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Chapter 4

The Changing Incidence of Carcinoma In-Situ of the Bladder Worldwide

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Additional information is available at the end of the chapter

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1. Introduction

Bladder carcinoma is the sixth most common cancer worldwide with increasing health-care burden and treatment costs [1-3]. The majority (70%) of bladder cancers are superficial tumours which require close observation with repeat cystocopy, timely resection and long term follow-up. Of these superficial bladder cancers, 10% are carcinoma in situ [4].

Originally described by Melicow in 1952 [5], carcinoma in situ(CIS) of the bladder is defined as a flat (e.g. non-papillary) high-grade non-invasive urothelial carcinoma (transitional cell carcinoma) [6]. An important distinction is that CIS of the urinary bladder, unlike testicular and prostatic CIS, 'in situ' disease is not a precursor to malignancy but is a malignant entity in its own right [6, 7] which has over 50% five-year progression rate in untreated disease and higher recurrence rates [8, 9].

CIS is characterised by a flat 'red velvet' lesion which is usually multifocal and predominantly found in the trigone region, peri ureteral areas and the bladder neck with frequent involvement of the posterior and lateral walls [10]. Extra-vesical CIS is frequently found in the ureters and prostatic urethra.

The microscopic features of CIS (Figure 1) are nuclear anaplasia (identical to that of high grade urothelial carcinoma) containing large irregular, hyperchromic nuclei (3 to 5 times the size of a lymphocyte) and frequent mitotic activity and usually observed in part of or the entire thickness of epithelium in the mid to upper urinary tract [11, 12]. Immunohistologically, these cells also stain diffusely positive for CK20 and expresses p53 [11].

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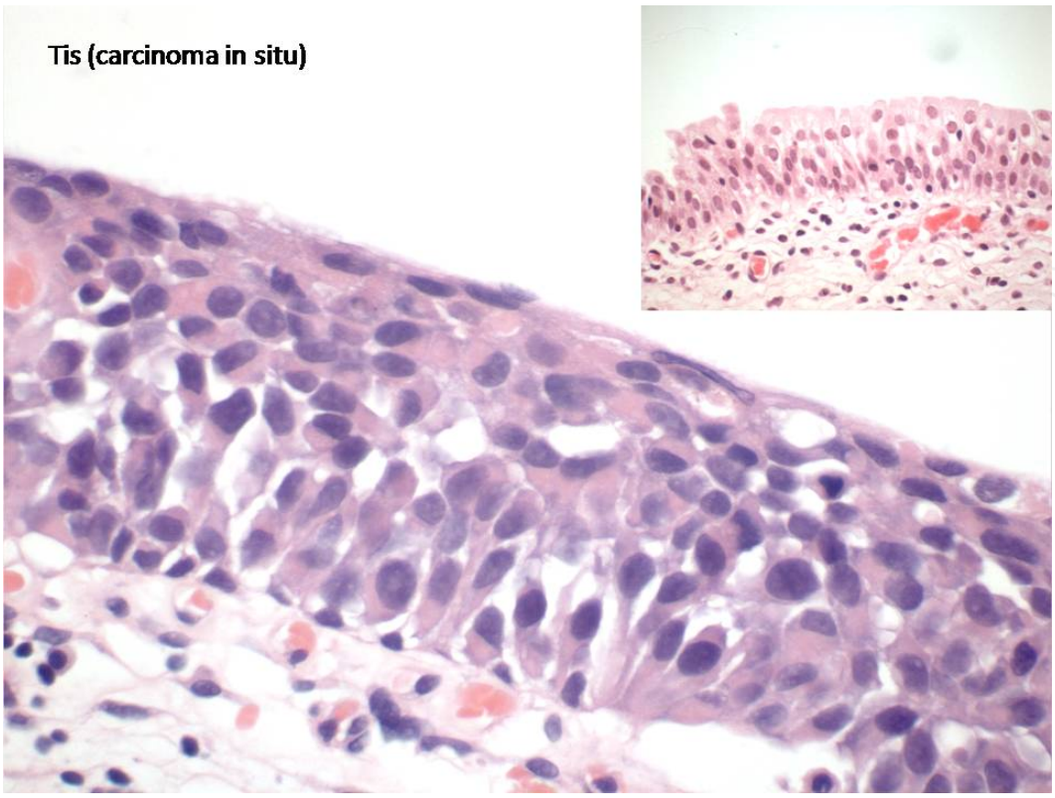


Figure 1. This figure demonstrates the histological features of CIS.

2. Classification of CIS

CIS was previously categorised under the broad term 'moderate/severe dysplasia or marked atypia' [11] where the grade was determined by the degree/severity of dysplasia. However, the grading of bladder cancers has been subject to much controversy and a more comprehensive classification system was published by the World Health Organisation and the International Society of Urological Pathology (WHO/ISUP) in 1998 [13]. The current WHO/ISUP classification states that *'by definition, all CIS are high-grade lesions. CIS should not be sub classified by grade, despite the spectrum of pleomorphism seen within this entity'* [11].

The TNM bladder cancer staging system also acknowledges CIS as a separate entity (Tis); however, it is classified along with the low grade Ta and T1 tumours in bladder tumours.

Different classifications have been suggested in order to stratify risk and prognosis of CIS. One of the methods used to determine the prognosis of CIS was by the presence of symptoms, number of sites of involved (multifocal vs. unifocal) and concurrent CIS with papillary tumours. However these features have not been completely validated [7].

A currently used classification of CIS [7, 10, 14] is:

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- Primary (isolated lesion in the bladder urothelium with no previous or concurrent papillary tumours).
- Secondary (CIS detected during the follow-up of patients with a previous papillary tumour).
- Concurrent (CIS in the presence of papillary tumours).

Primary CIS has a worse outcome with higher rates of progression to muscle invasive disease resulting in a higher rates of cystectomy; but is shown to respond better to BCG therapy compared to secondary CIS [15]. A further study confirmed the higher rates of progression to muscle invasive disease in primary CIS, while concurrent CIS was shown to have the worst survival rates [16]. This highlights the importance of differentiating between the types of CIS in determining the prognosis and also identifying primary CIS early.

3. Incidence

Although increases in the incidences of bladder cancer in the USA, Japan and European countries have been observed in recent decades [1, 2], the incidence of primary CIS remains largely unknown. This is mainly due to bladder CIS being classified as a 'premalignant condition' with other 'in situ' diseases and therefore is a non-reportable condition in many countries. An excellent example is that CIS and pTa bladder carcinomas are registered alongside malignant disease in North America but not the UK [17]. However, more cancer registries are recommended to include CIS as a reportable malignancy, as these 'unreported' increasing incidences can sometimes go unnoticed [18].

The literature suggests that between 5-10% of bladder carcinomas are CIS but this could be as high as 19 % [14]. Our analysis of the Surveillance Epidemiology and End Result (SEER) database [19] revealed an incidence of 14 per 100,000 persons where CIS was the primary coded tumour from 1973 -2009. The incidence of CIS in males and females in the US were 24.9 and 6.2 per 100,000, respectively. In comparison the incidence of malignant bladder cancer was 27 per 100,000 in males and 6.8 per 100,000 in females, for the same duration. In addition, there was a 28% increase in the overall incidence of CIS from 1975, with 27% and 20% seen in males and females respectively. On a Joinpoint regression analysis [20], there was a significant 0.3% annual percentage increase in males since 1990, but not in females. It should be noted that these CIS rates could also include secondary and concurrent CIS.

In Australia the incidence of primary CIS was 20.9 per 100,000 and 6.5 per 100,000 in males and females >50 years respectively, with an 11% and 14% annual increase seen from 2001 onwards [18].

There could be significant variation in the reported incidence of CIS in cancer registry data due to a variety of factors such as inter- observer variability in categorisation of the tumour, coding differences and increasing awareness of CIS. Similarly, re-resection of the tumours can upstage an initial diagnosis of a tumour. In addition, being an unreported malignancy,

there is significant emphasis being placed on the hospital coding to determine the incidence of CIS and it can also be difficult to determine if the diagnoses coded as CIS are histologically proven post biopsy or if they are based on cytology alone. Furthermore, increasing awareness with higher screening or investigation rates could play an important role in increased number of diagnoses of CIS.

These factors provide some limitations for determining the actual incidence of CIS. However, importance of recording the trends of CIS is essential and may help observe for any increases in incidence and initiate awareness and early intervention.

4. Risk factors

4.1. Gender and age

Male gender is a well documented risk factor in bladder cancer with males having a 4.1 fold increase compared to females [1]. As with bladder carcinoma, male gender tends to have a higher preponderance for CIS than females with 3.1-7 times risk of developing CIS [18, 21, 22].

Increasing age is also a risk factor for bladder cancer. The highest incidences of bladder cancer are seen in the >50 year olds [23] while the mean incidence for patients with CIS also occurs between the ages of 65-73 years [21, 22].

4.2. Smoking

Smoking is one of the major risk factors for bladder cancer. Smoking increases the risk of bladder cancer by 2- 6 fold which is augmented by increasing duration and frequency of smoking, while cessation of smoking decreases this risk [2]. The effects of long term smoking are found to carry similar risks for developing bladder cancer in both sexes [24].

Although not many studies have focussed exclusively on the relationship of CIS and smoking, there is evidence to establish smoking as a risk factor for CIS. In a study which focussed only on CIS, the 72% of patients who presented with CIS were either former or current smokers [15]. In a another study of all superficial bladder tumours, which included CIS, showed that those who continued to smoke after the diagnosis of the tumour, had worse bladder cancer related outcomes with a shorter time to disease recurrence, while ex-smokers tended to present with a tumour at a later age [25]. However, the link between smoking and failure of BCG therapy bladder tumours is not very clear [26].

Despite the strong links between smoking and bladder cancer, smoking can only partially account for the incidence of bladder cancer suggesting that other risk factors also contribute to the risks [27].

4.3. Schitosomiasis infection

Schistosoma haematobium or Bilharzia is a known pathogen for causing bladder cancer in the prevalent areas and accounts for about 3% of the world bladder cancer [2]. Infection with schistosomiasis increases the risk of bladder cancer by 5 fold and accounts for majority of the incidence squamous cell bladder cancers [2]. However, CIS has been also seen in patients with Schistosomial infection where the pathogenesis is thought to be linked to chromosomal loss [28].

4.4. Occupational carcinogens

There is a well established link between occupational carcinogen and bladder cancer with an estimated 20- 27% of bladder cancers attributed to occupational exposures. The main carcinogens associated with industrial occupational risk are aromatic amines (beta-naphthylamine, 4-aminobiphenyl and benzidine) which are used widely as intermediary compounds in the textile and rubber industries. The risk of occupational bladder cancer is dependent not only on the intensity and characteristics of the workplace exposures, but also on individual susceptibility to these cancers [29]. Similar to bladder carcinoma, CISs also develops in patients exposed to these carcinogens [30] where mutations of the p53 gene is thought to initiate the disease process [31]

4.5. Genes

Polymorphisms in the genes, NAT2 and GSTM1 are the main genetic modulations implicated in the bladder cancer. NAT 2 encodes the N-acetyltransferase 2 enzyme responsible for detoxification of aromatic amines by N-acetylation or activation by O-acetylation, while GSTM1 encodes the glutathione S-transferase M1 enzyme responsible for detoxification of carcinogens such as polycyclic aromatic hydrocarbons and reactive oxygen species. [32] In CIS however, the genetic mutations are different and characterized by loss-of-function of the tumour suppressor genes, such as p53, RB, and PTEN [33]. These genetic changes are discussed in detail in another chapter.

4.6. Diet

Dietary factors are also shown to be linked to bladder cancer. Fruit and vegetative intake correspond inversely with the risk of bladder cancer while there is evidence to show that Vitamin B and yellow orange vegetables (in individuals with the presence of GSTM1) may also reduce the risk of bladder cancer [32]. However, to our knowledge, there are no specific studies looking at the dietary risks and CIS.

5. Presentation

Presentation of primary CIS of the bladder can be very variable (Table 1). Majority of the patients with primary CIS present with only non-specific irritative bladder symptoms such

as dysuria, frequency, urgency or nocturia [15] [21, 22, 34]. Furthermore up to 22- 26% of patients are asymptomatic and less commonly may present with suprapubic fullness or pain, back or flank discomfort, lower abdominal pain, or pelvic-perineal pain [15, 21, 22]. In contrast with bladder cancer, fewer than 45% of the patients have macroscopic or microscopic haematuria in primary disease [22], highlighting the difficulty in diagnosing this condition. In contrast, the patients with secondary or concomitant CIS tend to present with gross haematuria, possibly due to the presence of a papillary tumour [15].

Symptom	% with symptom	
	Primary CIS	Secondary/concomitant CIS
Irritative	28.5(15)	9.8(15)
Asymptomatic	22(15)- 26(22)	21(15)
Macroscopic haematuria	31.2(15)	50.6(15)

Table 1. The percentage of patients presenting with various symptoms of primary and secondary/concomitant CIS.

6. Diagnostic workup

6.1. Biopsy of the red velvet lesion

The diagnosis of CIS can be challenging task due to the flat nature of the lesion, where the mucosa containing the lesion could be unremarkable or simply an erosion [21]. Therefore, biopsy of the lesion is the current advocated method for diagnosis of CIS of the bladder. However, even the characteristic 'red velvety patch' of CIS could be non-specific [21] and the specificity could be as low as 8% [35]. Thus it is recommended that the biopsies of even the normal mucosa are taken in high risk patient or in the presence of positive cytology [14, 21].

In addition, a second look transurethral resection (TUR) and bladder mapping biopsies are frequently warranted to reduce under staging, exclude residual disease and concurrent CIS in patients with other bladder tumours [15].

6.2. White light cystoscopy vs. fluorescent light cystoscopy

One of the difficulties during cystoscopy is the visualisation of this flat lesion in the bladder, which could be inconspicuous under normal white light cystoscopy and can be missed resulting in significantly under-reporting. The recent use of fluorescent light cystoscopy using 5-aminolevulinic acid or hexaminolevulinate has been shown to enhance the detection of CIS by more than 30%- 39% [36, 37] and also to reduce tumour recurrence at 1 and 2 years [38]. When using florescent light cystoscopy, both 5-aminolevulinic acid and hexaminolevulinate are shown to be equally effective at detecting CIS [37]. In addition, the use of HAL when resecting tumours is shown to reduce tumour recurrence in CIS and also in multifocal

tumours [39]. Despite the benefits of fluorescent light cystoscopy, one of its major drawbacks is the high false positive rates. The European Urology Association guidelines recommendations of the use of fluorescent light cystoscopy due to its high sensitivity [14], but it is not universally used in practice due to availability and cost implications.

6.3. Biomarkers

Biomarkers have been widely used in aiding the detection of CIS. Some of the routinely used biomarkers are urine cytology, UroVysion (fluorescent in-situ hybridization - FISH), immunocytology and Nuclear Matrix Protein (NMP22). Of these, urine cytology is the most frequently used in detecting CIS due to its high sensitivity. However the specificity of cytology, FISH and immunocytology are all below 30% limiting the diagnostic accuracy of CIS [40]. Even, NMP22 which has the highest specificity for CIS, is only 43% [40] (Table 2).

Modality	Percentage CIS detected
Biopsy of 'red mucosa'	8-78%(44), (35)
Florescent light cystocopy (using 5-aminolevulinic acid or hexaminolevulinic acid)	92.4%(45).
White light cystoscopy	60.5%(45)
Urine Cytology	90% - 92.3(6, 40)
UroVysion (fluorescent in-situ hybridization - FISH)	83.6(40)
Immune-cytology µCyt	81.3(40)
NMP22	79.1(40)
Combination of FISH+ CYT	85.3(40)

Table 2. The percentage of CIS detected by each modality of testing.

Therefore to optimise the accuracy of diagnosis, it is recommended that these biomarkers should be used in conjunction with each other rather than on their own [21]. The use of cytology and NMP22 together increase the specificity 55% and using all 4 modalities increase the sensitivity to 65% [40]. However, due to lower sensitivities of some of these tests, the overall sensitivity decreases as more tests are combined [40]. Therefore an optimum balance must be used to obtain the best sensitivity and specificity values in diagnosis of CIS.

Another very useful role of biomarkers is to predict response to treatment. A number of biomarkers, urine markers and genetic markers have been evaluated to predict which tumours will fail BCG therapy [41]. Interleukin -2 is shown to be promising in in identifying the tumours which will not respond to BCG therapy. However, currently none of the other markers have large studies or long term validation to predict treatment failure prior to starting BCG [41].

6.4. Screening for CIS

The usefulness of biomarkers as screening tools in detection of CIS is suboptimal. A study which screened a group of 183 smokers using a variety of screening tools, showed the true positive rates for detection of malignant tumours were only 50% for Dipstick, 6% for BladderChek, 37% for cytology and 61% for UroVysion (FISH) [42]. The 2 patients with CIS, had negative results for urine dipstick and cytology but were positive for UroVysion [42]. However, another study showed low cost effectiveness of the use of Uro Vysion as a screening tool, due to its high costs [43]. Thus screening for CIS may not be economically viable.

7. Treatment

Studies have demonstrated that the untreated natural history of CIS has a 50% progression rate to malignant disease at 5 years and even with optimal treatment, progression and recurrence rates are both high [8, 9].

7.1. Tumour resection

Transurethral resection (TUR) is essential in providing histological tissue and reducing the tumour load. When the muscularis mucosa is involved, a re-resection is usually necessary. Despite this, in treatment of CIS, solitary TUR is shown to be inferior compared to TUR when used in conjunction with BCG, with the latter having increased the 10 year progression free survival (71% vs. 50%) [46].

7.2. Intravesical Chemotherapy/Immunotherapy

Intravesical instillation of a chemotherapeutic/immunotherapeutic agent is the mainstay treatment for CIS. A number of agents such as Bacille Calmette-Guerin (BCG), mitomycin C, epirubicin, doxorubicin and adriamycin have been trialed. In comparison trails between these agent, BCG is shown to be superior to other chemotherapeutic agents with higher complete response rates (68% vs. 49%) and higher disease free rates (51% vs. 27%) [14]. Furthermore, the use of BCG with maintenance therapy was also superior to mitomycin C [47].

Despite the advantages of BCG therapy, studies have demonstrated that 20% to 40% fail to respond and progress [41]. In addition, up to 90% of patients experience side effects such as local cystitis symptoms such dysuria, frequency alteration, and occasional haematuria resulting a number of patients not completing the treatment schedule [41].

7.3. Radio therapy

Radiotherapy is a is also used as a treatment modality in bladder carcinoma, where radiotherapy is shown to complete local regression of muscle-invasive bladder cancer in upto 73% of patients [48]. However radiotherapy has been shown to be ineffective against CIS of the bladder. In CIS patients treated with EBRT have demonstrated persistent CIS

after treatment and was shown to be inferior to radical cystectomy [49, 50]. Furthermore in patients with concomitant CIS treated with radiotherapy, the presence of CIS carried a worse prognosis [51].

7.4. Cystectomy

Cystectomy is an important option in treating CIS of the bladder due to its high cure rates in high risk patients [52] and is advocated in high risk patients. This is especially useful in patients who do not respond to BCG, where early cystectomy is shown to improve long term survival [53]. However, studies have shown that the presence of CIS to be an independent risk factor for upper tract recurrence in patients who undergo cystectomy [54]. In patients with prostatic urethral involvement, immediate or delayed urethrectomy is advocated [55].

7.5. Photodynamic therapy

Photodynamic therapy works by light of a specific wavelength that is absorbed by a chemical photosynthesizer, which then transfers this energy to breakdown oxygen molecules into highly reactive intermediates [56]. An advantage of photodynamic therapy is that the whole bladder mucosa can be treated without having to localise multifocal superficial bladder tumours and occult CIS. A number of photo synthesizers have been used such as Hematoporphyrin derivatives and 5-aminolevulinic Acid (ALA). Photodynamic therapy has been shown to be very promising results in treating CIS, and may provide an alternative treatment for resistance disease [56].

7.6. Treatment for Non-intravesical CIS of the bladder

Extra vesical CIS of the bladder is seen most frequently in the ureters and in the prostatic urethra. In upper tract CIS, BCG therapy is shown to be very effective [57] and the long term data is seen to be as effective as nephroureteroctomy [58]. However, patients who undergo radical nephrectomy and have upper tract concomitant CIS have higher rates of recurrence and poorer cancer specific survival [59].

BCG therapy is also effective in patients with CIS of the prostatic urethra and transurethral resection is thought to have no added advantage [60] However, presence of CIS of the prostatic urethra carries a poorer prognosis and in primary high grade bladder cancers treated with BCG, it is recommended that the prostatic urethra is biopsied as it is a prognostic factor for recurrence, progression of disease and bladder cancer specific mortality [61]. Presence of CIS of the prostatic urethra is also an indication for early cystectomy [62].

7.6.1. Current recommendations for CIS

7.6.1.1. Treatment of primary CIS

The American Urology Association (AUA) guidelines [63] recommend re-resection in high grade disease in the absence of muscularis propria in the specimen as standard treatment

followed by an induction course of BCG and maintenance BCG therapy. They suggest that cystectomy also maybe an option in select CIS patients due to high cure rates.

The European Association of Urology (EAU) guidelines [64] state that the BCG installation should be administered for at least 1 year and if the prostatic urethra is involved, TUR of the prostate followed by BCG therapy is recommended for the management of CIS. Unlike the AUA guidelines, cystectectomy is only reserved for BCG failure due to concerns of over-treatment. They suggest 3 monthly follow up cytology with cystoscopy for 2 years and every 6 months thereafter until 5 years followed by annually thereafter. Annual upper tract imaging is also recommended.

7.6.1.2. Treatment of recurrent disease

The AUA guidelines [63] recommend repeat resection in order to aid accurate staging as standard treatment and also recommend cystectomy as an option due to high risk of progression to muscle invasive disease in these patients. They suggest that further intravesical therapy maybe an option.

The EAU [64] guidelines suggest that although further BCG instillation can be beneficial in non-muscle invasive recurrence post chemotherapy, it increase the risk of progression in CIS and they recommend the use of early cystectomy following BCG failure in suitable patients. They further acknowledge that although device assisted chemotherapy instillation and use of concomitant interferon alpha maybe beneficial in select patients, they feel that they are still experimental.

In conclusion, this chapter discusses the incidence, diagnostic difficulty and management of CIS and also the current recommended guidelines.

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