Bladder cancer epidemiology – Histological classification, geographical differences and temporal trends in incidence

Symposium „Occupation, Aromatic Amines, Polycyclic Aromatic Hydrocarbons and Bladder Cancer“

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Dr. Klaus Kraywinkel (National Center for Cancer Registry Data, Robert Koch-Institute, Berlin)

Dipl.-Soz. Wolf Ulrich Batzler (Epidemiological Cancer Registry of North Rhine-Westphalia, Muenster)
Bladder Cancer – histological types

- ~95% urothelial tumours
- Other tumours are:
  - Squamos
  - Glandular
  - Neuroendocrine
  - Melanoma
  - Sarcoma
  - Lymphoma
  - miscellaneous

from: de/wikibooks.org
WHO histological classification of tumours of the urinary tract

Histological coding & topography coding (C67) = Coding of diseases (ICD-10)

Infiltrating urothelial carcinoma 8120/3
- Micropapillary 8131/3
- Lymphoepithelioma-like 8082/3
- Sarcomatoid 8122/3
- Giant cell 8031/3
- Undifferentiated 8020/3

Micropapillary urothelial carcinoma 8131/3
- Inverted 8121/0

Lymphoepithelioma-like 8082/3
- Giant cell 8031/3
- Undifferentiated 8020/3

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Undifferentiated 8020/3
- Giant cell 8031/3
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- Sarcomatoid 8122/3

Urothelial carcinoma in situ 8120/2
- Non-invasive papillary urothelial carcinoma, high grade 8130/23
- Non-invasive papillary urothelial carcinoma, low grade 8130/21

Non-invasive papillary urothelial neoplasm of low malignant potential (PUNLMP) 8130/1
- Inverted urothelial papilloma 8121/0

C67 (malignant/invasive)

D09.0 (in situ)

D41.4 (borderline)

D30.3 (benign)

From: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs
World Health Organization Classification of Tumours, 2004
**T-classification and stage grouping**

**T-classification**

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour

- Ta **Non-invasive papillary carcinoma**
  - Tis Carcinoma in situ: "flat tumour"
- T1 Tumour invades subepithelial connective tissue
- T2 Tumour invades muscle
  - T2a Tumour invades superficial muscle (inner half)
  - T2b Tumour invades deep muscle (outer half)
- T3 Tumour invades perivesical tissue:
  - T3a Microscopically
  - T3b Macroscopically (extravesical mass)
- T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
  - T4a Tumour invades prostate, uterus or vagina
  - T4b Tumour invades pelvic wall or abdominal wall

**Stage Grouping**

- Stage 0a Ta N0 M0
- Stage 0is Tis N0 M0
- Stage I T1 N0 M0
- Stage II T2a, b N0 M0
- Stage III T3a, b N0 M0; T4a N0 M0
- Stage IV T4b N0 M0; any T N>0 M0; any T any N M1
Changes in histological classification of urothelial bladder tumours

- **1973 (WHO)**
  - New: 8130/3 *papillary urothelial carcinoma* (formerly viewed as benign)

- **1976 (ICD-O-1)**
  - 8120/0 transitional cell papilloma (not recommended in the German translation)
  - 8120/1 transitional epithelial papilloma
  - 8120/3 transitional epithelial carcinoma n.o.s.

- **1990 (ICD-O-2)**
  - Similar to ICD-O-1, some changes in wording

- **2000 (ICD-O-3)**
  - New: 8130/1 *papillary urothelial neoplasm of low malignant potential*
  - New: 8130/2 *non-invasive papillary transitional cell carcinoma*

- **2004 (WHO)**
  - 8130/3 *papillary urothelial carcinoma* no longer mentioned
  - 8120/3 now: infiltrating urothelial carcinoma (papillary and non-papillary)
  - 8120/0 urothelial papilloma (formerly benign transitional cell papilloma)
  - Grading Low/High (instead of G1-G3)
Bladder Cancer - a challenge for cancer registries and epidemiologists

- Classification not only by malignancy but also by growth pattern (papillary vs. non-papillary) and recently also by genetic stability

- Codes and definitions for the dignity of tumours changed over time
  - especially for:
  - **Non invasive papillary carcinoma**
    - Neither invasive nor in-situ, but carcinoma, relatively good prognosis
  - Urothelial papilloma
    - Benign or borderline?
    - Is a differentiation possible?

- Tendency of multifocal appearance of urothelial cancer in the urinary tract:
  - Urothelial tumours of bladder (C67), renal pelvis (C65) and ureter (C66) are now considered as one disease in most cancer registries (if they arise in the same patient over time) see IACR multiple primary rules
  - Some registries combine C66-C68
How Bladder Cancer is reported in different Cancer registries (ICD-10)

- C67 (Netherlands, England, Poland …)
- C66-C68 (Finland, + D09.0, separately)
- C67, D09.0 (USA, Hamburg)
- C67, D09.0, D41.4 (most German registries, RKI)

- Many cancer registries do not routinely collect in-situ or borderline tumours (or pathologists/clinicians do not routinely report them)
- Very difficult to compare incidence and survival rates and to interpret incidence trends
- Easier to compare mortality rates (over time, between regions) ?!
Some basic bladder cancer statistics

- 27,500 new cases in Germany estimated (2006, incl. non-invasive tumours)
  - 19,400 in men
- 5,442 deaths (3,649 in men)
- In 2007: 3,265 new cases in Westfalen-Lippe (2,450 in men)
  1,692 invasive tumours, 665 deaths
- 78 new cases and 28 deaths in Bochum (2007)
- Crude rate: ~ 50-60/100,000 men/year  
  ~ 20/100 women/year
- Median age at diagnosis 72/74 years
- Lifetime risk: ~ 5% in men; 1.5% in women
- Relative 5 year survival: 70-80% (published results from different countries), >90% for non-invasive tumours
Main histological subtypes (Westfalen-Lippe, 2007)

**Invasive (n=1692)**
- Infiltrating urothelial carcinoma 8120/3 908 (54%)
- Papillary urothelial carcinoma 8130/3 638 (38%)
- Other urothelial carcinoma 24 (1%)
- Other/unspecified malignant tumours 122 (7%)

**non-invasive (n=1536)**
- Non-invasive papillary urothelial carcinoma 8130/2 1447 (92%)
- Urothelial carcinoma in situ 8120/2 87 (6%)
- Non-invasive papillary urothelial neoplasm of low malignant potential (PUNLMP) 8130/1 13 (1%)
## T-stage distribution (Westfalen-Lippe, 2007)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>1011</td>
<td>47.1%</td>
</tr>
<tr>
<td>Tis</td>
<td>77</td>
<td>3.6%</td>
</tr>
<tr>
<td>T1</td>
<td>482</td>
<td>22.4%</td>
</tr>
<tr>
<td>T2</td>
<td>407</td>
<td>18.9%</td>
</tr>
<tr>
<td>T3</td>
<td>110</td>
<td>5.1%</td>
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<tr>
<td>T4</td>
<td>61</td>
<td>2.8%</td>
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<tr>
<td>T unknown</td>
<td>302</td>
<td>100%</td>
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<table>
<thead>
<tr>
<th>Stage</th>
<th>Women</th>
<th>Women</th>
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<tbody>
<tr>
<td>Ta</td>
<td>277</td>
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<td>23</td>
<td>3.3%</td>
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<tr>
<td>T1</td>
<td>140</td>
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<tr>
<td>T2</td>
<td>151</td>
<td>21.9%</td>
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<tr>
<td>T3</td>
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<td>11.1%</td>
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<tr>
<td>T4</td>
<td>23</td>
<td>3.3%</td>
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<tr>
<td>T unknown</td>
<td>124</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Diagrams

![Diagram of T-stage distribution](image)

- **Ta**: 47%
- **T1**: 22%
- **T2**: 19%
- **T3**: 5%
- **T4**: 3%
- **Tis**: 4%
## Grading (Westfalen-Lippe, 2007)

<table>
<thead>
<tr>
<th>Grade</th>
<th>invasive</th>
<th>non-invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (well diff.)</td>
<td>120 (7%)</td>
<td>812 (55%)</td>
</tr>
<tr>
<td>G2 (moderately)</td>
<td>503 (31%)</td>
<td>478 (32%)</td>
</tr>
<tr>
<td>G3/G4 (poorly)</td>
<td>985 (61%)</td>
<td>147 (10%)</td>
</tr>
<tr>
<td>Low</td>
<td>3 (0%)</td>
<td>29 (2%)</td>
</tr>
<tr>
<td>High</td>
<td>11 (1%)</td>
<td>5 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>1622 (100%)</td>
<td>1471 (100%)</td>
</tr>
<tr>
<td>Missing</td>
<td>69</td>
<td>102</td>
</tr>
</tbody>
</table>

**Pie Chart:**
- **G1:** 56%
- **G2:** 32%
- **G3/G4:** 10%
- **Non-invasive:**
  - **G1:** 7%
  - **G2:** 31%
  - **G3/G4:** 61%
Incidence and mortality of bladder cancer in German federal states
Age standardized rates (European standard, per 100,000)
Data from 2005/06 if not otherwise stated
Incidence and mortality of bladder cancer in men
German federal states

Age standardized rates (European standard, per 100,000/year)
Data from 2005/06 if not otherwise stated

- Inzidence incl. in-situ T.
- Inzidence invasive T. only
- mortality

![Graph showing incidence and mortality rates of bladder cancer in men across German federal states.](image)
Incidences and mortality of bladder cancer in German federal states

Age standardized rates (European standard, per 100,000/year)
Data from 2005/06 if not otherwise stated

Men

- Inzidence incl. in-situ T.
- Inzidence invasive T. only
- mortality

Women

- Inzidence incl. in-situ T.
- Inzidence invasive T. only
- mortality

[Graph showing incidences and mortalities for men and women in different federal states]
Incidence and mortality of bladder cancer in selected countries

Age standardized rates (European standard, per 100,000)
Data from 2006 unless where otherwise stated

- Incidence incl. in-situ T. (C67, D09.0)
- Incidence invasive T. only (C67)
- Mortality (C67)

*2005 **2002-2005

Men

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence incl. in-situ T. (C67, D09.0)</th>
<th>Incidence invasive T. only (C67)</th>
<th>Mortality (C67)</th>
</tr>
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<tbody>
<tr>
<td>Poland</td>
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<td>Germany estim.</td>
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<td>Hongkong</td>
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Women

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Long term trends of incidence of bladder cancer in men for selected countries
age standardized rates (European standard, per 100.000/year)
3- year averages
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Long term trends of incidence of bladder cancer in men for selected countries
age standardized rates (European standard, per 100,000/year)
3-year averages

- Saarland, C67
- US (SEER) C67+D09
- Finland, C66-68
- UK C67
Long term trends of incidence and mortality of bladder cancer in men for selected registries
age standardized rates (European standard, per 100.000/year)
3-year averages
Long term trends of incidence of bladder cancer in men for selected countries
age standardized rates (European standard, per 100.000) 3- year averages
Comparison of recent trends in bladder cancer incidence for men in two German registries, 1993-2006
age standardized rates (European standard, per 100,000)
3-year averages
Comparison of recent trends in bladder cancer incidence for men in two German registries, 1993-2006
age standardized rates (European standard, per 100.000)
3- year averages
Summary

- Up to 50% of bladder cancer cases in population based registries are non-invasive.
- To interpret time trends, it seems advisable to combine invasive and non-invasive tumors of the bladder.
- To compare incidence between regions, check what exactly cancer registries report as 'bladder cancer' (and which classification they use).
- Compare mortality rates and trends too.
- For cohort studies, exact definitions of the endpoint 'bladder cancer' are required.
- To get appropriate reference rates, classification changes and possible lack of completeness must be considered ("Contact your local cancer registry").
Thanks to

• My colleagues at the cancer registries of the ‘neuen Bundesländer‘ (GKR), NRW, Hamburg and Bremen for background information and data
• My coworkers at the RKI for advice

Contact: k.kraywinkel@rki.de