



Editorial – referring to the article published on pp. 777–785 of this issue

Foreseeing Cancer Metastases

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Metastatic potential reveals the true nature of cancer. In more advanced bladder cancer metastases occur during disease follow-up in >50% of cases, despite extensive local treatment. The “seed and soil” principle of metastases development was put forward more than a century ago, in 1889, by Stephen Paget [1]. For bladder cancer cells the soil seems widely available: metastases do occur in virtually all organs of the body. Research, therefore, has been focused mainly on tumour properties rather than on host/patient characteristics.

Tumour cell proliferative activity and p53 expression were shown to be associated with prognosis presumably through genetic instability causing genetic alterations in tumour cell populations that provide the potential for tumour seeding [2].

Loss of E-cadherin, a cell-to-cell adhesion molecule, was shown to be associated with poor prognosis in patients with all stages of bladder cancer [3]. Other cell-to-cell adhesion molecules such as γ -catenin [4] and CD44 also suggest the importance in cell-to-cell adhesion and cancer metastases [5]. In a careful literature review, Gontero et al. [5] examined data on several markers of metastases in bladder cancer and concluded that E-cadherin, sialosyl-LeX, laminin, collagen IV, thrombospondin-1, and microvessel density are useful markers for prediction of metastases. All these gene products are associated with cell-to-cell interaction and the extracellular matrix.

The findings of Agerbaek et al. in this issue of *European Urology* support the importance of cell-to-

cell interaction and metastases development in bladder cancer [6]. They found high focal expression of the S100A4 protein associated with an increased risk of bladder cancer metastases in 108 patients who underwent cystectomy for T1–T4 bladder cancer. S100A4 is a small calcium-binding protein that was initially described to be associated with melanoma metastases in the early 1990s. Initially, the calcium-binding properties of the protein were associated with its motility-promoting effect, but recent findings suggest that binding of the S100A4 protein to specific target molecules such as stromal myosin and annexin II may play a more important role in metastases development [7]. The role of S100A4 in angiogenesis was shown in a mouse model with S100A4 overexpression in which mice developed hemangiomas [8]. These findings indicate that S100A4 expression renders tumour cells more invasive and promotes angiogenesis.

In recent months, several reviews have discussed the relationship of S100A4 expression with tumour metastases in breast cancer, colorectal cancer, papillary thyroid carcinoma, and malignant melanomas [9,10]. For routine clinical purposes a positive marker such as S100A4 seems preferable over a negative marker such as E-cadherin. Interestingly, the data of Agerbaek et al. show that focal rather than general S100A4 staining correlated with metastases development, suggesting that clonal formation within the tumour needs to be considered for prediction of metastases. The importance of focal staining may hamper proper analysis in larger

tumours. Small areas of strong focal staining may determine prognosis and can easily be missed in larger tumours possibly explaining the 18% (3 of 17) “false-negative” rate in the presented data. Critical review of the data presented by Agerbaek et al. raises several issues. All patients received preoperative radiotherapy, which, according to the authors, renders pathologic staging of the cystectomy specimens impossible. Because pathologic stage is an important predictor of prognosis in bladder cancer, results of the multivariate analysis may have been completely different if this important marker had been available. The preoperative radiotherapy may also have influenced expression levels of S100A4, and conversely, the S100A4 expression levels may have influenced response to radiotherapy. Earlier studies revealed interaction between S100A4 and p53 that influenced the apoptotic response to radiotherapy. Because p53 is often lost in bladder cancer and S100A4 is, in part, regulated through p53, colocalisation of p53 and S100A4 would be an interesting further analysis in these patients.

A practical problem may also be the finding that strong focal staining for S100A4 is present in 60% of cases, whereas, despite the long follow-up of “at least 10 years” (median follow-up not given), only 58% of patients with a tumour with high focal expression experienced metastatic relapses during follow-up. Again in a population where 45% (49 of 108) of patients develop metastases overall, the improved prediction by using S100A4 staining intensity for the individual patient seems limited.

Two important points come forward from the data of Agerbaek et al.: (1) withholding pathologic tumour staging from multivariate prognostic analyses may render less strong predictors statistically significant, and (2) S100A4 is an interesting novel marker for bladder cancer prognostication. Combination analysis with, for example, p53 and

E-cadherin expression may further improve its true clinical value.

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