

Impact of carcinoma *in situ* of the bladder in the UK

WERANJA RANASINGHE, LUKE HOUNSOME, JULIA VERNE AND RAJ PERSAD

Although the incidence of carcinoma *in situ* of the bladder is increasing in men, it is not currently considered a reportable malignancy in the UK. The authors advocate increased awareness of the condition, given its aggressive nature and need for early detection and initiation of treatment.

BOX 1. Characteristics of carcinoma *in situ* of the bladder^{13–17}

RISK FACTORS

- Male gender
- Increased age
- Smoking status
- Occupational carcinogens
- Genetic mutations such as p53, RB and PTEN

PRESENTATION

- Irritative bladder symptoms: dysuria, frequency, urgency or nocturia
- Up to a quarter of patients are asymptomatic
- Suprapubic fullness or pain
- Back or flank discomfort
- Lower abdominal pain, or pelvic-perineal pain
- Fewer than half of patients have macroscopic or microscopic haematuria

to be effective against primary CIS, a significant proportion of patients still progress to muscle-invasive disease.⁵

CHALLENGES IN IDENTIFYING THE INCIDENCE OF CIS

Previously, CIS of the bladder was categorised along with bladder carcinoma, but with the introduction of the World Health Organization/International Society of Urological Pathology classification in 1998, it has been recognised as a separate entity.⁶ Unlike other premalignant '*in situ*' conditions, CIS of the bladder is recognised as a high-grade malignancy by definition, because of its high rates of progression and recurrence.^{1,2,7,8} In spite of this, CIS of the bladder is not currently considered a reportable malignancy in many countries, including the UK, and is therefore not registered as a malignant condition and not included in the bladder cancer statistics because of its nomenclature.⁹ As a result, the incidence of CIS of the bladder in many countries is unknown. However, an estimated 5–19 per cent of bladder carcinomas are shown to be CIS.³

Weranja Ranasinghe, MB ChB, MRCS(Ed), Urology Trainee, Alfred Hospital, Melbourne, Australia; **Luke Hounsome**, BSc, PhD, Principal Cancer Intelligence Analyst, South West Public Health Observatory, Bristol; **Julia Verne**, BSc, MB BS, MSc, PhD, FFPH, Director, South West Public Health Observatory, Bristol; **Raj Persad**, MB BS, FRCS, ChM, FRCS(Urol), FEBU, Consultant Urologist, University Hospitals Bristol NHS Foundation Trust

Carcinoma *in situ* (CIS) of the bladder is a flat, high-grade, non-invasive urothelial carcinoma.¹ This can occur in isolation in the bladder urothelium with no previous or concurrent papillary tumours (primary), during the follow-up of patients with a previous papillary tumour (secondary) or in the presence of papillary tumours (concurrent).^{2–4} The diagnosis of CIS of the bladder can be challenging because of the non-specific nature of presentation (Box 1). Although Bacille Calmette-Guérin (BCG) therapy is shown

Non-registration of a malignant condition can have significant implications on awareness and treatment, especially in CIS of the bladder, which warrants early detection and initiation of treatment. In the UK, CIS of the bladder is recorded separately from T1+ tumours and may not be reported as a malignant condition, while in Australia, CIS is not recorded or reported to cancer registries. Thus, we have demonstrated that, while the incidence of bladder cancer is declining

in Australia, the incidence of CIS of the bladder is increasing significantly without being noticed.¹⁰

TRENDS OF BLADDER CANCER AND CIS OF THE BLADDER IN THE UK

Bladder cancer is the fourth most common cancer in males in the UK, with an incidence of 18.8 per 100 000, and is the 11th most common cancer in females (incidence of 5.6 per 100 000).¹¹ Bladder cancer has shown an overall decrease in incidence of about 30 per cent over the past two decades.¹¹ One of the reasons for this decline is thought to be as a result of the reclassification of bladder tumours in the 1990s, where CIS of the bladder and bladder tumours of uncertain behaviour were recognised as separate entities.¹¹ However, the overall decrease in the trend of bladder cancer is largely attributed to a reduction in smoking and removal of industrial exposure.¹¹

In contrast, the rates of CIS of the bladder and bladder tumours of uncertain behaviour have increased from 12 to 23 per cent of all bladder neoplasms in the 1990s,¹² while the specific rates of CIS of the bladder have increased from less than 1 per cent in 1986–90 up to 35 per cent in some UK cancer registries in 1996–99.¹² Similar to bladder cancer, these large increases are likely to be the result of changes in the pathological classification and registry coding of bladder tumours by European registries.¹²

On analysis of the more recent data using the National Cancer Data Repository database, primary CIS of the bladder accounted for 17 per cent of all bladder cancers in males and 14 per cent in females in England from 2000 to 2010. In addition, there was a 12.6 per cent increase in the incidence of primary CIS of the bladder in men during this period, with an annual percentage increase of 0.65 per cent change; while the incidence of CIS of the bladder in females decreased slightly by 5 per cent, with an annual percentage

KEY POINTS

- **Carcinoma *in situ* (CIS) of the bladder is a flat, high-grade, non-invasive urothelial carcinoma**
- **CIS of the bladder is not always reported as a malignancy in many countries, including the UK**
- **While malignant bladder cancer appears to be on the decline, the rates of CIS of the bladder are increasing in males in the UK**
- **CIS of the bladder should be considered as a malignant condition and registered in the cancer registry as a malignancy alongside bladder cancer because of its aggressive nature**

.....

decrease of 0.48 per cent. However, the British Association of Urological Surgeons (BAUS) database demonstrated a much lower proportion of CIS: 1.4 per cent in men and 0.8 per cent in females. The BAUS database is voluntary and strongly dependent on submission by the surgeons, and the rates can fluctuate annually. Furthermore, it is possible that surgeons submit the more aggressive cancers to the BAUS database. However, this highlights the fact that, while prominence and awareness should be given to CIS of the bladder, its incidence should be readily available.

In keeping with the decrease in bladder cancer incidence, the mortality rates of bladder cancer in males have decreased by 35 per cent since 1992, which is evident in all age groups apart from men aged over 85 years.¹¹ In contrast, the mortality rates in females have declined by only 20 per cent over the past three decades, with an increase in mortality in females over 85 years similar to that of males.¹¹ Possible explanations for the discrepancy between the decreasing incidence of bladder cancer but increasing bladder-cancer-specific mortality in persons aged over 85 years

could be a result of the lead time bias of bladder cancer, but the impact of the increase on the incidence of CIS cannot be disregarded.

CONCLUSIONS

Given that the incidence of CIS of the bladder is seen to be increasing in males in the UK, it should be considered a malignancy and registered in the UK cancer registries alongside bladder cancer. Increased awareness should be advocated, given the aggressive nature of CIS of the bladder, and early detection and treatment is essential.

Declaration of interests: none declared.

REFERENCES

1. Witjes JA. Bladder carcinoma in situ in 2003: state of the art. *Eur Urol* 2004; 45:142–6.
2. Sylvester RJ, van der Meijden A, Witjes JA, *et al*. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. *Urology* 2005;66(6 Suppl 1):90–107.
3. van der Meijden AP, Sylvester R, Oosterlinck W, *et al*. EAU guidelines on the diagnosis and treatment of urothelial carcinoma *in situ*. *Eur Urol* 2005;48:363–71.
4. Lamm D, Herr H, Jakse G, *et al*. Updated concepts and treatment of carcinoma in situ. *Urol Oncol* 1998;4:130–8.
5. Chade DC, Shariat SF, Adamy A, *et al*. Clinical outcome of primary versus secondary bladder carcinoma *in situ*. *J Urol* 2010;184:464–9.
6. Pascin E, Josephson DY, Mitra AP, *et al*. Superficial bladder cancer: an update on etiology, molecular development, classification, and natural history. *Rev Urol* 2008;10:31–43.
7. Wolf H, Melsen F, Pedersen SE, Nielsen KT. Natural history of carcinoma *in situ* of the urinary bladder. *Scand J Urol Nephrol Suppl* 1994;157:147–51.
8. Lamm DL. Carcinoma in situ. *Urol Clin North Am* 1992;19:499–508.
9. Crow P, Ritchie AW. National and international variation in the registration of bladder cancer. *BJU Int* 2003;92:563–6.

10. Ranasinghe WKB, Attia J, Oldmeadow C, *et al.* Bladder carcinoma *in situ* in Australia: a rising incidence for an under-reported malignancy. *BJU Int* 2013. doi: 10.1111/bju.12052
11. Cancer Research UK. Bladder cancer statistics, 2010. www.cancerresearchuk.org/cancer-info/cancerstats/types/bladder/incidence/uk-bladder-cancer-incidence-statistics
12. Shah A, Rachet B, Mitry E, *et al.* Survival from bladder cancer in England and Wales up to 2001. *Br J Cancer* 2008;99(Suppl. 1): S86–9.
13. Ranasinghe WKB, Persad R. The changing incidence of carcinoma *in-situ* of the bladder worldwide. In: *Advances in the scientific evaluation of bladder cancer and molecular basis for diagnosis and treatment*, ch. 4. Intech, 2013.
14. Williamson SR, Montironi R, Lopez-Beltran A, *et al.* Diagnosis, evaluation and treatment of carcinoma *in situ* of the urinary bladder: the state of the art. *Crit Rev Oncol Hematol* 2010;76:112–26.
15. Castillo-Martin M, Domingo-Domenech J, Karni-Schmidt O, *et al.* Molecular pathways of urothelial development and bladder tumorigenesis. *Urol Oncol* 2010;28:401–8.
16. Cheng L, Cheville JC, Neumann RM, *et al.* Survival of patients with carcinoma *in situ* of the urinary bladder. *Cancer* 1999; 85:2469–74.
17. Hudson MA, Herr HW. Carcinoma *in situ* of the bladder. *J Urol* 1995;153(3 Pt 1): 564–72.