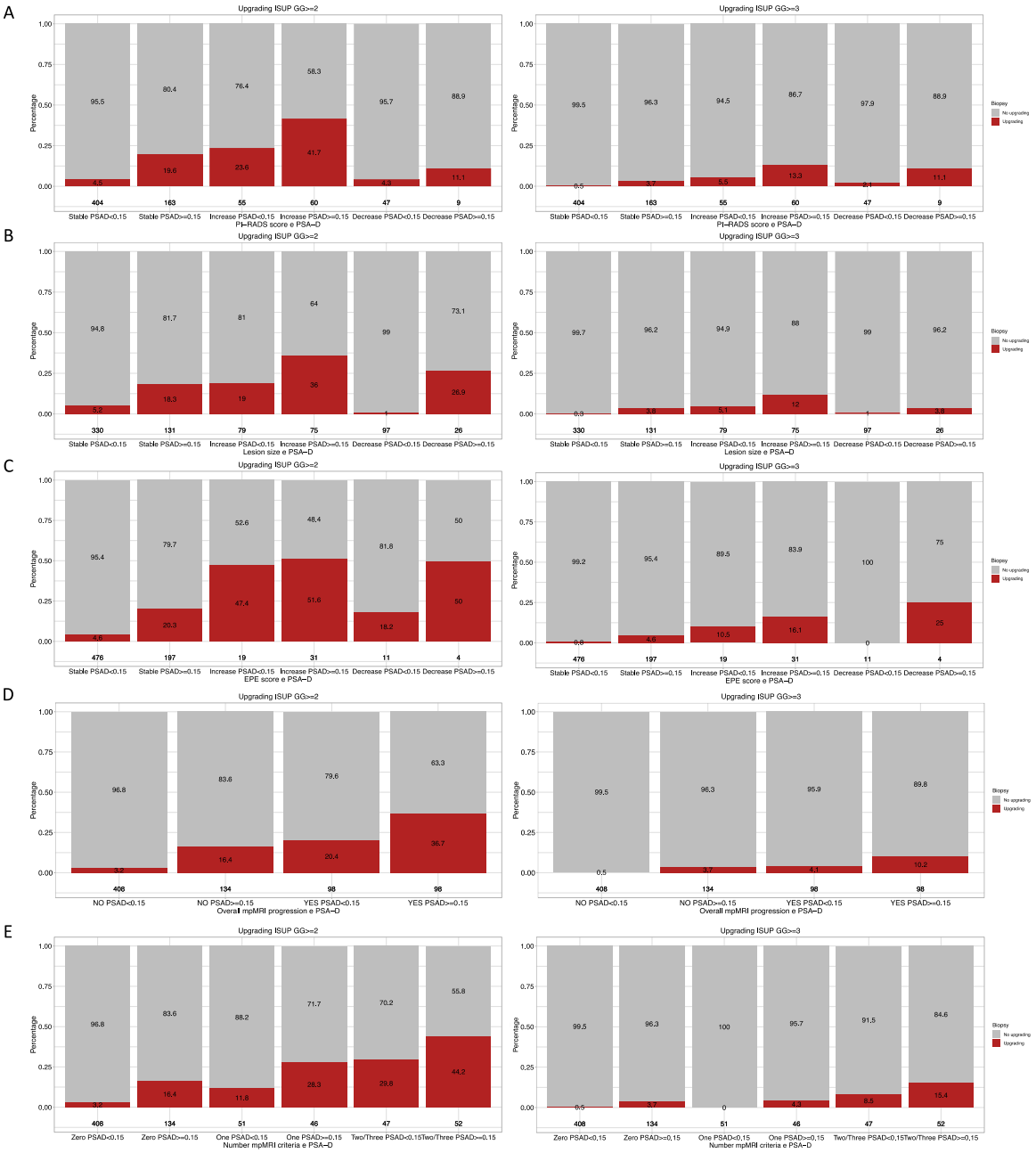
| ISUP GG≥2 with >10% of pattern 4 upgrading | | |
|---|---|---|
| | Odds Ratio (OR) [95% CI] | p value |
| PI-RADS score | | |
| stable | Ref. | |
| increase | 1.12 (1.04-1.21) | 0.002 |
| decrease | 0.94 (0.85-1.03) | 0.2 |
| Lesion size | | |
| stable | Ref. | |
| increase | 1.06 (1.00-1.14) | 0.04 |
| decrease | 0.99 (0.93-1.06) | 0.9 |
| EPE score | | |
| stable | Ref. | |
| increase | 1.34 (1.22-1.48) | <0.001 |
| decrease | 1.22 (1.04-1.43) | 0.01 |
| Overall mpMRI progression (yes vs. no) | 1.22 (1.16-1.29) | <0.001 |
| N° criteria for mpMRI progression | | |
| 0 | Ref. | |
| 1 | 1.12 (1.05-1.20) | <0.001 |
| 2 | 1.34 (1.15-1.43) | <0.001 |
| **ISUP GG≥3** | | |
| | Odds Ratio (OR) [95% CI] | p value |
| PI-RADS score | | |
| stable | Ref. | |
| increase | 1.04 (1.00-1.08) | 0.04 |
| decrease | 1.01 (0.96-1.06) | 0.5 |
| Lesion size | | |
| stable | Ref. | |
| increase | 1.03 (1.00-1.07) | 0.03 |
| decrease | 1.00 (0.96-1.03) | 0.9 |
| EPE score | | |
| stable | Ref. | |
| increase | 1.07 (1.02-1.13) | 0.004 |
| decrease | 1.04 (0.95-1.13) | 0.3 |
| Overall mpMRI progression (yes vs. no) | 1.05 (1.02-1.08) | <0.001 |
| N° criteria for mpMRI progression | | |
| 0 | Ref. | |
| 1 | 1.00 (0.96-1.03) | 0.8 |
| 2 | 1.11 (1.07-1.15) | <0.001 |

***Table 10.*** *Separate multivariable logistic regression models predicting prostate cancer upgrading (ISUP GG≥2 with >10% of pattern 4 or ISUP GG≥3) at surveillance biopsies in 364 AS patients enrolled between 2008 and 2020 and according to mpMRI progression criteria. All models are adjusted for: age (years), PSAD (ng/ml/ml), cT (cT1 vs. cT2/3), ISUP GG at biopsy (1 vs. 2).*

*AS: active surveillance; PSAD: prostate specific antigen density; cT: clinical T stage; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extra-prostatic extension. CI: confidence interval.*

### *6.3.5 Repeated mpMRI scans, PSA-D and baseline PI-RADS score*

ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading rates according to mpMRI progression criteria and PSA-D cut-off of 0.15 mg/ml/ml and 0.20 mg/ml/ml are, respectively displayed in Figure 21. Upgrading rates according to baseline PI-RADS score are depicted in Figure 22.



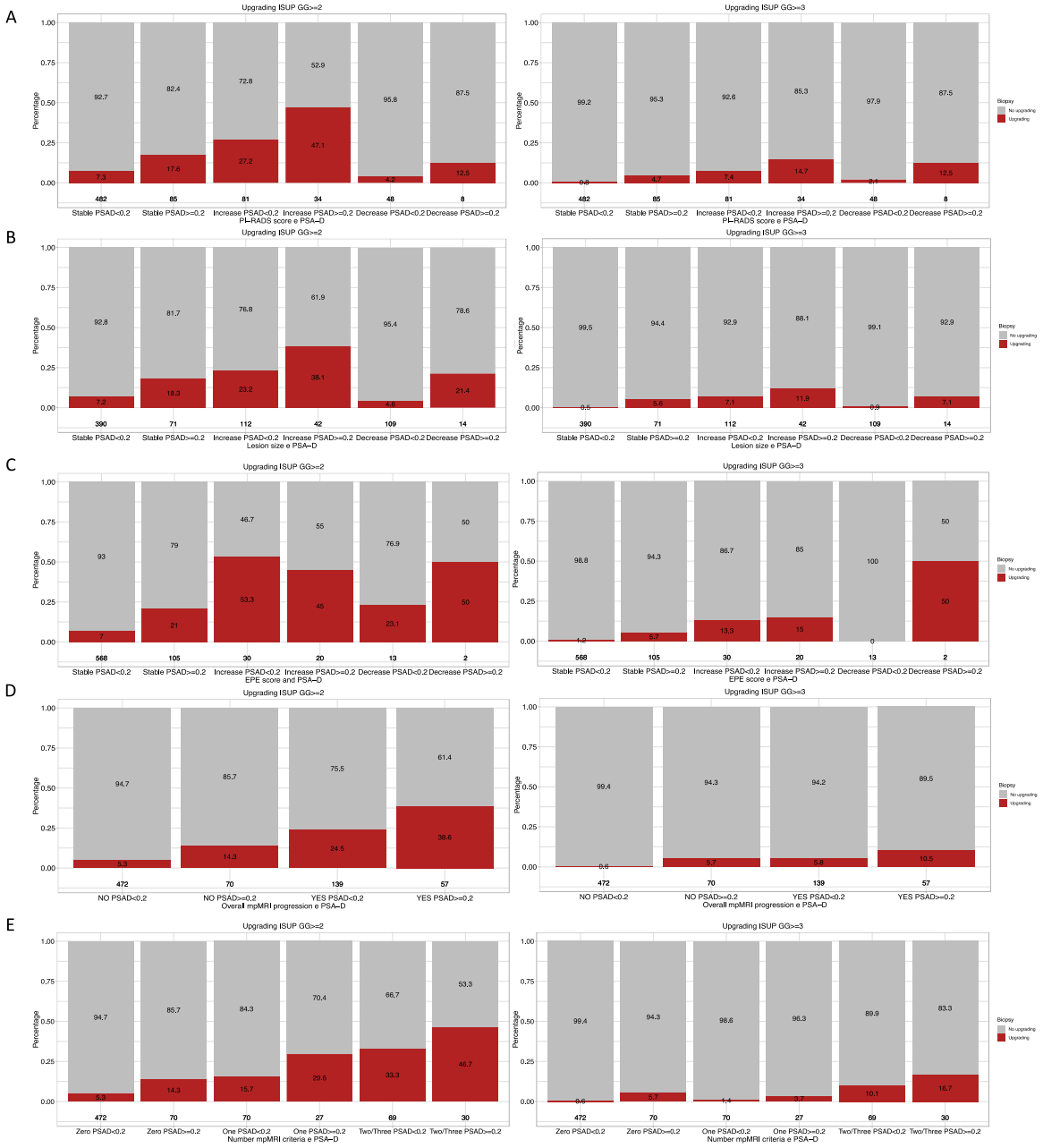



***Figure 22.*** *Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to mpMRI progression criteria and PSAD (cut-offs: 0.15 ng/ml/ml and 0.2 ng/ml/ml), in 364 AS patients enrolled between 2008 and 2020. a) PI-RADS score; b) Lesion size; c) EPE score; d) Overall mpMRI progression; e) Number of criteria for mpMRI progression.*

*AS: Active Surveillance; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension.*

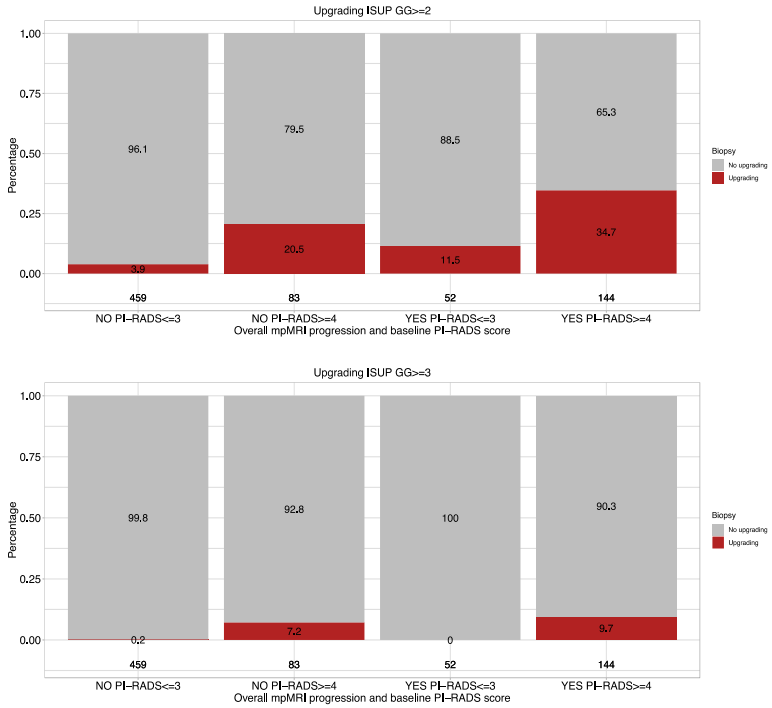



***Figure 23.*** *Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to overall mpMRI progression (NO vs. YES), in 364 AS patients enrolled between 2008 and 2020, according to baseline PI-RADS score.*

*AS: Active Surveillance; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System.*

## 6.4 Discussion

The vast majority of AS patients are reluctant to undergo repeated prostate samplings [258]. Indeed, it was estimated that the compliance rate for prostate biopsies decreases over time (81%, 60%, 53% and 33% at 1, 4, 7 and 10 years, respectively) [257]. MpMRI has been proposed as an alternative to monitor PCa progression [260,261]. However, conflicting results have been previously observed in several AS cohorts that investigated the reliability of repeated mpMRI scans over time [262–272]. Due to the lack of robust data to support the use of serial mpMRIs during AS, we tested mpMRI diagnostic accuracy in the largest series to date (n=558) of AS patients submitted to confirmatory mpMRI at AS begin and followed with repeated scheduled mpMRI scans. Specifically, we analysed five different criteria of mpMRI progression: 1) PI-RADS score increase, 2) lesion size increase, 3) EPE score increase, 4) overall mpMRI progression, 5) number of mpMRI progression criteria. Our results showed several important findings.

First, we focused on the natural history of mpMRI prostatic lesions after serial repeated mpMRI scans during AS (from 1 to 4). Here, we observed lower rates over time of all five mentioned criteria for mpMRI progression. To the best of our knowledge, these results were not previously reported in none of the mentioned AS series. Conversely, our findings are consistent with three previous reports that focused on the natural history of mpMRI suspicious lesions (no AS setting) [279–281], which confirmed that overall changes in size and PI-RADS score over time are infrequent. Our results should be used for patient counselling and for optimizing AS interval imaging follow-up. Specifically, patients should be informed about the 27% probability of overall mpMRI progression at first repeated scan. Moreover, the observed lower rates of progression at subsequent mpMRIs (from 2 to 4) should discourage the use of too frequent repeated mpMRIs during follow-up. Our results are supported by the use of trend analyses (EAPC) that were, to the best our knowledge, not previously reported. This said, the observed trends over time could be a product of the definitions used for the five mentioned criteria of mpMRI progression. However, it should be stated that these definitions are consistent with other analyses that focused on the same topic [262,266].

Second, we tested the ability of serial mpMRI scans to exclude PCa progression during AS. To not overestimate the diagnostic accuracy of mpMRI, we analysed only patients

submitted to repeated surveillance biopsies during follow-up (n=364) and we used two different definitions of PCa upgrading, as previously reported by Gandaglia et al. [278]. We observed that the NPV of serial mpMRIs spans from 90.5 to 93.5% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and from 98 to 99% (ISUP GG≥3 PCa upgrading), according to the different criteria used for mpMRI progression. PSA-D provided other important information in this patient category. Specifically, patients without mpMRI progression (regardless of mpMRI criteria used) and with PSA-D levels<0.15 ng/ml/ml could safely skip surveillance biopsies, since only 4-5% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and 1-2% (ISUP GG≥3 PCa upgrading) of them exhibit PCa progression. Our data are consistent with other previous analyses that tested the NPV of mpMRI to exclude csPCa [118] and the ability of PSA-D to sub stratify those patients who require a prostate biopsy [282,283]. Moreover, our results support other previous retrospective series [263,267,268] and the recently published MRIAS trial [266] that suggested the possibility to omit surveillance biopsies in patients with stable mpMRI findings during AS. However, our results also contrast other previous analyses in which mpMRI alone resulted insufficient to detect grade reclassification during AS [262,265,269,270,272]. Our findings are supported by the non-negligible follow-up time (median: 36 months) and by the use of five different definitions for mpMRI progression. This said, it should be stated that our analysis is biased by its retrospective and single-centre nature. In consequence, results from other multi-institutional and, ideally, prospective studies are needed before recommending AS programs modifications.

Third, we then tested the ability of serial mpMRI scans to predict PCa progression during AS. Again, to not underestimate the diagnostic accuracy of mpMRI, we restricted our analysis to patients submitted to repeated surveillance biopsies during follow-up (n=364). Here, we observed that all mentioned criteria for mpMRI progression achieved independent predictor status in multivariable logistic regression models predicting PCa upgrading at surveillance biopsies. Moreover, we tested for dose-response and we confirmed that an increasing number of mpMRI progression criteria (0 vs. 1 vs. 2-3) is directly proportional to the magnitude of the two examined endpoints. Despite the use of multivariable models, that were fully adjusted for all available patient and tumor characteristics, we cannot recommend immediate switch to AT in those patients who

experience mpMRI progression during AS. Specifically, the PPV of serial mpMRIs spans from 33 to 50% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and from 7 to 14% (ISUP GG≥3 PCa upgrading), according to the different criteria used for mpMRI progression. In consequence, mpMRI progression should only be considered a trigger for immediate re-biopsy and not a valid criterion for discontinuing AS, as previously suggested by all other AS series [262–265,267–272].

Taken together, we provided robust data to support the use of repeated mpMRI scans during AS and to optimize interval imaging follow-up. First, we demonstrated that approximately 27% of patients experience mpMRI progression at first repeated scan. However, too frequent repeated mpMRIs during follow-up should be discouraged. Second, we demonstrated that patients without mpMRI progression and with PSA-D levels<0.15 ng/ml/ml could safely avoid prostate biopsies. Third, we also demonstrated that mpMRI progression should only be considered a trigger for immediate re-biopsy and not a valid criterion for discontinuing AS. This said, it should be stated that our results were obtained after excluding patients that did not undergo repeated prostate biopsies during AS. Specifically, 101 (52%) men were lost at follow-up after performing baseline mpMRI and a single repeated mpMRI scan at 12 months after AS begin. Moreover, the remaining 93 (48%) patients underwent only repeated mpMRI scans during follow-up, but were not submitted to repeated prostate biopsies due to patient/clinician preference. Specifically, 56 (60%) vs. 27 (29%) vs. 10 (11%) of them underwent 2 vs. 3 vs. 4 repeated mpMRIs and, of those, 4 (4.3%) men were switched to AT. In consequence, over-/underestimation of the accuracy of repeated mpMRI scans during AS could not be excluded.

Despite its novelty our study has limitations. First, the current data are retrospective and influenced by inherent selection bias. Second, as previously stated, our results could be a product of the definitions used for mpMRI progression. Moreover, we did not rely on the PRECISE criteria for documenting changes in MRI findings during AS, as recently published [263,264,267,272,284–286]. However, previous analyses that tested the reliability of the PRECISE criteria in men on AS showed discordant results [264,267,268,272]. Third, we scored suspicious lesions according to PI-RADS v1 (2013-2015) and PI-RADS v2 (2015-thereafter) [103,277]. Although this limitation

could have generated heterogeneity of the data, it represents daily practice. Fourth, we tested only two commonly used PSA-D cut-offs, namely 0.15 and 0.2 ng/ml/ml. In consequence, other analyses should test the most accurate PSA-D threshold for recommending prostate biopsies in men on AS [282]. Fifth, we were unable to distinguish PCa progressions within and without the target. Sixth, we did not rely on other scales, rather than the one proposed by the ESUR prostate MRI Guidelines [277], to assess the probability of EPE [287–289]. Seventh, we used specific AS inclusion criteria. Moreover, all mpMRI scans were evaluated by expert radiologists [290] and, in consequence, no low quality images were taken into account. Therefore, external validation of our findings is urgently needed.

# 7 CONCLUSIONS

During AS, approximately 27% of patients experience mpMRI progression at first repeated scan. However, the rates of mpMRI progression decrease over time at subsequent mpMRIs. Patients with stable mpMRI findings and with PSA-D<0.15 ng/ml/ml could safely skip surveillance biopsies. Conversely, patients who experience mpMRI progression should undergo a prostate biopsy.

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