Acta Oncologica, 2011; 50(Suppl 1): 49–52

informa
healthcare

REVIEW ARTICLE

Pathology in prostate research: Optimizing the pathological data

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Abstract

Pathology remains the gold standard for the diagnosis and local staging and grading of prostate cancer. However, as in any discipline, there are variations in national standards and protocols leading to possible significant intra-observer variations. This can significantly impact on the data supplied to clinical trials. *Diagnostic and grading criteria*. Error rates in the diagnosis of prostate cancer have improved but the possibility that diagnostic error may be discovered has to be addressed in any research series. Major changes in Gleason grading have occurred in the past 40 years and this may lead to suboptimal application of grades in research cohorts, falsely raising the prognostic power of new biomarkers. *Tumor measurements and staging criteria.* Further information that may provide additional prognostic information include various measures of tumor extent and peri-neural invasion in biopsy specimens. Standardization of measures of tumor extent is necessary to give more useful assessments of prognosis. In radical prostatectomy specimens there are a number of other staging measurements which might be applied, including tumor volume, margin status, extra-capsular extension and nodal positivity though many of these variables are interdependent. *Conclusion.* Appropriate utilization of such pathological material will produce improved cohorts in which it will be possible to test new biomarkers with increased rigor.

Pathological data in clinical research

Validation of the diagnosis

The pathological diagnosis of prostate cancer on needle biopsy is still recognized to be a challenging area. Retrospective analyses of cases has revealed error rates of between 7–20% [1,2] though modern immunohistochemical methods may have reduced this [3]. Nevertheless, recent series still reveal significant errors in both the under-diagnosis and over-diagnosis of cancer [4]. Specialist uropathologists have been shown to have lower error rates than non-specialists. Error rates will also probably increase in older series. However it should be realized that review of old cases may lead to ethical questions of whether the patient should be informed of such changes if cases are reviewed rather than case notes abstracted. This may be handled in a number of ways. In one retrospective series, the patients were informed, after 20 years if their diagnosis of prostate cancer was incorrect [1]. No legal action resulted from this (personal communication from the author). A second similar series had built-in anonymization to their results and was given ethical approval that the patients would not be informed of such changes [2]. These issues have to be addressed before the commencement of any review.

Gleason scoring

Gleason scoring, devised over 40 years ago, remains the most powerful predictor of prostate cancer behavior in any biopsy or resection specimen [5,6]. However, significant changes have occurred in Gleason scoring since it was devised in the late 1960s and early 1970s [7]. This has resulted in significant shifts in Gleason scoring, invariably to higher scores. The reasons for this are many, but include the recognition that the lowest Gleason scores probably do not represent cancer, meaning they are no longer diagnosed. The ISUP 2005 consensus conference made a number of significant changes to Gleason scoring. Unfortunately these were not fully validated, and it remains uncertain whether traditional or 'revised' Gleason

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(Received 3 August 2010; accepted 16 September 2010)

ISSN 0284-186X print/ISSN 1651-226X online © 2011 Informa Healthcare
DOI: 10.3109/0284186X.2010.525223

scoring is a better predictor of behavior [8], especially for the crucial cut-off between Gleason pattern 3 and Gleason pattern 4. It should also be recognized that the modern criteria are a 'consensus' and therefore there may be variations between different laboratories and different pathologists in how Gleason grading is calculated [9]. The results of this Gleason drift is the so called 'Will Rogers' phenomenon, where survival curves appear to show improvement over time due to upgrading of the disease [10].

Examples of this include the calculation of Gleason score from a biopsy series. Some pathologists will calculate a composite score, taking into account the appearances in every core with cancer. Other groups report the 'worst' score seen in any of the cores sampled. A second example is the calculation of tertiary grade [11]. There was no consensus at the meeting in radical prostatectomy specimens as to whether the worst pattern seen, if it was a tertiary element should be incorporated into the main Gleason score.

Unfortunately it is not yet possible to state on the optimal method. However there is evidence that abstraction of notes from a retrospective series will provide much poorer information than a single pathologist reviewing to modern criteria [12]. This is important in any biomarker assessment since merely using abstracted information from multiple centers will considerably under-estimate the power of Gleason scoring and therefore lead to a falsely more powerful assessment of a given tumor biomarker.

Therefore for both retrospective and prospective studies there is considerable variation how Gleason score has been and is calculated, and any utilization of Gleason score should include a description of the methodologies used.

Tumor extent and staging in diagnostic samples

Estimates of tumor extent are being increasingly used in estimation of recurrence and progression risk and should therefore be used in multivariate analyses. Unfortunately multiple methods of assessment are available leading to non-comparability of large series. Tumor extent in TURP specimens may be measured counting the number of positive chips or by visual estimates of involved tissue though one paper suggests these are comparable [13].

Measurements of tumor extent are prognostically more important in prostate biopsies, and most series have shown that tumor content of prostate biopsies yields prognostic information on multivariate analysis. A systematic review [14] has shown that multiple methodologies for core measurement and assessment preclude proper analyses. However, tumor extent does appear in nomograms and tables and some assessment of tumor extent should be regarded as standard practice in the evaluation of new biomarkers on needle biopsies [15].

Perineural invasion

The importance of reporting perineural invasion prostate cancer is still controversial. A recent review concluded that variations in study design precluded meta-analysis [16] but that the weight of evidence suggested that in localized disease, the presence of perineural invasion might favor the use of more radical therapy.

Pathologic data in radical prostatectomy specimens

As in biopsy specimens, details of the methods by which Gleason grade is calculated should be regarded as an essential criterion in any multivariate assessment of disease progression after RP in clinical trials. However there are other important assessments of disease extent which are not routinely of importance in biopsy specimens. The International Society of Urological Pathologists has recently published guidelines to standardize the acceptable approaches to radical prostatectomy processing [17–21].

a. TNM Stage. The major decision in radical prostatectomy (RP) specimens is to distinguish between tumors limited to the prostate (organ confined, pT2) or involving extra-prostatic tissues (pT3) [22]. In radical prostatectomy specimens tumor volume measurements and subdividing the category of organ confined tumors (pT2) does not appear to provide useful independent prognostic information as it is less informative than other prognostic parameters such as stage, capsular involvement, margin positivity and lymph node status. Assessments of tumor volume in this scenario have yielded contradictory information [23,24].
b. Margin status**.** Many studies have reported on the prognostic significance of involved margins and the extent of positivity is also of prognostic significance [25,26].
c. Seminal vesicle involvement (SVI, pT3b) is a poor prognostic factor after radical prostatectomy [27].
d. Vascular invasion. The presence of vascular invasion is an independent predictor of biochemical recurrence following radical prostatectomy [28].
e. Nodal positivity is a poor prognostic factor and the diameter of the largest metastasis appears to be more predictive of cancer-specific survival than the number of positive nodes alone. However the presence of extranodal extension was not prognostic [29,30].

Conclusions

There is an urgent need for new biomarkers to predict outcome in prostatic carcinoma. However the search for such markers must be backed up with full and thorough assessment of all pathological criteria which might compete with a novel assessment. There is a concern that novel markers may appear more promising if measured in series with suboptimal or incomplete pathological assessments. Utilization of the maximum amount of pathological data will obviate these concerns and hopefully lead to biomarkers progressing from the research laboratory into clinical practice.

Declaration of interest: The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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