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Editorial

Prostate Cancer: Fine Tuning our Ability to Accurately Grade and Stage the Disease Prior to Therapy

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In the last decade, we have witnessed numerous improvements and refinements in the diagnosis, staging and treatment of prostate cancer. However, an optimal management and therapeutical approach to this neoplasm is hampered by our relative inability to predict, with certainty, the exact pathological stage and aggressiveness of the neoplasm based on the results of biopsies only.

Several authors have shown that there are sometimes large discrepancies between the Gleason score on the biopsy specimen and the definitive pathological report [1,2]. Djavan and co-workers showed, retrospectively reviewing the records of 415 patients who underwent radical prostatectomy, that independent of the setting, about 50% of all Gleason scores assignments by needle biopsy specimen were revised in the direction of a worse score category [1].

This is certainly very important for clinicians, when consulting with patients regarding treatment choices, if grade of disease has to be taken into consideration when proposing a therapy [2,3].

In this issue of EUROPEAN UROLOGY, Elabbady and co-workers show that, in their study, there was only a 50% agreement between the biopsy and the prostatectomy Gleason sum, with half of the cases being 'undergraded' by biopsies, if only sextant biopsies were taken. On the other hand, although the limitation of this study is the reduced number of cases, when a 12-core prostate biopsy core scheme was adopted, there was an agreement between the biopsy and the prostatectomy specimen in over 85% of the cases, leaving 15% of cases only where the biopsy underestimated the actual final Gleason sum on the specimen.

In other words, although it really makes sense that, if one increases the number of biopsies, we will increase the prostate cancer detection rate, this might also translate into a better characterisation of the cancer aggressiveness [4]. A large variety of different biopsy schemes have been proposed by, and it is currently unclear which one is the best to choose from, both at diagnosing significant cancer and accurately predicting the biology of the cancer [5–7]. The future may be in the use of biopsies, not only for diagnosing, but above all for characterising the detected cancer.

Another grey area which also hampers our possibilities to efficaciously propose an effective therapy for prostate cancer, is our relative inability to accurately stage this disease. At the present time, and this holds true for nearly all neoplasms, imaging modalities are able to point out metastatic tumour burdens around half a centimetre, but are not able to demonstrate microscopic foci of neoplastic cells that have migrated to lymph nodes for instance.

In prostate cancer, we have been helped by parameters such as the Gleason score or the PSA to statistically predict whether there is a high likelihood of lymph node invasion or not. Many authors have shown that the standard lymphadenectomy area of the obturator fossa was far from being the only site where neoplastic cells would

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migrate out of the prostate. Some are strong advocators of extensive lymph node dissection, not only for better diagnosis purposes, but also because they have shown that it could directly impact on the prognosis of patients [8].

What are the currently available technologies in prostate cancer staging, or the ones that are in the pipeline?

Recently, a new non-invasive technique for detecting lymph node metastases in prostate cancer, using highly lymphotropic superparamagnetic nanoparticles which gain access to the lymph nodes by means of interstitial-lymphatic fluid transport, demonstrated the ability of the this technique to detect small and other wise undetectable lymph node metastases in patients with prostate cancer [9].

The sentinel lymph node is another concept that has been applied to many cancer with various successes. Some authors have found that it may facilitate the detection of occult metastases in clinically otherwise negative regions and that it may decrease morbidity by preventing unnecessary lymph node dissections. In this issue, Corvin and co-workers, from the University of Tuebingen, have evaluated the ability of laparoscopic radio-isotope guided sentinel lymph node dissection in the staging of prostate cancer. The vast majority of the patients had quite elevated PSA levels, most of them well above 20, and with some of them even over 200 ng/ml!

The number of lymph nodes removed was variable, but in most cases over 20 lymph nodes. Noteworthy, this study further demonstrated that close to 50% of the lymph nodes were found outside the obturator foci. There was a slight decrease in the accuracy of the intra-operative measurement as compared to the pre-operative imaging. Laparoscopic sentinel lymph node dissection could be an option in patients where the risk of lymph node metastases is elevated according to their pre-operative parameters. It could also have been interesting to compare the sentinel lymph node dissection to an extensive lymph node dissection to get a rough idea of the sensitivity and specificity of this technique.

The ability to pin point lymph node metastases in patients where all imaging techniques are negative, is certainly appealing and might dramatically impact on the management of prostate cancer. Too often, we consider local therapeutic approaches for diseases which are unfortunately far from being confined to the gland only!

In this issue of EUROPEAN UROLOGY also, Erich and co-workers have shown that some LHRH-analogues fail to reach testosterone castration levels with 3-monthly formulation depots. The number of patients in each group (40 and 25) is not huge, but still about 10 patients failed to reach the castration level with leuprolide.

Too often, the measurement of testosterone during therapy or even before therapy of prostate cancer has been overlooked and it has been assumed that all LHRH-analogues achieve similar castration levels as does surgical orchiectomy. There is certainly a large debate with respect to what is considered as an adequate castration level. It is interesting to note that in the present study, the group of Norway considered a pretty high level (81 ng/ml), whereas many other groups would consider a 50, if not as recently [10], a 20 ng/dl cut off value after LHRH-agonist therapy. Whether achieving such low levels of testosterone after therapy for prostate cancer has a direct relevance and clinical implication is far from proven, but it is in the ''air'' that the lower, the better holds true for testosterone castration levels after LHRH-analogues [10].

These studies further prove that androgen levels have to be monitored during therapy of prostate cancer. There is also a current trend to measure those testosterone levels before any therapy, since some patients with low levels may harbour more aggressive neoplasms than patients with normal testosterone levels.

There is certainly limited information available on the relation that exists between testosterone values before therapy, after therapy and clinical outcomes, but there is a current consensus that, during therapy with LHRH, testosterone levels should be closer to those observed after surgical orchiectomy.

Although certainly not representing the entire urological community, during the last 2005 International Consultations on Developments of Prostate Cancer and Prostate Diseases in Paris that gathered a large group of delegates, more than 60% of this group agreed that they would consider a castrate level as any level below or equal to 20 ng/ml, which is again far from the level used by the authors in the present study. It would have been interesting, in fact, to look at the number of patients in this series that were considered as castrated at 20 and 50 ng/ml [10]. Taking into account the combination of PSA and testosterone level as an adjunct to the monitoring of LHRH-agonists in prostate cancer is an avenue worth investigating in the future.

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