Lymphovascular invasion (Required)

Reason/Evidentiary Support

The data on lymphovascular invasion (LVI) in urothelial carcinoma in the urinary bladder has continued to grow with many large series now reported.[1-5] These have included very large multi-institutional series (e.g. Kluth et al[4] – 8102 patients), cases from phase 3 clinical trials (von Rundstedt et al[5] – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al[3] – SPARC Score) all of which have found LVI to be a highly significant predictor of outcome.

Studies that have evaluated the significance of LVI on biopsy or transurethral resection of bladder tumour (TURBT) material specifically are much more limited.[6-16] These have almost all been based on H&E evaluation with limited utilisation of immunohistochemistry. The frequency of identification of LVI has ranged from <10% to as high as 67%. Among the better studies are the paper by Olsson et al (2013) which is population based [all newly diagnosed T1 tumours (N=211)] in the Southeastern region of Sweden with relatively uniform treatment.[16] These authors identified LVI in 8% of cases and also included an indeterminate category (22% of cases).[16] The presence of LVI was an independent predictor of recurrence free-, progression free- and cancer specific survival.[16] The prospective study by Orsola et al (2005) in contrast found no significant association with progression-free or cancer specific survival.[17] This study is limited by the short follow up. Overall the majority of these studies have found LVI to be important but, as indicated, data is limited.

Specific data on LVI determination in biopsy/ transurethral resection (TUR) specimens of upper tract and urethra are not available. There are several reports that have found LVI to be significant (various endpoints) in resection specimens for upper tract urothelial carcinoma.[18-21] These large, contemporary series have consistently identified LVI as a significant parameter in upper tract urinary cancer. For example, the study by Cha et al (2012) was a multi-institutional retrospective analysis of 2244 patients treated by radical nephroureterectomy.[18] The cases were divided into a development and an external validation cohort. LVI (based on the pathology reports) was an independent predictor of recurrence free survival and cancer specific survival in both cohorts and was included in the 2-year and 5-year recurrence-free and cancer-specific survival nomograms.[18]

For urethral carcinoma there is no substantive literature available. In the 2013 Guidelines on Urethral Carcinoma by the European Association of Urology (EAU), LVI is not recognised as a prognostic indicator.[22]

The role of immunohistochemistry in determining the presence or absence of LVI has been limited. The problem with recognising LVI on H&E sections has been demonstrated for urothelial carcinoma. Algaba[23] and Lopez-Beltran[24] among others have pointed out the importance of utilising strict criteria and these should be followed. Criteria recommended by Algaba (2006) included tightly cohesive tumour cells with a smooth border and the cells at the periphery having a shell-like appearance, the tumour thrombus floating free in the lumen of a space with an unequivocal endothelial cell lining, the presence of fibrin and/or red blood cells around the thrombus, and the space preferably associated with an arteriole with the surrounding stroma appearing normal.[23]

The possibility of routinely performing immunohistochemistry on T1 cases is much discussed but with little data. In one report[8] immunohistochemistry for D2-40 and CD34 was performed on 25 TUR

specimens and the H&E evaluation of LVI was changed in only one case. This contrasts with the report by Larsen et al (1990) who found that only 14% of cases diagnosed as LVI by H&E were confirmed by immunohistochemistry.[6] It is likely that the Larsen study overstates the problem of overcalling of LVI in current practice. The International Consultation on Urologic Disease (ICUD) pathology committee noted that there is well documented value to using immunohistochemistry in other organs to maximize detection of LVI (e.g. breast, etc) but little for urothelial carcinoma. They concluded "The general use of immunohistochemistry in the routine setting cannot however be recommended since performing two immunohistochemical stains on even selected paraffin blocks with bladder cancer would be extremely time consuming and cost intensive."[25]

Although the data on LVI in biopsy/TUR specimens is limited, the compelling evidence in large resection studies of urothelial carcinoma of the urinary bladder and upper tract support inclusion as a required element in this dataset.

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