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Platinum Priority – Editorial

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Small Renal Mass and Low-Risk Prostate Cancer: Any More for Active Surveillance?

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In Europe in 2010 there were approximately 88 400 new cases of renal cell carcinoma (RCC) and 39 300 RCC-related deaths. Within this overall number, the incidence of small renal masses (SRMs) has shown the largest relative increase, with a 3.7% per year rise in incidence [1]. The incidental detection rate of SRMs has risen from 7% to 13% in the 1970s to 48% to 66% today, and in keeping with this stage migration, 38% of tumours excised are now classified SRMs [2]. The median age of diagnosis of RCC is 65 yr, and most SRMs are diagnosed in an elderly population. With the life expectancy of central Europe continuing to rise, it is estimated there will be 173 million people >65 yr of age in Europe in 2025. Combine this with the liberal use of abdominal imaging, said to identify a renal lesion in 13–27% of cases [3], and clearly we will be faced with a huge number of newly diagnosed SRMs in an ageing comorbid population.

The natural history of SRMs is now better appreciated, and it is accepted that most SRMs follow an indolent course [4]. The mean rate of growth is no more than 2–3 mm/yr, and 30% of SRMs show no growth over observation periods of 2–3 yr. It is not possible to predict from the initial size or subsequent growth rate the malignant potential of an SRM because an SRM that shows no growth is as likely to be malignant as benign [4]. However, it is known that the smaller the SRM, the more likely it is to be lower grade, lower stage, papillary subtype, benign histology, and nonmetastatic. An SRM <2 cm is high grade in 4.2% of cases compared with 25.5% and 57.7% for masses 3–4 cm and >7 cm, respectively. Clear cell RCCs (ccRCCs) are histologically unfavourable compared with other types of RCC and are underrepresented in SRM series [5]. The percentage of ccRCC increases from 25.6% if <1 cm to 82.4%

if >4 cm; the percentage of papillary RCC decreases from 74.4% in tumours <1 cm to 11.9% for tumours >4 cm. Overall, 20% of SRMs are benign on formal histologic analysis, but if stratified according to size, a renal mass <1 cm or >7 cm is benign in 46.3% and 6.3% of cases, respectively [6]. For each 1-cm increase in size, the calculated prevalence of synchronous metastases increases by 3.5% [7]. The figure quoted for the risk of developing metastases while on surveillance is approximately 1% [4]. Over recent years the management options available for SRMs have expanded immensely and include partial nephrectomy, cryoablation, radiofrequency ablation, and active surveillance (AS). A meta-analysis of 6471 SRMs, comparing all techniques, showed no difference in the incidence of metastases regardless of whether SRM was excised, ablated, or observed [7]. This suggests that delaying treatment does not adversely affect outcome, and surveillance data do provide reassurance that treatment is not necessary urgent in most cases.

In this issue, Jewett et al reported the findings of a prospective clinical trial of AS of incidental SRMs with presurveillance renal mass biopsy (RMB) to determine growth rates and progression [8]. Between 2004 and 2009, eight centres recruited 178 patients (209 SRMs), with a mean age of 73 yr and a mean axial SRM dimension of 2.1 cm, who were unfit for or refused treatment. They defined progression as either an SRM becoming >4 cm, doubling tumour volume in <12 mo, or development of metastases. Overall, 127 patients (with 151 SRMs) were followed for >12 mo; 99 patients consented to RMB. The RMB was nondiagnostic in a high proportion (33%), and RCC was identified in 56 patients (55%). The mean overall

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growth rate was 0.13 cm/yr and no different between malignant and benign masses. Of note, the authors had growth data on only 37 pathologically confirmed RCC, and of these, 10 (27%) actually *decreased* in size during follow-up. Overall, 27 patients (15.2%) progressed; 13 (7.3%) with SRM >4 cm, 12 (6.7%) with “rapid growth” (doubling time <12 mo), and 2 developed metastases. The authors concluded that even for RMB-proven RCC, rapid local progression or development of metastasis is rare during the first 2 yr of surveillance, and they advocate an initial period of conservative management with serial imaging in elderly and/or infirm patients.

AS is not a new concept in RCC, but in recent years the increased incidence of SRMs in elderly patients coupled with our improved knowledge of the indolent natural history of the majority has renewed interest in AS [7], a management strategy more synonymous with low-risk prostate cancer (PCa). In both scenarios, it remains a controversial area and is not a standardised method of management. AS for SRM and low-risk PCa share common characteristics including stage migration and overtreatment of disease as catalysts to its recommendation, lack of a defined protocol, unknown effect on overall survival, and no strict inclusion criteria on who is a suitable candidate. However, distinct differences exist. AS in SRM is performed without the three main prognostic indicators for RCC, namely grade, histologic subtype, and pathologic stage, whereas in PCa AS is based on tumour grade, clinical stage, and prostate-specific antigen. Reserving definitive curative treatment until disease progression is relevant to both diseases but has different implications in the long term. For PCa, if a man moves outside the “window of opportunity” for definitive treatment in the presence of significant disease progression, he has in reserve the option for hormonal treatment. In SRM, the rationale for delaying treatment in elderly and/or infirm patients until progression, based on radiologic not biologic progression, is flawed. With time, the elderly patient will be even older and even more medically unfit. We need to be able to risk-stratify patients, and in any disease this has to be based on various factors including clinical, radiologic, pathologic, and molecular parameters. However, there are no predictive clinical (age, sex, symptoms) or radiologic (size, multifocality, cystic) factors that accurately predict SRM biologic potential and behaviour. Currently, we base decisions mainly on serial radiologic imaging because histologic information from RMB has not been incorporated into regular clinical practice. Contemporary series of RMB have a sensitivity, specificity, and diagnostic accuracy of 80–92%, 83–100%, and >90%, respectively, and could add valuable information to stratify SRMs [9]. Even radiologic assessment is nonstandardised because most series use maximum axial diameter to determine growth rates, whereas tumour volume is probably a more accurate reflection of the malignant load, as this increases exponentially with each 1-cm increase in diameter; a 2-cm, 3-cm, and 4-cm spherical mass has a volume of 4.3 cm³, 14.4 cm³, and 33.5 cm³, respectively.

If AS for SRM is to become established and widely adopted, a clear protocol needs to be defined that urologists

can use to plan treatment. This has not occurred as yet in AS for low-risk PCa, and we are a long way from being able to write such specific guidance for SRM because many unanswered questions remain. Deferring to active surgical treatment from AS, aside from patient/physician anxiety, is based on arbitrary values of a SRM becoming >4 cm and a doubling size in <12 mo [9]. Currently, we have not been able to identify a growth rate that differentiates a biologically significant malignant lesion from an indolent tumour or even a benign lesion. In addition to this key information, we also do not have answers to more simple questions such as how often to scan and what modality to use (ultrasound, computed tomography, or magnetic resonance imaging), but obviously issues of cost, radiation, and reproducibility are important.

Jewett et al [8] showed in a small prospective clinical trial that AS for SRM in elderly patients is safe in the short term, but larger studies will be required before we can produce clear guidance to help manage the further significant rise in SRM diagnosis we are going to see over the next few years. The ultimate goal, although difficult, will be to derive an accurate validated internationally applicable nomogram specifically for SRM or a risk classification system akin to the D’Amico classification for PCa [10]. A key to this will be the incorporation of histologic and molecular data alongside clinical and radiologic parameters, and to fulfil this requirement we will need to see an increase in the use of RMB for SRM. This will allow clinicians to select out the patients, including some younger less morbid patients, who have an SRM with good prognostic variables and can be safely managed on a predetermined AS protocol. However, current evidence still only allows us to safely advocate AS for SRMs in elderly patients with comorbidity, something we have known for a while and a policy that excludes a lot of other patients. We hope that SRM and low-risk PCa only share an affinity with “active surveillance” and we do not get embroiled in a debate over “screening” for SRM! Then we would have a large number of patients to counsel wisely.

Conflicts of interest: The authors have nothing to disclose.

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