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Clinical significance of cancer in radical prostatectomy specimens: analysis from a contemporary series of 2900 men

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Summary

With prostate specific antigen (PSA) testing, up to 49% of detected tumours are small and in some of these cases there is a possibility that the tumour will remain clinically insignificant during the patient's remaining lifetime. The current study was performed to characterise the extent of cancer in men treated by radical prostatectomy (RP) in a community without population-based PSA screening. Clinical and pathological data of 2900 patients who underwent RP between 2008 and 2012 were analysed. Specimens were entirely embedded and evaluated by routine haematoxylin and eosin staining. Tumours were graded using recent modifications to the International Society of Urological Pathology (ISUP) modified Gleason grading system, and staged according to the ISUP recommendations. Tumours were considered pathologically insignificant if organ confined, with a volume of <0.5 cc and a Gleason score (GS) of <7. The mean age of patients in the series was 63 years (range 32–79 years) and the mean preoperative PSA was 7.16 ng/mL (range 0.4–69). In total, 2614 (90.1%) were classified as cT1; however, insignificant tumours were found in only 150 (5.2%) patients following examination of the radical prostatectomy specimen. A total of 2681 cases (92.4%) had a final GS of ≥ 7, 1144 (39.4%) had extraprostatic extension (EPE), of which 88.7% were classified as established; 669 (23.1%) had a tumour volume of >3 cc and 284 (9.8%) had surgical margin positivity. Seminal vesicle involvement was seen in 159 (5.5%) cases. Of 693 patients who had a lymphadenectomy, 31 (4.5%) had lymph node metastases. Aged ≤ 50 years were 212 (7.3%) patients (mean age 47 years). Of these, 194 were classified as cT1 while 192 (90.6%) were found to have significant cancer on examination of the radical prostatectomy specimen. We have shown in our series that although 90.1% of tumours were cT1, an overwhelming majority of tumours were found to be pathologically significant following RP, with a high proportion of cases showing high stage disease, seminal vesicle involvement and lymph node metastasis. These results suggest that, contrary to estimates from international trials, *ad hoc* PSA testing is associated with low levels of over-treating.

Key words: Active surveillance, adenocarcinoma, grade, prognosis, prostate, radical prostatectomy, stage.

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INTRODUCTION

There is debate regarding the value of prostate specific antigen (PSA) screening for the diagnosis of prostate cancer.[1–3] While population-based screening has not been embraced in either Australia or New Zealand, extensive PSA testing is undertaken on an *ad hoc* basis. This testing is performed for a variety of reasons including patient request, abnormal digital rectal examination, a family history of prostate cancer or lower urinary tract symptoms. Clinicians are now taking greater numbers of cores as a routine diagnostic strategy and this means that many more cases of prostate cancer are being detected.[1] It has been suggested that many of these cancers, especially those diagnosed in older men, are unlikely to cause symptoms during the man's remaining lifetime, and are therefore said to represent 'over-diagnosis'. In these cases, radical prostatectomy (RP) may be unnecessary and could be regarded as overtreatment.[2] Conversely, without PSA testing significant prostate cancer will remain undetected, with resultant cancer related morbidity and mortality.[3]

While prostate cancer is readily diagnosed following histological examination of thin core biopsies, current risk nomograms are limited in their ability to determine which cancers are unlikely to cause symptoms in the patient's lifetime and remain clinically insignificant. In order to overcome this, attempts have been made to define insignificant cancer in RP specimens. Several sets of criteria have been proposed; however, those of Epstein *et al.* have gained widest acceptance. According to these criteria, clinically insignificant tumours, considered suitable for deferred treatment and active surveillance, are those with Gleason score (GS) of ≤ 6 without evidence of Gleason pattern 4 or 5, being organ confined and with a volume <0.5 cc[4,5]

In 2005, the modified Gleason grading system of the International Society of Urological Pathology (ISUP) expanded the criteria for defining Gleason pattern 4 in radical prostatectomy specimens; as part of these recommendations, fused glands, poorly formed glands and most forms showing a cribriform architecture were included in this category.[6] This was in contrast to the original Gleason system in which a variety of cribriform glands were considered pattern 3 and has resulted in

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a significant upgrade of many tumours from GS 6 to GS 7a and 7b.[7,8] More recently it has been suggested that these recommendations be further modified, with all cribriform glands, regardless of architecture, now being considered Gleason pattern 4.[8,9] The result of these modifications is likely to decrease the prevalence of insignificant cancer post-2005. In addition to this, the 2009 RP consensus conference of the ISUP introduced refined criteria for the handling and staging of prostate cancer in RP specimens,[10] and this is likely to have an impact on the incidence of 'insignificant' cancers detected in patients who have undergone definitive surgical treatment for their prostatic malignancy.

In this study we have evaluated the extent of prostate cancer in a large series of patients treated by RP. We also compared these findings in patients who were aged $\leq$50 with those of patients who were >50 years of age. In addition, we have compared the findings from the examination of RP specimens with those of the pre-surgical clinical assessment. Specifically we sought to determine the proportion of cases where the tumour was upstaged following pathological assessment of the RP specimen, with evaluation based upon the criteria of the recent recommendations of the 2009 consensus conference on handling and staging of RP specimens.[11–13]

MATERIALS AND METHODS

A total of 2900 RP specimens, accessioned consecutively from patients treated for clinically localised prostate cancer from November 2008 to July 2012, were retrieved from the surgical pathology files of Aquesta Pathology, Queensland, Australia. None of the patients had undergone androgen deprivation or radiation therapy prior to undergoing RP. Ethical approval for this study was obtained from the Aquesta Ethics Committee.

Immediately after removal, each prostate gland was transported to the pathology laboratory where it was weighed and measured. After fixation in 10% neutral buffered formalin, the specimen was painted with two colours to indicate laterality. The prostate gland was sectioned and embedded in its entirety. Specifically, the seminal vesicles and vas deferens were removed by a transverse section taken as close as possible to the prostatic base and weighed. The next transverse slice, which represented the prostate base, was serially sectioned in a vertical parasagittal plane, allowing visualisation of the superior surface of the gland. The body of the prostate was serially sectioned at 3–4 mM intervals in a transverse plane perpendicular to the rectal surface. The apical slice was then serially sectioned in a vertical parasagittal plane. Each seminal vesicle was transversely sliced and the entire gland was blocked. All submitted lymph nodes were also completely sampled as previously described.[14]

On histological examination of the prostate gland, the location of each tumour nodule was noted. Gleason scoring was undertaken using the recent modifications to the 2005 ISUP modified Gleason scoring system.[6,9] In accordance with the recommendations of this scoring system, the GS of the tumour nodule having the highest GS was taken to be the final score of the carcinoma in each case. The tumour volume was determined using a three-dimensional volume estimation method.[15] Tumours were assigned a pT staging category following examination for extra prostatic extension, resection margin involvement, and involvement of seminal vesicles and lymph nodes, using the recommended criteria from the 2009 ISUP consensus conference.[11–13] Also in accordance with the recommendations of the 2009 ISUP consensus conference, seminal vesicle invasion was reported when the muscular wall of the seminal vesicle was infiltrated by carcinoma.[13]

RESULTS

Table 1 summarises the clinical and pathological characteristics of patients divided according to age at presentation ($\leq$50 years and >50 years). For the entire group, the mean age was 63 years (range 32–79 years); 212 (7.3%) patients were aged $\leq$50, with mean age 47 years. In total, 2681 tumours (92.4%) had a final GS of $\geq$7, 1144 (39.4%) had extraprostatic extension (EPE) with 1015 (35.0%) displaying established EPE, and 669 (23.1%) had a tumour volume of >3 cc. Seminal vesicle involvement was seen in 159 (5.5%) cases. Of 693 patients who had a lymphadenectomy, 31 (4.5%) had lymph node metastases.

Comparing patients aged $\leq$50 years with those >50 years of age, high grade disease (GS $>3+4=7$), tumour volume >3 cc, EPE, seminal vesicle involvement, surgical margin positivity and lymph node involvement occurred in 34.4% and 53.2%, 11.7% and 23.9%, 21.2% and 40.9%, 1.0% and 5.8%, 7.1% and 10.0%, and 3.5% and 4.5%, respectively. Pathologically insignificant cancer occurred in 9.4% of patients <50 years of age in comparison with 4.8% of patients >50 years of age.

DISCUSSION

Using Epstein's criteria, previous clinical studies have shown that 5–31% of prostate cancers in RP series are potentially clinically insignificant,[5,16–20] while in a separate screening study, 49% of patients were considered to have clinically insignificant cancer.[21] However, this may not reflect the true prevalence within the community as there has been shown to be poor correlation between the pre-treatment clinical assessment of tumour volume and EPE following pathological examination of the RP specimen.[22] There is similarly poor correlation between grading assigned to thin core biopsies and the final grading determined from the subsequent RP specimen.[23] Further, thin core biopsies have been shown to be poor predictors of EPE of tumour in patients treated with RP.[24] In addition to these factors, the method and adequacy of sampling of prostatectomy specimens, as well as the thickness of individual tissue blocks and the method of tumour volume estimation, may result in a marked variation in the prevalence of insignificant prostate cancer in RP. Regional bias relating to patient selection for RP, including the likelihood of the patient undergoing RP for apparently low risk disease, may also have a compounding effect.

Recent changes to the criteria for Gleason scoring of prostate cancer, as defined in the 2005 ISUP recommendations, as well as more recently suggested amendments, appear to have resulted in a general trend towards the upgrading of cancers. Specifically, this has principally resulted from the reclassification of all tumours with cribriform glands as Gleason pattern 4. In support of this strategy it has been demonstrated, using image analysis studies, that the presence of cribriform glands is associated with a less favourable outcome.[25] It has also been shown that in patients upgraded from classical GS $3+3=6$ using contemporary grading criteria, biochemical progression rates and risk of metastasis are intermediate between patients with modified GS $3+3=6$ and patients with classical GS $3+4=7$.[26]

Utilising the recommendations of the 2009 ISUP consensus conference on the handling of radical prostatectomy specimens,[27] as well as the most recent guidelines regarding the grading of prostatic carcinoma,[9] we have shown in this study that insignificant cancer in RP, as defined by Epstein,[5] was found in only 5.1% of patients. More importantly we have also shown that, while 90.1% of cases were determined to have clinically inapparent or clinically confined cancers, detailed pathological examination showed 39.4% of cases to exhibit