

depends on the reliability of cytology in detecting high-risk disease when it is present. Unfortunately, this did not appear to be available to the investigators in this study.

The investigators tried to explain the apparent deficiency of cytologic interpretations as possibly reflecting the “variability across multiple facilities” because “cytologic examinations were conducted either within the participating institutions or at reference laboratories, according to standard practice at each facility.” However, if these results are as unreliable as they seemed to be, another conclusion would be that there is an urgent need to enhance cytologic capabilities generally available to urologists and to educate cytopathologists regarding the important role they have in detecting cancer or declaring its absence (at least in high-risk disease) so that patients may benefit from the higher standard of care their physicians might then provide. Certainly in this study it would have been appropriate to have a central reference laboratory to avoid the criticism that urinary cytology effectively came to be used as a “straw man” in comparing its diagnostic efficacy with that of NMP22.

Each of these considerations suggests that further refinement for the use of the NMP22 assay must be obtained if it is to become clinically useful. Its low

sensitivity (49.5%) argues against its use in displacing cystoscopy for surveillance (though prolongation of intervals between consecutive cystoscopies for low-risk disease is not at issue). Its specificity (87.3%) does little to reduce the risk of anxiety when the test is positive, suggesting that a cancer may be present when, in fact, it is not. That 72 of 123 patients (59%) with a positive NMP22 assay did not have cancer would thus do little to allay the concerns of both patients and their physicians and might actually prompt multiple unnecessary interventions to find a malignancy that is not present.

There is clearly a need to develop reliable tumour markers that have better performance in the detection of urothelial cancer than was shown in this study. Of critical and ultimate importance is an understanding of the role that these markers may play in different clinical contexts in diagnosing disease, suggesting the biologic potential of different forms of disease, and in guiding appropriate treatment.

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Re: Detection of Occult Nodal Metastases in Locally Advanced Node-Negative Prostate Cancer

Pagliarulo et al.

J Clin Oncol 2006;24:2735–42.

Expert's summary:

The authors explored the incidence of occult nodal metastases in a cohort of 180 lymph node-negative and pT3 patients submitted to extended pelvic lymph node dissection (ePLND) and radical prostatectomy (RP). All lymph nodes originally considered negative by routine histopathologic assessment were evaluated for occult metastases by immunohistochemistry using antibodies to cytokeratins and subsequently prostate-specific antigen (PSA). Interestingly, the authors found occult lymph node invasion (LNI) in 13% of patients without histopathologic evidence of LNI. More importantly, the presence of occult LNI was an independent multivariate predictor of disease recurrence and overall survival. Indeed, outcome of patients diagnosed with occult LNI was significantly worse compared with patients without evidence of LNI and was

similar to a cohort of patients with histopathologic evidence of LNI.

Expert's opinion:

This study is important in that it delivers several important data and raises clinically significant questions about the outcome of patients with prostate cancer and LNI.

First, it clearly confirms that LNI represents one of the strongest predictors of disease progression, regardless of apparent success in eradicating local disease. Patients with either histopathologic evidence of LNI or with occult nodal metastases had significantly worse outcome compared with patients with locally advanced disease without LNI. However, in this study, patients were not stratified according to volume of nodal involvement, which represents a key parameter for the outcome of patients with LNI. In fact, it has been reported that patients with low-volume LNI (either expressed as number of nodes or node density) undergoing an ePLND showed comparable outcome to those without LNI [1,2]. Therefore, the question of a potential curative effect of ePLND in

particular subgroups of patients with LNI remains unanswered in this study.

Second, this manuscript underlines the need for accurate staging of patients undergoing RP. A more accurate staging allows one to better clarify patient expectations and to deliver adjuvant systemic therapy in a more timely and specific fashion. These benefits are clinically relevant because patients with histopathologic evidence of LNI who received early adjuvant systemic therapy showed better survival than patients with false-negative nodes who did not receive hormonal therapy. However, the lack of significant difference in overall survival between these two groups of patients might be due to the fact that only 26% of patients with histopathologic evidence of LNI received adjuvant hormonal therapy. Therefore, the rationale for a more expensive and time-consuming pathologic assessment could reside on the potential application of early systemic adjuvant therapy in patients with occult LNI. However, this benefit still needs to be demonstrated. Although an accurate LNI staging is needed, it is noteworthy that patients enrolled in this study were affected by a locally advanced disease (pT3a/b), and therefore, more likely to be affected by LNI, which may explain the surprisingly high rate of patients with false-negative nodes submitted to an ePLND (13%). However, it is now evident that not all patients with clinically localized prostate cancer might benefit from a PLND. Patients should be stratified according to their preoperative parameters (including PSA, clinical stage, and biopsy Gleason sum) with regards to their risk of histopathologic LNI. The majority of LNI predictive tools relied on limited PLND data and cannot be

used for estimation of LNI probability in ePLND specimens. Briganti et al. [3] addressed this void and developed a nomogram that can predict LNI in ePLND specimens with 76% accuracy [3].

Finally, as correctly underlined by the authors, it is still to be proven in prospective randomized trials, whether patients with occult LNI might benefit from a more accurate staging, which would lead to early administration of adjuvant systemic treatment. If this benefit were demonstrated, a more expensive and time-consuming pathologic assessment would be eventually justified in highly selected categories of patients.

References

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Re: Defining Biochemical Failure Following Radiotherapy With Or Without Hormonal Therapy in Men With Clinically Localized Prostate Cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference

Roach 3rd M, Hanks G, Thames Jr H, et al.

Int J Radiat Oncol Biol Phys 2006;65:965–74.

Expert's summary:

The most appropriate definition of biochemical progression after external beam radiotherapy (EBRT) and radical prostatectomy [1] is uncertain. Since the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus in 1996 [2], the biochemical failure after EBRT was defined as

occurring after three consecutive rises in prostate-specific antigen (PSA) after a nadir, with the date of failure as midway between the nadir date and the first rise.

This second consensus conference sponsored by ASTRO and the Radiation Therapy Oncology Group (RTOG) on January 2005 has revised the ASTRO definition and recommended a rise of 2 ng/mL or more above the nadir PSA as the new standard definition for biochemical failure after EBRT with or without hormonal therapy (HT), with the date determined “at call” (not backdated). To avoid the artefacts resulting from short follow-up, the reported date of control should be listed as 2 yr short of the median follow-up.