WATER: Washing Away Tumour Cells to Reduce Recurrence in Urothelial Carcinoma

BACKGROUND

Bladder Cancer (BC) diagnosis, staging & natural history. BC is common globally, with more than 3000 new cases diagnosed in Australia annually. Diagnosis and initial treatment involve inspection of the bladder (cystoscopy) and transurethral resection of bladder tumour. Further management is guided by histology with sub-classification by stage (extent) and grade. Most BC present as low-grade NMIBC, which rarely metastasise but frequently recur. This necessitates prolonged follow-up, including repeated cystoscopy to detect and resect recurrent tumours, resulting in high cost, substantial resource utilisation, and detrimental impact on health-related quality of life (HRQoL). Left untreated, recurrent tumours ultimately cause symptoms and concerningly, some can progress to higher-grade or stage, with resulting risk of metastasis or death.

Recurrence risk & mitigation. The risk of recurrence of NMIBC ranges up to 60% at 1 year, depending on risk factors including: tumour stage, grade, size, multiplicity, and prior recurrence. One of the mechanisms known to be responsible for BC recurrence is re-implantation of free tumour cells, with BC known to have a particularly re-implantable phenotype. TURBT leads to the exfoliation of tumour cells, which reimplant into the bladder mucosa, leading to recurrent tumours. Thus, ***effective measures to reduce the numbers of viable implantable tumour cells can prevent recurrences.***

Immediate post-resection chemotherapy. Cytotoxic chemotherapy delivered intravesically (i.e. directly into the bladder) after TURBT reduces recurrence by killing exfoliated tumour cells, preventing reimplantation. An individual patient data meta-analysis (n=2278) of 11 randomised controlled trials (RCTs) assessing intravesical chemotherapy demonstrated a 35% relative reduction in the risk of recurrence. Mitomycin, epirubicin, and pirarubicin were each found to be effective agents, while a subsequent trial has also demonstrated the effectiveness of intravesical gemcitabine. Based on cumulative evidence, current guidelines strongly recommend intravesical chemotherapy within 24 hours of TURBT, particularly for low-risk NMIBC.

Despite the strong evidence favouring intravesical chemotherapy post-TURBT, the ***real-world use of intravesical chemotherapy remains low internationally***. A survey of 259 urologists from the United States found 66% never administer intravesical chemotherapy and only 2% do so for all cases, with overall use in only 171 of 1010 eligible patients. Similarly, a European study of 324 urologists across five countries reported only 413 (43%) of 954 TURBTs were followed by intravesical chemotherapy, with substantial variability of practice. The global RESECT study of TURBT practice found only 42% use of intravesical chemotherapy across contributing sites. Our local survey also documented similar practices in Australia and New Zealand (see Preliminary Data section of Project Methodology). Practical barriers to the delivery of intravesical chemotherapy include the cost of drugs and their instillation, co-

ordinating availability with the timing of surgery, and staff accreditation to handle cytotoxic agents in surgical settings. ***These issues mean that the known and recommended best practice is not routinely used globally.***

Continuous bladder irrigation and recurrence risk. Haematuria, which is common following TURBT, is managed by the placement of a urinary catheter and irrigation of the bladder for a period of time dictated by the duration and amount of bleeding. The primary aim is to wash out blood and prevent it from clotting and occluding bladder drainage, but ***irrigation may also reduce recurrence by washing out exfoliated tumour cells from the bladder that could otherwise re-implant.***

Pooled comparison within the aforementioned meta-analysis of intravesical chemotherapy RCTs showed that bladder irrigation use was associated with a 21% reduction in the relative risk of recurrence, even adjusting for intravesical chemotherapy use and EORTC (European Organisation for Research and Treatment of Cancer) recurrence risk score. BC recurrence was also reduced in two RCTs comparing irrigation to no irrigation, whereas in three RCTs comparing irrigation to intravesical chemotherapy, recurrence rates were comparable in both arms but fewer adverse events (AEs) were observed in the irrigation arm. ***Collectively, these data suggest that bladder irrigation can be considered as an alternative to intravesical therapy***, as summarised in our recent systematic review (see Preliminary Data section of Project Methodology).

However, this interpretation comes with two caveats. Firstly, the extant trials are small, and hence lacked power to detect a true difference. Secondly, the duration of post-operative irrigation, being between 18 and 24 hours, would preclude day-case TURBT, thus adding substantially to costs. Nonetheless, the European Association of Urology (EAU) guidelines have recently been updated to include irrigation as an alternative to consider when post-TURBT chemotherapy is not feasible. The optimal irrigant, volume, and duration of irrigation have not been specified.

Osmotic lytic effects of water used as an irrigant. Isotonic saline is usually used as an irrigant after TURBT and has been used in most studies assessing the effect of irrigation on NMIBC recurrence, including three of the RCTs. ***However, water may be a better choice as, in addition to its mechanical effect of washing out exfoliated luminal cells, it can exert an osmotic lytic effect on cells***, confirmed by in-vitro experiments on cell lines and exfoliated cells.

Initial retrospective clinical studies of water irrigation post-TURBT demonstrated outcomes comparable to intravesical chemotherapy and Bacillus Calmette-Guérin (BCG) instillation. A prospective RCT from India of 24h of water irrigation versus intravesical chemotherapy showed similar relapse-free survival (RFS) at 1 year but fewer adverse events with water irrigation. We have established that bladder cancer cells exposed to water are fully lysed within about an hour, suggesting that a short period of water irrigation following TURBT may be effective at reducing implantable cell numbers. We have also completed a pilot study of 3 hours of water irrigation, establishing feasibility and safety of this approach, as well as demonstrating a striking impact on reducing cell numbers in irrigant effluent to a greater extent than saline.

There is thus a clear rationale to assess whether 3 hours of bladder irrigation using water after TURBT is comparable to intravesical chemotherapy in reducing recurrences.

PROJECT SIGNIFICANCE & IMPACT

The key significance of this trial will be its potential reduction of BC recurrences, leading to substantial cost savings and improved health outcomes in Australia, New Zealand and globally.

Intravesical chemotherapy can reduce recurrence, but is not widely used due to expense, inconvenience, and potential toxicity. Water irrigation is simpler, cheaper, and more feasible to deliver than intravesical chemotherapy, and is likely to result in fewer negative impacts on HRQoL. However, currently there is insufficient evidence regarding its effectiveness compared to intravesical chemotherapy. Practice guidelines have only recently included irrigation as an intervention to reduce bladder cancer recurrence, but only when intravesical chemotherapy is not feasible, and with no specification of duration or the nature of the irrigant.

If established to be non-inferior to intravesical chemotherapy, water irrigation would be feasible to deliver more widely, as many of the barriers to current use can be overcome. Globally, this will have substantial health and health economic benefits, especially in poorly resourced health care settings. For example, intravesical chemotherapy has significant logistical issues in rural and remote Australia, unfairly impacting those communities, including Aboriginal and Torres Strait Islander people. Conversely, water irrigation would be easily achievable at any centre providing urological services, including in these settings.

Even in well-resourced settings, water irrigation will provide an intervention for reducing NMIBC recurrence that can have wider, even near-universal, uptake, in contrast to intravesical chemotherapy. ***The optimal outcomes related to current best practice (intravesical chemotherapy), not currently being achieved due to poor uptake, could therefore be realised by using water irrigation.***

If the trial does not demonstrate non-inferiority of water compared to intravesical chemotherapy, there will still be benefit because participating sites will have better established processes for delivering intravesical chemotherapy post-TURBT. This will help overcome many of the existing barriers to use of this recommended standard of care. ***Thus, regardless of the outcome of the study, it will lead to improved clinical practice and optimization of evidence-based care.***

The wider implementation of effective strategies to reduce recurrence rates of bladder cancer will reduce the patient burden of symptoms and other issues related to recurrent tumours. Fewer recurrent tumours will mean lower need for ongoing surveillance and subsequent treatments such as invasive surgery. Progression to advanced or metastatic disease will also be reduced. ***All of these improvements will result in lower morbidity, health care expenditure, and symptom burden, with improved health related quality of life and survival.***