Letter to the Editor

Spinal Cord (2003) 41, 475–477. doi:10.1038/sj.sc.3101469

Should spinal cord clinicians be proactive in preventing spinal cord injuries and decreasing secondary complications caused by spinal cord injury?

We read with great interest the valuable contribution made by Silver¹ on the prevention of spinal cord injuries (SCIs) in rugby players. According to the Foundation for Spinal Cord Injury Prevention, Care & Cure,² many spinal cord injuries are preventable, and as the most effective preventative measures are often those recommended by victims themselves, it urges SCI patients actively to promote such measures.

Clinicians caring for SCI patients are uniquely placed to help develop preventative strategies; they also have a duty to minimise the complications of SCI. Emphasis has traditionally been given to the prevention of pressure sores, deep vein thrombosis and depression. It should not be forgotten, however, that SCI patients are 15.2 times more likely to develop bladder cancer than the general population; moreover, at least part of this increased risk is iatrogenic, relating to bladder drainage regimes.³ Appropriate bladder management (in particular, the avoidance of indwelling catheterisation) not only reduces the incidence of urinary tract infection in the neuropathic bladder,⁴ but may also reduce the risk of bladder cancer.^{3,5}

Not only are SCI patients at greatly increased risk of developing bladder cancer, but their cancer is more likely to be diagnosed at a later stage (Figure 1), less likely to be amenable to surgical treatment and more likely to kill them.⁶ Therefore, if prevention fails, early diagnosis becomes crucial. Cystoscopy traditionally remains the mainstay for detection of bladder cancer but, particularly in SCI patients with chronic or recurrent cystitis and abundant debris within the bladder, even advanced tumours may not be easily recognisable cystoscopically. Yang and Clowers⁷ have shown that cystoscopy does not satisfy the accepted criteria for screening for bladder cancer in SCI patients; one of their patients had a negative cystoscopy only 4 months before presenting with bladder cancer. This is reflected in our recent experience: flexible cystoscopy and biopsy in a 42-year-old male SCI patient showed moderate inflammation with no definite evidence of malignancy (Figure 2). After 3 weeks, however, an open bladder biopsy revealed a widespread, extensively necrotic, keratinising squamous carcinoma of the bladder (Figure 3). The patient died 5 months later.

We, therefore, believe that noninvasive or minimally invasive tests to replace or supplement cystoscopy for the detection of early, premalignant urothelial abnormalities are likely to prove useful in selected SCI patients. This is applicable particularly to those SCI patients with high cervical injuries, who are at increased risk of complications such as intraoperative autonomic dysreflexia and postoperative respiratory or cardiovascular problems. Elderly patients with significant comorbidity would also benefit from such developments, as exemplified by one of our patients. A 66-year-old man had sustained an SCI at the C-6 level about 45 years previously with consequent tetraplegia. He subsequently developed multiple other medical problems including insulin dependent diabetes mellitus, anaemia, renal insufficiency and elevated liver enzymes. This patient underwent cystoscopy and biopsy under spinal anaesthesia died 8 h later from cardiorespiratory failure.

Of particular interest in this context are tests applicable to voided urine samples or bladder washings, such as

- (a) detection of human telomerase mRNA expression in exfoliated cells in bladder washings;⁸
- (b) measurement of bladder cancer-specific nuclear matrix protein BLCA-4 levels in urine;⁹
- (c) immunofluorometric assay for detection of ectopic expression of the DNA replication protein Mcm⁵ (minichromosome maintenance 5 protein) in urine;¹⁰
- (d) microsatellite analysis of exfoliated cells in urine: in one study, three-quarters of the cases of recurrent carcinoma were detected by this method between 1 and 9 months earlier than recurrence became apparent cystoscopically.¹¹

Advances in optical technologies have yielded yet more diagnostic tests that can be carried out during cystoscopy itself, including fluorescence endoscopic imaging and spectroscopy, Raman spectroscopy, optical coherence tomography, light scattering spectroscopy, chromoendoscopy, confocal fluorescence endoscopy and immunofluorescence endoscopy.¹² For example, premalignant changes in epithelial cells can be detected *in situ* by light-scattering spectroscopy.¹³ In light-scattering spectroscopy, the size distribution and chromatin content of epithelial-cell nuclei can be measured by delivering white light from a xenon-arc lamp to the mucosal surface through an optical-fibre probe and collecting the returning light. This has the potential to provide real-time, quantitative evidence of premalignant change in endoscopically invisible lesions without the need for tissue biopsy.

Figure 1 Histology of cystectomy specimen in which transitional cell carcinoma (here showing squamous differentiation) extends through the full thickness of the bladder wall, approaching the inked resection margin (top)

Figure 2 Histology of bladder biopsy taken with flexible cystoscope, showing inflamed, oedematous mucosa with no evidence of malignancy

Figure 3 Histology of the repeat (open) biopsy from the same patient as in Figure 2, showing bladder tissue heavily infiltrated by a keratinising, moderately differentiated, squamous carcinoma

These new diagnostic modalities therefore promise significant improvements in the diagnosis of early lesions by allowing for targeted mucosal biopsies, and perhaps may even provide 'optical biopsies' of

equivalent histological accuracy. Ideally, this enhancement of the endoscopist's ability to detect subtle preneoplastic changes in the mucosa in real time would lead to curative endoscopic ablation of these lesions, and thereby improve patient survival and quality of life.

In summary, therefore, we believe that spinal cord clinicians should be proactive in introducing new diagnostic methods to their clinical practice. Spinal cord clinicians must continue to educate the public about measures to prevent SCI in the first place, and minimise the risk of SCI patients developing bladder cancer by appropriate management of the neuropathic bladder. In addition to these preventative measures, they must also exploit the potential of new tests to detect bladder cancer at an early stage. Full prospective evaluation of both noninvasive tests, performed on samples of urine or bladder washings, and minimally invasive tests performed during cystoscopy, is needed.

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Acknowledgements

The authors thank Mr Gary Hunter, Hunter Urology Ltd, Woodhayes, Honiton, Devon EX14 4TP, and UCI Healthcare Ltd, Charlbury, Oxon OX7 3EW United Kingdom for sponsoring the printing of the colour illustrations in this article.

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