UICC Technical Report Series – Volume 60

# Bladder Cancer

A Series of Workshops on the Biology of Human Cancer
Report No. 13

*Edited by P. Skrabanek and A. Walsh*

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# BLADDER CANCER

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TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| 4-ABP | : | 4-aminobiphenyl |
| AMSA | : | 4'-(9-acridinyl-amine) methane sulphon-M-anisidine |
| BCPN | : | N-butyl-N-(3-carboxypropyl)nitrosamine |
| BHBN | : | N-n-butyl-N-(4-hydroxybutyl)nitrosamine |
| CEA | : | Carcinoembryonic antigen |
| CIS | : | Carcinoma in-situ |
| DBN | : | N,N-dibutylnitrosamine |
| DDP | : | cis-platinum; cis-diamminedichloroplatinum(II) |
| EHBN | : | N-ethyl-N-(4-hydroxybutyl)nitrosamine |
| FANFT | : | N-[4-(5-nitro-2-fryl)-2-thiazolyl]formamide |
| FNT | : | formic acid 2-[4-5-nitro-2-furyl)-2-thiazolyl]hydrazide |
| 5-FU | : | 5-fluorouracil |
| HTB | : | heterotopically transplanted bladder |
| MMC | : | mitomycin C |
| MNU | : | N-methyl-N-nitrosourea |
| 2-NA | : | β-naphtylamine; 2-naphthylamine |
| NFTA | : | N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide |
| TTP | : | Thio-TEPA; N,N',N''-triethylene thiophosphoramide |

## PREFACE

This workshop on Bladder Cancer, sponsored by UICC, was held at the UICC Headquarters in Geneva from June 1 to June 5, 1981. Eleven people representing a wide variety of disciplines and from various countries, all active workers in research into the basic problems of Bladder Cancer or in patient management, were brought together for a week of intense discussion with the object of producing this Technical Report.

The purpose was to summarize present knowledge of the aetiological factors, pathology and biology of Bladder Cancer; to indicate how this knowledge might influence treatment and to collate ideas pointing to future research. Each member of the Workshop was assigned a topic and asked to prepare and distribute in advance a working paper. During the daily sessions each topic was discussed in depth and at length and changes were made in the text to reflect the consensus of the whole working party.

As Chairman, I am deeply grateful for the dedicated professionalism of every member of the group, all of whom worked long hours, often into the night, to revise the texts in the light of the discussions.

This Report is in no sense and indeed could not be a total review of Bladder Cancer. It was, for example, no part of our brief to consider the relative merits of radio-therapy and/or surgery in the treatment of invasive cancer.

We were, however, aware that there is some polarization on the two sides of the Atlantic, with cystectomy gaining favour in North America but being used less in parts of Europe: no doubt this reflects the doubts of urologists about what is best for the patient. Bladder Cancer presents an almost unique spectrum: at one end of the scale there is a large number of patients, those with low-grade, non-invasive papillary tumours, who

should do very well with transurethral surgery complemented perhaps with topical chemotherapy. At the other end of the scale are those patients with deeply invading solid tumours, most of whom have a gloomy prognosis. In between these two extremes there is a very significant number of patients whose survival and quality of survival depend on the judgment of the urologist who makes the diagnosis. In this middle group, failure to treat radically at an early stage may doom the patient to death from cancer whereas unnecessary radical treatment may have equally unpleasant consequences. Much of our effort is directed to making judgement easier.

The stratification of patients using evidence additional to stage and grade is beginning but as yet it is uncertain how far this process will aid difficult individual decisions.

In this connection, it rapidly became clear during the workshop that we must clarify our thinking about carcinoma-in-situ: hence the inclusion of a special chapter on this subject which is not based on a working paper but is the distillation of the combined efforts of five members of the group - Doctors Murphy, Oyasu, Soloway, Walsh and Webb.

We must acknowledge the debt that this workshop and other UICC workshops owe to the inspiration of Dr Donald Metcalf.

As for Dr Delafresnaye, Executive Director of UICC, I can do no better than quote the words of Dr Cohn, chairman of a previous workshop, who wrote of Dr Delafresnaye "he made the entire project possible and enjoyable, a difficult task when you consider that 11 strangers came together in a new environment for the specific purpose of working very hard".

The key task of collating all the material, consolidating the bibliographies and editing every chapter has been carried out with superb and gentle efficiency by Dr Petr Skrabanek. Every member of the Workshop is immensely grateful for Dr Skrabanek's untiring work.

Anthony Walsh, F.R.C.S.I.

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June 1981

# CHAPTER 1

## PATHOLOGY*

1. Introduction

2. Classification of bladder carcinoma, grading, staging

3. Metastatic spread in fatal cases

4. Pathogenesis and histogenesis

5. Ultrastructural studies

6. Cytology

* based on the working papers of W.M. Murphy and J.N. Webb

## 1. INTRODUCTION

Bladder cancer is a disease of worldwide distribution and varied incidence and histology. In the USA, for example, this disease accounts for approximately 30,000 new cases and 10,000 deaths per year. The vast majority of bladder cancers are carcinomas and, with the exception of predominantly squamous carcinoma in areas where Schistosoma haematobium is endemic, 90% of the carcinomas are of the transitional-cell type. Transitional-cell carcinoma was one of the first human cancers to be linked to chemical carcinogens (533) and it is estimated that as many as 20% of cases result from exposure to environmental agents. The disease is heralded by few signs and symptoms although most patients have haematuria, dysuria, and/or frequency by the time their neoplasms are well established. Empirical observations over the past century have revealed two basic types of bladder carcinoma, superficial papillary and solid infiltrating, each having a rather distinctive histology and cytology. Recognition of these tumours and their precursors, an essential step in the development of effective therapy, is currently one of the most exciting areas of bladder cancer research.

## 2. CLASSIFICATION

There are already many publications describing the various types of bladder tumours which are broadly in agreement with the W.H.O. publication (7, 224, 357, 440). (The term urothelial is taken to be synonymous with transitional-cell). The epithelial tumours are classified as follows:

1. Urothelial papilloma.

2. Urothelial carcinoma.
   - i) Papillary, superficial.
   - ii) Solid, infiltrating.
   - iii) Papillary and solid infiltrating.
   - iv) Carcinoma-in-situ.

3. Squamous carcinoma.

4. Adenocarcinoma.

5. Mixed forms, i.e. any combination of urothelial, squamous and glandular carcinoma.

6. Undifferentiated carcinoma.

Some words of explanation are required for this classification. Papillomas are rare tumours as currently defined. These tumours have fine papillary processses with a delicate fibro-vascular stalk covered by urothelium which does not differ in any appreciable degree from normal bladder urothelium. It is unhelpful in clinical practice to refer to small, superficial Grade 1 papillary carcinomas as "papillomas" and is not in accord with accepted classifications. However, it should be added in parentheses that some academically minded pathologists may have reservations about labelling a superficial papillary lesion which closely resembles the epithelium from which it is derived as carcinoma particularly when there may be no evidence of invasion over a period of years.

Koss estimates that 90% of bladder tumours are papillary when first seen (359). It has also been estimated that 90 to 95% of bladder tumours are urothelial carcinomas (419). Of these perhaps 80% are papillary. However, in a recent study of 106 consecutive new cases of urothelial carcinomas in Edinburgh, U.K., 68 were papillary (64%) (105). This may indicate a changing pattern of the disease, but perhaps it is more likely that there are distinct geographic differences. Friedell et al (223) have analysed a series of 457 bladder tumours of which 76% were classified as urothelial carcinomas and 14% as squamous carcinomas.

TABLE 1.1 (adapted from Friedell et al [223])

457 cases of bladder tumour

| TYPE | | | NUMBER |
|---|---|---|---|
| Papilloma | | | 2 |
| Urothelial carcinoma | | | |
| 1. | Superficial papillary (Ta) | (167) | |
| 2. | Invasive | (172) | 346 |
| 3. | Ca-in-situ | ( 7) | |
| Squamous carcinoma (invasive) | | | 63 |
| Adenocarcinoma | | | 2 |
| Carcinoma - mixed pattern (invasive) | | | 19 |
| Undifferentiated carcinoma | | | 8 |
| Others | | | 17 |

This is a much higher incidence of squamous carcinoma than almost all other reported series from Europe and North America. Probably an incidence of between 1 and 5% would be nearer most pathologists' experience of squamous carcinoma of the bladder except for those parts of the world such as Egypt where such tumours are common.

Grading

The generally accepted grading system is to place urothelial carcinomas into three categories - Grades 1, 2 and 3 (357, 440, 623). Grade 1 tumours are those papillary tumours whose epithelium most closely resembles normal urothelium and show only a limited degree of cellular atypia. At the other extreme, Grade 3 tumours show pronounced atypia: loss of cellular polarity, variation in cell size, increased cell size, pleomorphic often hyperchromatic nuclei, increased nuclear/cytoplasmic ratio and increased numbers of mitotic figures. Grade 2 tumours are an intermediate group falling between the two extremes. In practice it can be difficult to decide whether a given tumour is Grade 1 or 2. A further difficulty arises in that a tumour may not be of uniform grade. For example if the bulk of a tumour is Grade 1 or 2 but a small focus is of Grade 3 - should such a tumour be classified as a Grade 3 tumour? And if so, how much or how little of the worst grade must there be to classify it as such? In practice with tumours of variable grade, we accept the highest grade however small that area may be.

In the UICC booklet of 1978 (623), Grade 3 tumours also include undifferentiated carcinomas, i.e. those tumours lacking any features of a urothelial origin. It is likely however that many pathologists do not follow this particular grading guide-line so that this has to be borne in mind when comparisons are being made between series from different institutions. It is unclear whether squamous and adenocarcinomas should be graded on the same lines as urothelial carcinomas but one suspects that this is commonly practised.

Inevitably in a disease with such varied manifestations, different centres will give different incidences for the various grades of urothelial carcinoma. In a recent survey of 106 consecutive new cases of urothelial carcinoma seen at the Western General Hospital, Edinburgh (105), the cases were distributed almost equally amongst the three grades.

The grade of a urothelial tumour appears to correlate well with the ploidy of the nucleus (616) in that is has been shown that Grade 1 tumours are usually near diploid as defined by modal DNA content whereas

Grade 3 tumours are aneuploid. Grade 2 tumours may be near diploid or aneuploid. These findings in a certain sense re-inforce and give an objective basis for the histological grading of these tumours.

Staging

The UICC (623) has drawn up rules for classifying bladder carcinoma. This is a clinical classification describing the extent of malignant disease, and is known as the TNM system. The T category refers to the primary tumour, N category to lymph node involvement and M to distant metastases. Although the assessment of the extent of a malignant disease is generally known as "staging" this term is, strictly speaking, not applied to the TNM system, presumably to distinguish it from all other systems of recording extent of malignant disease, and from which it differs significantly.

The T categories may be summarised as follows:

TIS = Carcinoma-in-situ

$T_a$ = Entirely superficial papillary tumour (i.e. non-invasive)

$T_1$ = Invasion of lamina propria

$T_2$ = Invasion of superficial muscle

$T_3$ = Invasion of deep muscle or peri-vesical fat

$T_4$ = Invasion of adjacent extra-vesical structures, e.g. prostate, vagina, pelvic wall.

Rules are also described for pathological "staging" which is given the prefix p, e.g. pTa etc. These rules specify that the pT category is based on examination of the definitive surgical specimen. However, since in some countries, partial or total cystectomy is now relatively infrequently performed, the pT classification has decreased somewhat in importance. The surgical pathologist, one suspects, may have difficulty in deciding whether or not a pT category should be assigned to a particular surgical specimen. (A transurethral resection may represent the definitive surgical specimen). If the pathologist sees extensive muscle fragments infiltrated by tumour in

such a specimen he has no means of knowing whether it is superficial or deep muscle as defined in the UICC booklet. There is an element of confusion here which requires to be resolved. Probably the best course is for the pathologist simply to describe any invasion and to leave the classification to the physician who would supplement his T classification with the information supplied in the pathological report of the definitive resection specimen.

A careful search for evidence of invasion of lymphatic or vascular channels by carcinoma should be made by the surgical pathologist since there is evidence that this finding adversely affects the prognosis (325). However, more work is required in cases of low grade $T_1$ carcinomas to see if the prognosis is significantly affected where the pathologist can identify lymphatic or vascular invasion.

In general one may say that the extent of invasion or lack of it correlates with the grade of the tumour, i.e. Grade 3 tumours tend to be deeply invasive while Grade 1 tumours are superficial. Friedell et al (223) have analysed the Grade of urothelial carcinoma in relation to invasion as follows:

| GRADE OF TUMOUR | 1 | 2 | 3 |
|---|---|---|---|
| Percentage of invasive cases | 6% | 52% | 82% |

One final point about "staging" of bladder tumours concerns the histological changes in selected biopsies from normal mucosa in tumour-bearing bladders. There might be a case for incorporating into the existing TNM system a notation whereby any atypia in "normal" mucosa adjacent to a tumour and more remote from it can be recorded in a standardised manner.