Limiting overdiagnosis of low-risk prostate cancer through an evaluation of the predictive value of transrectal and power Doppler ultrasonography

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Abstract

Purpose Overdiagnosis induced by prostate cancer screening makes necessary a better selection of candidate patients for prostate biopsy. The objective of our study is to assess the probability of having a high- or low-risk lesion that could require active surveillance (AS) after biopsies and a normal or abnormal examination, including transrectal and power Doppler ultrasonography (TRUS-PDS). **Methods** Four hundred and twenty-nine consecutive patients with a PSA level <10 ng/ml and a normal digital rectal examination (DRE) had guided biopsies in a prospective study. We used D'Amico's criteria to assess the risk of a biological recurrence and Dall'Era's criteria to assess possible AS. The TRUS-PDS was considered positive if one biopsy was positive in the same sextant as the suspect image.

Results One hundred and seventy-seven out of 429 (41 %) T1c cancers were diagnosed; 131 out of 177 (74 %) could be qualified as low risk, and 119 out of 177 (67 %) could require AS. The TRUS-PDS was normal in 285 of 429 patients (66 %). With a normal TRUS-PDS, the probability of not having cancer with a high or intermediate risk was 96 % (negative predictive value). With an abnormal TRUS-PDS, the probability of having a positive biopsy

was 59 %, and the probability of having a significant cancer was 30 %, according to the Dall'Era criteria. When TRUS-PDS was normal, these probabilities significantly decreased to 32 and 5 %, respectively ($p < 0.01$).

Conclusions Patients with a PSA level <10 ng/ml, a normal DRE, and a normal TRUS-PDS have a less than 5 % risk of high- or intermediate-risk cancer.

Keywords Prostate cancer · Transrectal ultrasound · Power Doppler sonography · Overdiagnosis · Low risk cancer · High-risk cancer

Sommario

Scopo Lo screening per la prevenzione del cancro alla prostata può portare a un eccessivo di falsi positivi; pertanto è necessaria un'attenta selezione dei pazienti candidati alla biopsia della prostata. L'obiettivo del nostro studio è quello di valutare la probabilità di avere una lesione ad alto o basso rischio che potrebbe richiedere una sorveglianza attiva (AS) dopo biopsia, e un normale o anormale esame rettale trans e power Doppler (TRUS-PDS).

Metodi In uno studio prospettico, sono state eseguite 429 biopsie in pazienti consecutivi con un livello di PSA <10 ng/ml e un DRE normale. Sono stati usati i criteri di D'Amico per valutare il rischio di una recidiva biologica, e quelli di Dall'Era per la sorveglianza attiva (AS). Se anche una sola biopsia risultava positiva, anche la TRUS-PDS di conseguenza era considerata positivo.

Risultati Sono stati diagnosticati 177 tumori/429 (41 %) tumori T1c: 131/177 (74 %) Sono stati qualificati come a basso rischio e 119/177 (67 %) possono richiedere un AS. La TRUS-PDS era normale in 285 dei 429 pazienti (66 %). Con un normale esame di TRUS-PDS, la probabilità di non avere un cancro con un rischio elevato o intermedio era del 96 % (valore predittivo negativo). Con una TRUS-PDS positivo per

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neoplasia, la probabilità di avere una biopsia positiva è stata del 59 % e la probabilità di avere un cancro significativa era del 30 % in base ai criteri Dall'Era. Queste probabilità diminuivano in modo significativo quando TRUS -PDS erano normali, al 32 % e 5 %, rispettivamente ($p < 0.01$). L'accuratezza diagnostica della TRUS -PDS era del 65 %, quando tutti i tumori T1c sono stati diagnosticati. L'84 % dei tumori presentano un rischio intermedio o alto secondo D'Amico e 83 % nella diagnosi di tumori significativi che possono non richiedere un AS secondo Dall'Era ($p < 0.01$).

Conclusioni I pazienti con un livello di PSA <10 ng/ml, un DRE normale e un normale valore TRUS-PDS hanno meno del 5 % del rischio di avere un cancro ad alto o medio rischio.

Introduction

The limited benefit–risk ratio and the overdiagnosis induced by prostate cancer screening (Pca) make necessary a better selection of candidate patients for a prostate biopsy [1]. The screening includes an assay of the PSA level for which the upper limit is generally set at 4 ng/ml [2]. However, some aggressive cancers are below this level [3]. The value of transrectal ultrasonography combined with color Doppler sonography (CDS) and power Doppler sonography (PDS) in the detection of Pca has been the subject of many evaluations [4–8]. The increased use of individual screening, as well as the number of biopsies, has led to the early detection of tiny lesions. The value of the transrectal and power Doppler ultrasonography (TRUS-PDS) was low, because a significant number of cancers were non-palpable and not visible [9, 10]. However, the findings that PDS offers a few benefits may be questioned; low-risk prostate cancers, as defined by D'Amico [11], are found in 40–50 % of newly diagnosed men in a screened population and represent overdiagnosis in most cases [12]. The ERSPC group performed a critical analysis of the tumor volume threshold for clinically insignificant prostate cancer [13], and their conclusion was a cancer volume <1.3 cc. This means that a better test for prostate cancer would ignore small-volume disease and identify cancers of only 1.3 cc or greater. Combining different ultrasound modalities and the new ultrasound techniques can potentially improve PCa detection, grading, and staging. [14–18]. This paper aims to assess a prospective series of 429 patients for the probability of having a low-risk lesion that could require active surveillance (AS) after prostate biopsies in patients with a normal digital rectal examination (DRE), a PSA level between 4 and 10 ng/ml, and a normal or abnormal TRUS-PDS examination.

Materials and methods

This study was prospective and declared to the French National Commission for Information Technology and Civil Liberties (CNIL). Patients included in the series received an information form from the French Association of Urology and signed their informed consent [17]. Between January 2010 and December 2014, 729 consecutive patients (aged from 49 to 87 years old, with a mean age of 61 years and a median age of 64 years) underwent a series of biopsies; 521 presented a PSA level between 4 ng/ml and 10 ng/ml. A urologist performed DRE, and the results were abnormal in 92 patients, who were, therefore, excluded from the study. The final study population was 429 patients, with PSA between 4 and 10 ng/ml and a non-palpable prostate nodule (mean PSA: 6.1 ng/ml; median: 6.8 ng/ml, from 4.01 to 10 ng/ml). Of them, 177 (41 %) had cancer after the biopsies; these cancers lacked clinical signs and were found only by biopsy, so they were classified as T1c according to the TNM classification for prostate cancer (tumor, node, and metastasis staging system).

Sonography technique and power Doppler mode

This study was carried out with Toshiba Aplio MX Doppler sonography instruments (Toshiba MS, Nasu, Japan) coupled with a biplane PVT-770RT endocavity probe (5–10 MHz). The differential tissue harmonic imaging mode with a frequency of 9 MHz was used, and an exploration with power Doppler was carried out with all patients. Doppler settings were optimized to remove background noise. We privileged a low PRF that was adjusted to 500 Hz in standard value. A weak compression with the end of the probe was systematically executed when there was a hypoechoic area, in the search for a modification of its echostructure. The mean time for a Doppler sonography of the prostate was about 15 min.

Ultrasound semiology and power Doppler

In B mode, the peripheral area was normal in appearance and was homogenous and more echogenic than the transition area.

The suspect echostructure anomalies in the peripheral prostate area may be qualified as hypoechoic, weakly hypoechoic, or subtle, or as having a heterogeneous echotexture. The power Doppler mode searched for the presence of intralesional vessels in a suspect lesion in the B-mode sonography. A visible lesion in B mode was hypervascularised if at least one vessel in this lesion was clearly identified [18] (Fig. 1). The TRUS-PDS results for

Fig. 1 Little non-palpable hypoechoic and hypervascular nodular lesions (one vessel present) in the right median sextant (*white arrow*). PSA: 7.4 ng/ml, Gleason score 6 (3 + 3): two positive biopsies. TRUS-PDS was rated class 4

the 429 patients were rated from 1 to 4: (1) normal and without any vessels (249 patients); (2) slightly hypoechoic avascular lesion in which the hypoechoicity disappears after slight compression with the probe (Fig. 2) or weakly hypoechoic the midline (36 patients); (3) hypoechoic avascular nodule (78 patients); and (4) hypervascularised lesion with abnormal echogenicity (hypoechoic or weakly hypoechoic) or heterogeneous echotexture (66 patients) (Fig. 1). Classes 3 and 4 were considered to be pathological.

Biopsies

A Doppler sonography examination was performed on each patient before biopsy. In the case of a visible lesion, the location was determined by sextant and indicated in the information sheet attached to the samples sent to the

pathologist. In the same session, the radiologist (because of PDS) guided the biopsies performed by the urologist surgeon. Twelve samples were taken systematically according to the recommendations for good biopsy practices [18]. One to three additional samples were added in the case of suspect lesions in the PDS. All non-palpable cancers (clinical stage T1c) with a PSA level below 10 ng/ml were classified according to D'Amico's criteria (PSA level <10 ng/ml, Gleason score ≤ 6 , no grade 4 or 5), and D'al'Era criteria (<33 % positive biopsies, <50 % cancer by biopsy) [19, 20] to define if the lesion was significant or not, because these criteria appear to have the greatest consensus among the European community [21].

Statistical analysis

The imaging results were correlated with the pathological examinations of the biopsies. A result was declared to be a true positive if at least one biopsy was positive in the same sextant as a class 3 or 4 image. The predictive values and the accuracy of PDS were calculated for diagnosing high-, intermediate-, and low-risk cancer as well as for diagnosing significant and not significant cancer. A Chi-square test was used for statistical comparisons. We regarded a p value <0.05 as statistically significant.

Results

In our study, the 429 screened patients had a PSA level below 10 ng/ml without palpable lesion, and 177 patients presented a cancer (41 % of the cases) (Fig. 3). Among the 177 patients, 131 (74 %) had low-risk T1c cancers, and 119 (67 %) required active surveillance. The TRUS-PDS was normal in 285 of 429 patients (66 %), and with a normal TRUS-PDS, the probability of not having a cancer with a

Fig. 2 a TRUS-PDS with a weakly hypoechoic without vascular anomaly (*white arrow*); **b** in the left peripheral prostate, the hypoechoic appearance disappears under compression (PSA: 6.2 ng/ml, negative biopsies). TRUS-PDS was rated class 2

Fig. 3 Flow chart with results of transrectal ultrasound and power Doppler (TRUS-PDS) and biopsies in 429 patients with a PSA level less than 10 ng/ml and a normal digital rectal examination (DRE)

high or intermediate risk was 96 % (NPV). With an abnormal TRUS-PDS, the probability of having a positive biopsy was 59 % (PPV), and the probability of having a significant cancer was 30 %, according to the Dall'Era criteria (Table 1). With a normal TRUS-PDS, these probabilities decreased in a significant manner to 32 and 5 %, respectively (NPV = 95 %, $p < 0.01$) (see Fig. 4; Table 2).

Discussion

The combination of different ultrasound modalities significantly improves diagnostic performance [16], and examination using transrectal and power Doppler ultrasound remains accessible and cheap. New modalities, such as differential tissue harmonic imaging with high-frequency probes, perform better than fundamental sonography. In this study, TRUS-PDS examination was considered normal when the peripheral gland was homogenous and more echogenic than the transition area (class 1) or if it had a slightly hypoechogenic avascular lesion in which the hypoechogenicity disappeared after slight compression with the probe (class 2) (Fig. 2). In all other cases, TRUS-PDS results were considered to be pathological. With this classification, sensitivity and negative predictive values increased.

Various authors reported additional value of the Doppler techniques over TRUS [9, 16, 18]. For Eisenberg et al. [22], adding PDS to TRUS improved specificity from 47 to 74 %, although the sensitivity decreased from 58 to 47 %. Our results were similar: 76 % for the specificity and 48 % for the sensitivity in T1c cancers. T1c cancers associate low-risk lesions with other high-risk lesions. By selecting patients without palpable lesions and whose PSA level did not exceed 10 ng/ml, we have two of the three conditions included in D'Amico's group of low-risk cancers.

Some studies have shown a correlation between the grade of tumor and the Doppler sonography imaging [4–7]. Prostate cancer requires angiogenesis to develop into clinically significant disease. Power Doppler ultrasound can detect flow in vessels as small as 1 mm and, therefore, allows visualization of a tumor's feeding vessels. However, the true angiogenic microvessels are in the 10–50 μm range [23, 24]; for larger feeding vessels, Doppler US is more sensitive to higher Gleason grade lesions [9, 16, 24]. Overdiagnosis affected 40 % of the screened patients [25]. Without a non-invasive diagnostic tool, the risk of overdiagnosis cannot be evaluated before the biopsy results. Today, MRI seems to be the best imaging technique for the prostate, with a negative predictive value of 90 % and an accuracy of 98 % in diagnosing significant cancers [26]. However, this high sensitivity also favors the overdiagnosis

Table 1 Probability of having a positive biopsy in case of normal transrectal ultrasound and power Doppler sonography (TRUS-PDS–) and abnormal transrectal ultrasound and power Doppler sonography ((TRUS-PDS+) according to the D'Amico and Dall'Era criteria (429 patients)

	TRUS-PDS+ (%)	TRUS-PDS– (%)	<i>p</i> values
Positive biopsies risk	59	32	<0.01
Low risk			
D'Amico	35	28	Non-significant
Dall era	29	27	Non-significant
High risk			
D'amico	24	4	<0.01
Dall era	30	5	<0.01

Fig. 4 One hundred seventy-seven patients with T1c cancer. Results of transrectal ultrasonography and the power Doppler sonography (TRUS-PDS) according to the D'Amico risk criteria and active surveillance (AS) by Dall'Era

Table 2 Diagnostic value of transrectal ultra sonography and the power Doppler sonography (TRUS-PDS) in 429 consecutive patients presenting a PSA level <10 ng/ml in T1c cancers, T1c cancers with a high risk of biological recurrence according to D'Amico and in the T1c cancers that may not benefit from active surveillance according to Dall'Era

	T1c	D'Amico	Dall'Era
True negative	193	274	270
True positive	85	85	85
False negative	92	11	15
False positive	59	59	59
Sensitivity	48	88.5	85
Specificity	76.6	82.3	82
Positive predictive value	59	59	59
Negative predictive value	67.7	96.1	95
Accuracy	65	83.68	82.75

of many lesions with a volume under 0.5 cc. The MRI has a negative predictive value in the diagnosis of high-risk cancers of a peripheral area not much higher than that of TRUS-PDS, and low machine availability and high examination cost forbid its systematic use before biopsies. However, MRI may play a role when the kinetics of the PSA level is suspect and when no target is visible in the TRUS-PDS examination.

Our study shows that the PDS may limit the risk of overdiagnosis; with an abnormal PDS, the probability of a positive biopsy is 59 % (PPV) and the probability of a significant cancer is 30 %, according to the Dall'Era criteria. With a normal PDS, these risks decrease to 32 and 5 %, respectively, in this same population. Can biopsy be legitimately delayed when an indolent lesion is suspected? The existence of latent or non-significant cancers has been suspected since publishing the results of the first series after autopsies. Epstein [27] considered that after radical prostatectomy, lesions are probably indolent when the tumor volume was less than 0.5 cc and accompanied by a Gleason score of less than 7. The idea of non-significant lesions based on the results of biopsies has less consensus,

because the biopsies underestimated the volume of the tumor and cell differentiation.

To assess the risks of biological recurrence after treatment, D'Amico's criteria have gained a wide consensus [11]. The criteria proposed by Dall'Era [20] are most often used in Europe [21] and have been validated over long periods of time. Studies on cohorts of patients with clinically localized and non-treated prostate cancer have shown that overall survival is excellent in patients with a Gleason score of less than 7. According to Dall'Era, there is no significant prognostic difference between the low-risk patients immediately treated and those who benefited from active surveillance before surgery [28].

Our study presents several limitations. It is based on only the results of biopsies and lacks correlation with the radical prostatectomy specimens. The biopsies underestimate the volume and the grade of the lesions. After radical prostatectomy, 23 to 35 % of the cancers qualified as low risk present an extraprostatic extension or impairment of the seminal vesicles [29]. The grade of tumor is an important predictive factor in the recurrence of cancer after treatment. The absence of biopsy in the cases of negative PDS may underestimate small lesions with a high grade. The criteria of D'Amico and Dall'Era were established with biopsy results. However, Thompson [3] observed that 10 to 25 % of the cancers associated with a PSA level ranging from 0.6 to 4 ng/ml had a Gleason score equal to or higher than 7. This risk is unanimously accepted in the individual screening strategy. In our study, 59 patients had false positive results of TRUS-PDS; these results are the origin of useless biopsies. However, the abnormal PSA level would indicate biopsies in these patients.

Conclusion

TRUS-PDS may be an alternative solution to avoid overdiagnosing prostate cancer, but it risks misdiagnosing some aggressive cancers. However, the risk of high-risk cancer is

less than 5 %. In patients, particularly in those who are older, biopsies could probably be deferred when the PSA rate does not exceed 10 ng/ml, the DRE is normal, and the TRUS-PDS is negative.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest concerning this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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