Bladder: transitional cell carcinoma

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Identity


Classification

Existence of different histologic types:
- Transitional cell carcinoma of the bladder, herein described,
- Squamous cell carcinoma,
- Adenocarcinoma (2%), rare,
- Poorly differentiated carcinoma/small cell carcinoma, exceptional.

Clinics and pathology

Disease
Cancer of the urothelium.

Epidemiology
Transitional cell carcinoma is the most frequent bladder cancer in Europe and in the USA, representing 90-95% of cases, while squamous cell carcinoma represents...
only 5% in these countries, but up to 70-80% of cases in the Middle East. Annual incidence: 250/10³, 2% of cancers, the fourth cancer in males, the seventh in females, 3M/1F. Occurs mainly in the 6th-8th decades of life. Risk factors: cigarette smoking and occupational exposure (aniline, benzidine, naphtylamine); 20 to 30 years latency after exposure.

**Clinics**

Hematuria, irritation.

**Pathology**

Grading and staging: tumours are:

- pTIS carcinoma in situ (but high grade), and
- pTa papillary carcinoma, both mucosally confined;
- pT1 lamina propria invasive;
- pT2 infiltrates the superficial muscle, and
- pT3a, the deep muscle;
- pT3b invasion into perivesical fat;
- pT4 extends into neighbouring structures and organs.

**Treatment**

Resection (more or less extensive: electrofulguration -- > cystectomy); chemo and/or radiotherapy, BCG-therapy.

**Evolution**

Recurrence is highly frequent.

**Prognosis**

According to the stage and the grade; pTa is of good prognosis (> 90% are cured); prognosis is uncertain in pT1 and G2 tumours, where cytogenetic findings may be relevant prognostic indicators. 20% survival at 1 year (stable at 3 years) is found in T4 cases; however, identification of individual patient's prognosis is often difficult, although of major concern for treatment decision and for follow up.

**Cytogenetics**

**Cytogenetics Morphological**

Highly complex: pseudo diploid karyotypes with only a few abnormalities in early stages, evolving towards pseudo-tetraploides hyper complexes karyotypes with numerous unrecognizable markers in advanced stages; pseudo-octoploidy may arise; the most frequent anomalies are: +7, -9, -11 or del(11p), del(13q), del(17p), and rearrangements of chromosomes 1, 5, and 10; monosomy 9 is a very early event, that may even appear at the dysplastic stage; we will use indifferently the terms deletion and loss of heterozygocity (LOH) for chromosome regions, and preferably LOH for genes.

**Chromosome 3**: implicated in 30%, mostly in complex karyotypes; amplifications 3p21-24, 3q24 have been found; del(3p) is associated with high grade/stage.

**Chromosome 4**: deletions in 20%, in particular in 4p16 and 4q13-23; amplification of 4q26 has been noted.

**Chromosome 5**: i(5p) occurs in 35% of cases.

**Chromosome 6**: del(6q) in 25%; may be correlated with tumour invasion.

**Chromosome 7**: trisomy 7 is frequent in this cancer, as well as in many other cancers, but also in normal tissues; may still be of bad prognostic significance.

**Chromosome 8**: del(8p) in 25%; deletion of 8p12-pter, 8p22 in particular, may be associated with high grade/stage; gains of 8q (especially 8q23-qter) may be associated with tumour progression; however, C-MYC (8q24) is rarely amplified.

**Chromosome 9**: monosomy 9 or deletions of chromosome 9 are found in about 50% of cases; at times found as the sole anomaly, demonstrating that it is an early event, found equally in TPa stage and in more advanced stages; not associated with a given grade, and not correlated with P53 expression; it has, however, recently been hypothesised that monosomy 9 could indicate a risk of recurrence; LOH appear to be numerous with a given chromosome (e.g. LOH in 9p21, 9q22, 9q31-32, 9q33 and 9q34), but loci remain to be precised, as reports are controversial; homozygous deletions of CDKN2A/MTS1/P16 (9p21) have been documented; LOH + mutation on the second allele of CDKN2A are rare, but of significance; CDKN2A is implicated in Pta stage but not in PTIS, where P53 is found mutated; CDKN2B/INK4B/P15 (9p21) is also implicated in a small subset of cases; PAX5 (9p13) may be over-expressed in tumours; GSN (9q34) has a very low expression in tumours in comparison with its expression in normal bladder; LOH + mutation on the second allele of TSC1 (9q33-34) has recently been described.

**Chromosome 10**: del(10q23-25) has been noted; PTEN (10q23), appears to be implicated in a very few percentage of cases (homozygote deletion has been found); Fas/APO1/CD95 (10q24); loss of one allele and mutation in the second allele has been reported; a hot-spot of mutations has been determined; amplification 10q13-14 has been found.

**Chromosome 11**: monosomy 11 or del(11p) is found in 20 to 50% of cases, more often in high grade and invasive tumours, associated with tumour progression, often found at the time of tetraploidisation; LOH in 11p15.1-p15.5; HRAS1 (11p15.5) is mutated in 15% of cases; amplifications of 11q13-22 have been noted, but would not be a prognostic factor.

**Chromosome 12**: del(12q) in 20%; amplification of 12q13-15 and/or 12q15-24 may be found.

**Chromosome 13**: del(13q) is found in 25% of cases; correlated with high grade/stage; an altered Rb (13q14) is expressed in 30 to 40% of tumours; these are high
stage, invasive, and indicate a short survival; 90% of tumours expressing Rb are invasives; disruption of the normal P16-Rb interactions have been documented, with hyperexpression of Rb and loss of function of P16; amplification in 13q21-31 has been noted.

**Chromosome 14:** del(14q) in 25% of cases (especially 14q12 and 14q32); may be associated with tumour progression.

**Chromosome 17:** del(17p) in 40% of cases; LOH are mainly in 17p12-13, 17q11-22, and 17q 24-25; del(17p) is a late event, mainly found in pT2 to pT4; also found in a subset of pTIS, which might be a relevant prognostic indicator for these tumours; P53 (17p13) alterations are correlated with grade and stage (often PT3), and tumour progression; P53 is mutated in more than 50% of high grade/stage tumours, and in most PTIS; P53 is a prognostic factor: by high grade/stage tumours, those expressing P53 are of better prognosis; by low grade/stage, those not expressing P53 are of better outcome; there is usually LOH + mutation on the second allele of P53; ERBB2/P185 (17q21) is expressed in high grade/stage tumours, in metastases, and is associated with relapses; NF1 (17q11) expression may be very low in tumours; amplification of 17q22-23 has been noted.

**Chromosome 18:** del(18q) in 25%; associated with high grade/stage; amplifications of 18q11 and 18q22 have been found.

**Chromosome 22:** amplification of 22q11-12 has been noted.

**Chromosome Y:** Y loss in 30%; probably not associated with stage, grade, Ki67, or P53 expression.

**Other:** double minute are found in high grades/stages; multifocal tumours exhibit genomic instability; this genomic instability is already present in normal tissues and is increased in tumour tissues from the same specimens, suggesting that a general genetic instability is a reason for multifocality.

### Cytogenetics Molecular

Flow cytometry for DNA index measurement has been used in the past, but comparative genomic hybridization (CGH) is now a major tool for deletions and duplications determination; multi-FISH (M-FISH) could be very useful in early-stage cases (with pseudodiploid karyotypes) to determine structural rearrangements.

### Genes involved and proteins

**Note**
The process 1- is multistep, 2- can take major and minor routes, still to be determined; genes involved in transitional cell carcinoma of the bladder are therefore numerous and most are still unknown; some are quoted above.

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