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ORIGINAL ARTICLE

A phase 2 pilot study of water irrigation after transurethral resection of bladder tumor (WATIP) demonstrating safety, feasibility and activity

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Abstract

Purpose Non-muscle-invasive bladder cancer (NMIBC) can recur, partly due to seeding of free tumour cells after transurethral resection of bladder tumour (TURBT). Intravesical chemotherapy post-TURBT can reduce the risk but is used infrequently and inconsistently due to cost, complexity and side effects. The objective of this study was to prospectively assess continuous bladder irrigation using water, which may be a safer and easier alternative with comparable effectiveness.

Methods WATIP was a prospective, single-arm phase 2 study of water irrigation during and for at least 3 h after TURBT for bladder tumours noted on imaging or flexible cystoscopy. Participants were assessed clinically for adverse effects and with blood tests within 24 h for sodium, haemoglobin and lactate dehydrogenase. The primary endpoints were safety (defined as < 10% adverse events of CTCAE grade ≥ 3), and feasibility (defined as the intervention being delivered as planned in > 90% of cases) and secondary endpoint was recurrence-free rates (RFR).

Results Water irrigation was delivered as planned in 29 (97%) of 30 participants (median age 67 years, 25 (83%) males). The only adverse event (grade 2) was clot retention in one (3.3%) participant. Water irrigation significantly reduced urothelial cell counts in catheter effluent over time, unlike saline irrigation which did not. RFR was 56.2% (9/16 participants with low-risk NMIBC) at first cystoscopy (median interval 108 days) and 62.5% (5/8 evaluable low-risk NMIBC) at 12 months.

Conclusion Water irrigation during and after TURBT is feasible and safe. Prospective assessment of its effect on NMIBC recurrence compared to post-TURBT intravesical chemotherapy is needed before recommending its use in routine clinical practice.

Trial registration ANZCTR registration ID ACTRN12619000517178 on 1 April 2019.

Keywords Urinary bladder neoplasms · Therapeutic irrigation · Neoplasm recurrence · Local · Clinical trial · Administration · Intravesical

Introduction

Globally, bladder cancer remains a significant problem despite some improvements in incidence and mortality over time [1]. Most bladder cancers present at a non-muscle-invasive stage (NMIBC), and although associated with a low risk of progression to invasion or metastasis, can frequently recur (in 15–60% over 12 months) [2]. This necessitates repeated cystoscopic surveillance and treatment over many years, leading to a significant medical and financial burden.

Conventional transurethral resection (TURBT) of bladder cancer leads to exfoliation of cancer cells into the bladder lumen, shown to implant on the urothelium, thereby contributing to subsequent recurrence [3]. Intravesical instillation of cytotoxic chemotherapy within 24 h of TURBT reduces recurrences, as demonstrated in multiple randomised clinical trials (RCT) [4, 5]. Although current guidelines strongly recommend intravesical chemotherapy immediately after TURBT [6, 7], usage remains sporadic and relatively infrequent [8–10]. Cost, potential morbidity and complexities in administration contribute to its low uptake [9, 10].

Continuous bladder irrigation is often utilised following TURBT, primarily to manage haematuria. There is some

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evidence that continuous bladder irrigation may also reduce recurrence, putatively by washing out exfoliated cancer cells, preventing their reimplantation [11]. However, although continuous bladder irrigation was shown to be comparable to intravesical chemotherapy in three RCTs, the trials are each small and lacking in power to conclude non-inferiority [12–14]. In addition, most studies assessing the effects of continuous bladder irrigation on recurrence after TURBT have utilised 24 h of irrigation, precluding day-case management, as occurs in most cases [11].

Continuous bladder irrigation utilising water rather than isotonic saline may have additional effectiveness in reducing recurrence by lysing as well as washing out luminal tumour cells. Notably, as bladder cancer cell lines exposed to water undergo lysis within a few minutes [15], a short duration of irrigation after TURBT may be an effective intervention to reduce recurrence. In this pilot study, we prospectively evaluated water irrigation during and for at least 3 h after TURBT, primarily for feasibility and safety, and secondarily for recurrence-free rates (RFR).

Participants and methods

Trial protocol

The WATer Irrigation Post-TURBT (WATIP) trial was a single-centre single-arm prospective phase II pilot study, registered with the Australian New Zealand Clinical Trials Registry (Trial ID ACTRN12619000517178) and conducted with approval from the Eastern Health Human Research Ethics Committee.

Inclusion criteria

Age 18 years or older; planned to undergo TURBT for suspected bladder cancer based on imaging or flexible cystoscopy findings; and capable of providing informed consent.

Exclusion criteria

Tumour deemed to be too large (> 3 cm), or vascular, or potentially muscle-invasive (pre-operative or intra-operative exclusion at surgeon's judgement); risk of water toxicity (history of hyponatremia, or significant renal impairment defined as eGFR < 30 mL/min, or significant congestive heart failure defined as left ventricular ejection fraction < 25%); suspected or confirmed pregnancy.

The study intervention comprised the use of sterile water (Baxter Healthcare Australia, Old Toongabbie, NSW, Australia) for irrigation during and after TURBT, run by passive gravitational flow from a height of approximately 1 m with the flow-control fully open. The surgical technique for resection was as per surgeon's preference. Smaller tumours underwent cold-cup biopsy and diathermy where appropriate. After resection, water irrigation was continued for at least 3 h. Subsequently, irrigation was slowed and titrated according to the degree of haematuria in keeping with standard practice. At clinician discretion, this could be continued with water or switched to saline if needed. The duration and volume of water and/or saline irrigation was recorded. Thereafter, catheter removal, trial of void, and discharge were as per clinician instructions based on institutional care pathways.

Adverse events reported by participants and/or noted by treating clinicians were documented and graded using the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5) [16]. Blood samples were analysed for serum electrolytes, urea and creatinine, LDH and haemoglobin within 24 h post-operatively to document significant alterations, with derangements also graded as per CTCAE v5.

Participants underwent usual post-operative follow-up, including additional treatment and surveillance as indicated based on pathology. Follow-up outcomes were documented up to 12 months post-operatively.

Effluent sample collection and assessment

For a subset of participants, irrigant effluent specimen samples of 200 mL were collected immediately after TURBT, and then at 1, 2 and 3 h post-operatively. Water irrigation samples were collected into four, pre-prepared 50 mL FALCON® tubes, each containing 5 mL of 10 × Phosphate Buffered Saline (PBS) to restore iso-osmolarity and minimise ongoing ex vivo lysis of cells during transportation. Suspended cells were collected by centrifuging at 1000 g, and then resuspended in 1 ml of PBS for cell counting. Control samples for comparison were obtained from otherwise eligible patients who did not wish to enrol in the trial of water irrigation (and hence were undergoing standard irrigation outside of the trial) but had provided informed consent for sample collection only (Fig. 1). Their samples were processed similarly, with the exception of not adding 10 × PBS.

For each sample, 10 µL of cell suspension was combined with 10 µL of Trypan Blue, and 10 µL of the resulting mix loaded into a haemocytometer for cell counting. The total number of urothelial cells and numbers and proportions of viable cells (as assessed by Trypan Blue exclusion) were recorded at each time point.

For samples exhibiting substantial contamination with blood, the cell pellets were pooled into a single 50 mL FALCON® tube, to which 5 mL of red cell lysis buffer (BD Biosciences, Melbourne, Australia) was added, and the pellet resuspended. The tube was agitated 10 min, after which 20 mL of PBS was added to neutralise the lysis buffer. The tube was centrifuged for 5 min at 1000 g, the supernatant

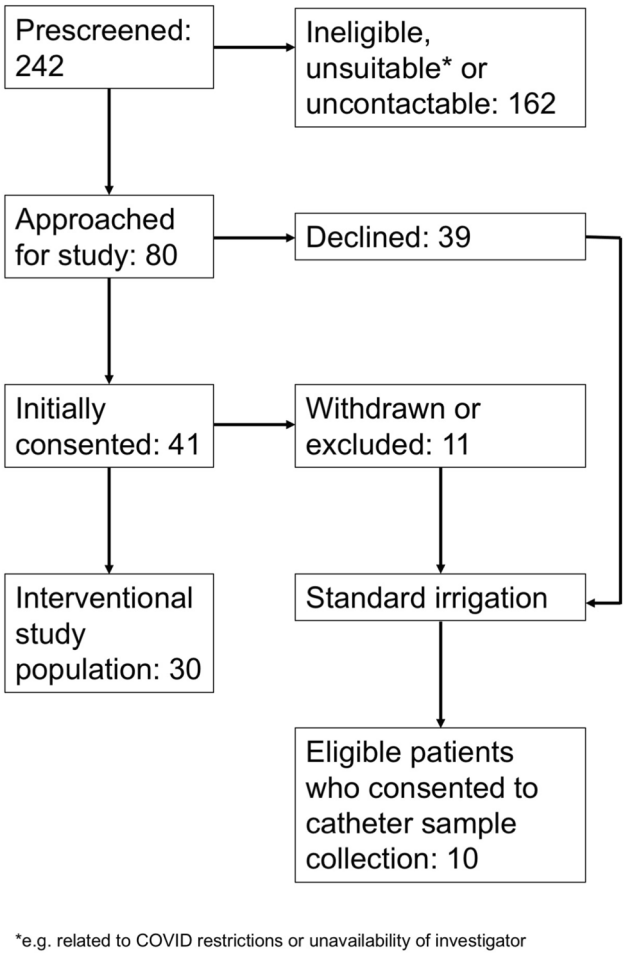

Fig. 1 Consort diagram outlining patient inclusion in study

discarded, and the pellet was resuspended in 1 mL of PBS for cell counts.

Some samples were also assessed immunohistochemically to confirm the presence of urothelial cells in the catheter effluent at the conclusion of TURBT and at the 3-h timepoints. Samples remaining after counting were transferred into an Eppendorf® tube and spun at 1000 g for 5 min. The supernatant was discarded, and the cell pellet resuspended in double the pellet volume of human plasma. Thrombin was added in a final ratio of 1:10 and mixed, after which the tube was kept at room temperature for 5–10 min to allow a clot to form. Each cell clot was transferred onto filter biopsy pads (Trajan Scientific Australia, Melbourne, Australia), inserted into tissue cassettes and fixed using neutral-buffered formalin (POCD Healthcare, Sydney, Australia). The cell samples were embedded in paraffin and sectioned with assistance from the Anatomical Pathology Department at Box Hill Hospital. Subsequently, individual 5 µm sections from each sample were stained using haematoxylin and eosin (H&E) and cytokeratin 7 (CK7) as a urothelial marker. Slides were assessed using white light and photographed using a Moticam Pro 282B and Motic Images Plus 3.0 (×86) software.

Study endpoints and statistical considerations

The co-primary endpoints were feasibility and safety, with pre-specified thresholds of at least 90% deemed to qualify water irrigation as being feasible and safe. Feasibility was defined as the planned water irrigation being successfully delivered during and for at least 3 h following TURBT. Safety was defined as the absence of any adverse events of grade 3 or higher by CTCAE v5 criteria.

Secondary endpoints were the RFR at first cystoscopy (for all patients with low-grade NMIBC) and at 12 months (for those who had undergone subsequent follow-up cystoscopy). Recurrence was defined by cystoscopic and/or histological findings. If cystoscopic suspicion of recurrent bladder cancer was noted, it was counted as a recurrence unless non-malignant histology was confirmed.

Cell counts in catheter effluent at the conclusion of TURBT and hourly intervals thereafter were quantified (as detailed above) in a subset of study participants as a tertiary/exploratory endpoint and compared to control samples from a group of patients who were otherwise eligible for study intervention but undergoing standard irrigation.

Data are summarised as counts with percentages or median with range as appropriate. Graphical representation of data was using Prism v7.01, (GraphPad Software Inc, Boston, MA, USA). All statistical analyses were undertaken using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Pre- and post-operative sodium and haemoglobin levels were compared using paired t-tests. Time-trends in cell counts were statistically assessed within each group using Friedman's test, and comparisons between groups were not undertaken as they were not randomised or matched. Statistical significance was ascribed to p values < 0.05.

Results

Between May 2019 and November 2021, 80 patients planned for TURBT were approached, with 41 consenting to proceed. Four patients subsequently withdrew consent prior to TURBT, and seven were excluded based on medical concerns or unsuitability of tumour (Fig. 1). Clinical and pathological characteristics of participants are summarised in Table 1.

All bladder tumours underwent conventional TURBT using monopolar diathermy except 7 small tumours which were treated with cold-cup biopsy followed by monopolar diathermy. All tumours were completely resected or diathermied. In 6 (20%) instances, intra-operative note was

Table 1 .

Characteristic	Values
Age (years)—median (range)	67 (44–89)
Sex—male:female	25:5
Tumour size (mm)—median (range)	10 (3–40)
Resection time (min)—median (range)	15 (5–80)
Tumour pathology—*n* (%)	
Benign	5[a] (17)
Low-grade NMIBC and PUNLMP	16 (53)
High-grade NMIBC	7 (23)
Muscle-invasive cancer	2 (7)
Duration of water irrigation (hours)—median (range)	3 (3–6)
Volume of water irrigation (L)—median (range)	8 (2–18)

NMIBC non-muscle invasive bladder cancer; *PUNLMP* papillary urothelial neoplasm of low malignant potential

[a]2 of the 5 had prior history of low-grade NMIBC

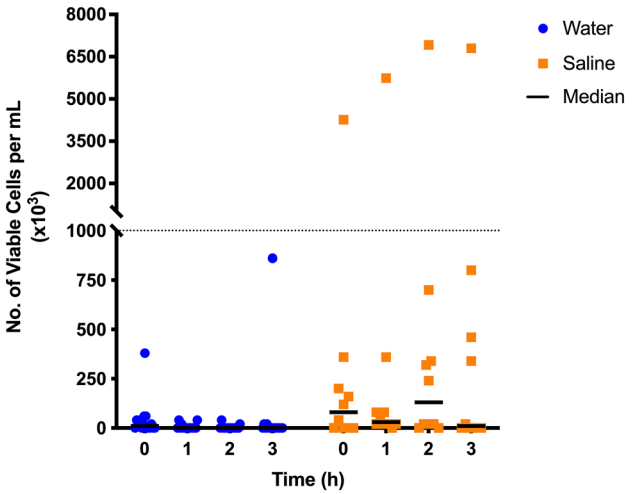

Fig. 2 Cell counts in individual catheter effluent samples over time among patients undergoing water or saline irrigation following TURBT

made of a deep resection, but the surgical team did not feel that this precluded water irrigation for any. Among the 30 participants, water irrigation was successfully completed as planned in 29 (97%). In one case, the lack of available bags of sterile water precluded its use. The median duration of resection was 15 min (range 5–80). Post-operative water irrigation was undertaken for a median duration of 3 h (range 3–6), delivering a median volume of 8 L (range 2–18) of water. Six participants also received a further period of saline irrigation for 4–17 h using 4–16 L of saline.

The only adverse event noted was of CTCAE grade 2, being clot retention needing manual irrigation of the catheter in one (3.3%) participant. There were no statistically significant differences in pre- and post-TURBT serum sodium (mean 141.0 vs 139.9 mmol/L, $p = 0.08$) or haemoglobin (mean 141.3 g vs 137.0 g/L, $p = 0.19$) levels. Post-operative serum LDH levels were all within normal range with a mean of 168.0 IU/L.

The irrigant fluid at the end of TURBT was assessed in 16 study participants and found to have a median of 4×10^3 cells/mL (range 0–380 x 10^3). This decreased to a median of 0 cells (range 0–860) after 1 h of water irrigation and remained so at subsequent time-points, $p < 0.005$ for the trend over time (Fig. 2). In contrast, among ten comparable patients undergoing isotonic glycine and saline irrigation, samples obtained at the end of TURBT contained a median of 80×10^3 cells/mL (range 0–4260 x 10^3) and samples at 3 h contained a median of 10×10^3 cells/mL (range 0–6800 x 10^3), which was not a statistically significant change. At each time point, water-irrigated samples had lower cell counts compared to saline-irrigated samples, but statistical comparison was not undertaken as the groups were not randomised or matched.

Immunohistochemistry confirmed the presence of urothelial cells on initial post-TURBT samples from water and saline-irrigated samples, with fewer cells noted in the former (Fig. 3). Samples obtained after 3 h of irrigation contained insufficient cells in water-irrigated participants but demonstrated the persistence of some urothelial cells with saline irrigation.

On histological evaluation of TURBT specimens, five were benign. Two patients with a prior history of NMIBC, found to have keratinous debris and cystitis cystica respectively, have continued cystoscopic surveillance and remain recurrence-free at 12 months. One patient with an inverted papilloma underwent a single follow-up cystoscopy at 6 months, with no evidence of recurrence. The other two patients with cystitis cystica have had no further cystoscopic follow-up.

Two participants had muscle-invasive cancer, one subsequently undergoing cystectomy and the other receiving radiation therapy. Seven participants were found to have high-grade NMIBC and underwent induction intravesical BCG treatment; all were recurrence-free at first cystoscopy but one (14%) had recurred with carcinoma in situ by 12 months.

The remaining 16 participants with low-grade NMIBC or papillary urothelial neoplasm of low malignant potential (PUNLMP) underwent their next surveillance cystoscopy at a median interval of 108 days (range 67–294) with 9 (56.2%, 95% CI 28.9–80.3%) remaining recurrence-free. At 12-month follow-up, 8 of them had undergone follow-up cystoscopy with 5 (62.5%, 95% CI 24.5–91.5%) recurrence free.

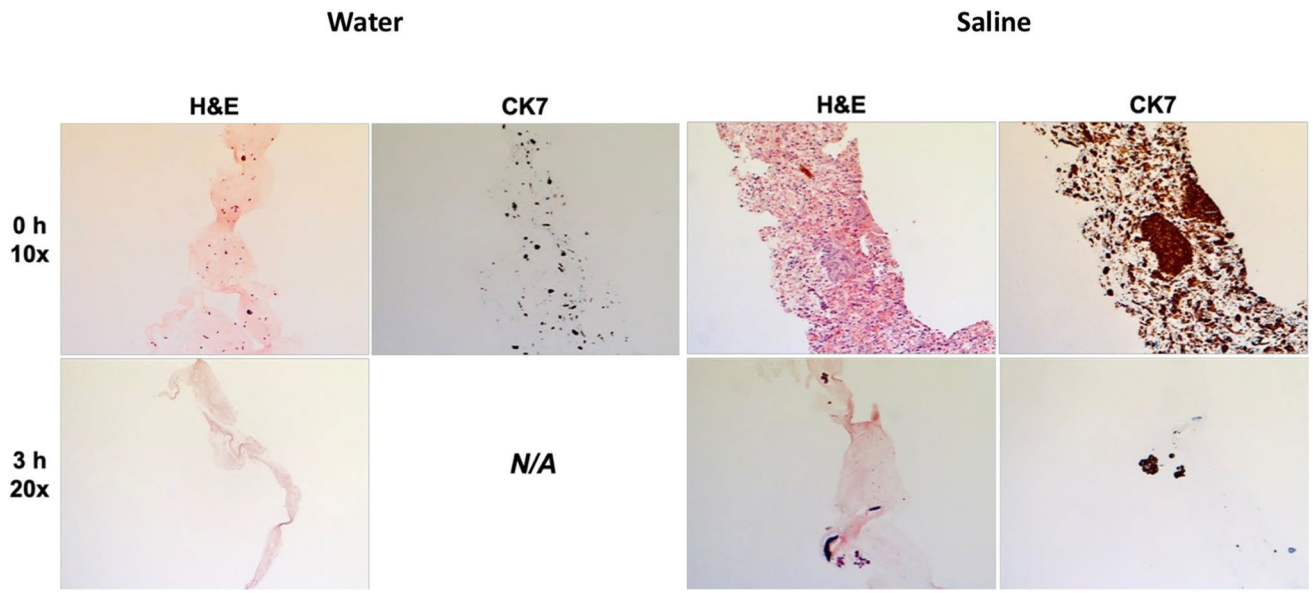

Fig. 3 Histological examination of cells in catheter effluent samples immediately and 3 h following TURBT, from representative patients undergoing water or saline irrigation, with Haematoxylin and Eosin (H&E) and Cytokeratin 7 (CK7) staining

Discussion

This study has demonstrated that water irrigation during and for at least 3 h post-TURBT is a feasible and safe intervention and defined resulting recurrence rates over 12 months of follow-up. All participants were able to receive the planned irrigation, except one where irrigant bags were not available, indicating a high degree of feasibility. The duration of the procedure or depth of resection, considered relative contra-indications for water irrigation, did not preclude its delivery, even in the two participants with resection time of an hour or more and the six with documented deep resection. Another potential barrier to water irrigation is the lack of catheterisation in case of fulguration of small bladder tumours, although that also precludes intravesical chemotherapy. However, these bladder cancers are associated with a low recurrence risk and hence there is a lower imperative for any post-TURBT treatment.

Water irrigation was found to fit easily into the standard post-operative management after TURBT, and did not require any additional nursing expertise or credentialling as for intravesical chemotherapy. In addition, the 3-h duration of treatment meant that patients planned for day-case TURBT could still have their catheter removed for timely discharge.

No irrigation-related adverse events or clinical concerns were noted. The only adverse event, being clot retention in one participant, was related to the TURBT itself rather than the irrigation. Post-operative blood tests also showed no significant effects on serum electrolytes or evidence of haemolysis. Although some patients were excluded from this study based on potential risks of water reabsorption, these findings suggest that, with appropriately close monitoring, many of them may be able to safely receive a short period of water irrigation. The low rate of adverse events contrasts with that seen for intravesical chemotherapy, reported in 27–48% of cases in published trials [11].

The evaluation of cells within the irrigant effluent at the end of TURBT and at timed intervals during post-operative irrigation showed that water irrigation was associated with low numbers of viable cells, reducing to no detectable cells within an hour post-operatively in most cases. In contrast, there were higher numbers of cells at the end of resection using glycine and some detectable cells persisted over 1–3 h during post-operative saline irrigation in many cases. These findings are in keeping with the demonstrated lytic effect of water on cancer cells in vitro [15], and suggest a biological rationale for reducing recurrences.

The cells found in the effluent were confirmed immunohistochemically to be of urothelial origin, although cytological detail was insufficient to confirm whether malignant. However, it may be reasonably assumed that at least a proportion of the detected cells are derived from the bladder tumour, as this is the basis for urine cytology analysis. In addition, the rationale for the use of intravesical chemotherapy to reduce recurrence after TURBT is based on the demonstrated presence of potentially implantable tumour cells in the bladder lumen [3]. Hence, the effect of water irrigation on reducing luminal urothelial cell numbers can be taken to demonstrate a biological mechanism by which it can prevent recurrence.

The impact of water irrigation on recurrence is most meaningful in the subgroup of participants with low-grade NMIBC, representing just over half the study participants. Given the limitations of small numbers, these data need to be interpreted with caution, and should guide further research rather than clinical practice. The recurrence-free rate of 62.5% noted at 12 months among patients with low-grade NMIBC is encouragingly comparable to respective rates of 52.6% and 47.1% for 24-h water irrigation and intravesical chemotherapy reported in the only published RCT comparing the two interventions [12]. Of note, that RCT was based on less than 20 patients in each arm, and hence likely to have lacked power to detect clinically significant differences. Similarly, two additional RCTs[13, 14] comparing saline irrigation and intravesical chemotherapy demonstrated comparable recurrence rates in both arms but were also small and likely under-powered. Thus, definitive conclusions regarding whether continuous bladder irrigation is as effective as intravesical chemotherapy in reducing recurrence are difficult to draw from existing data [11].

The findings of this study establish the feasibility and safety of 3 h of water irrigation and provide justification for undertaking further comparative assessment against intravesical chemotherapy. We currently have a proposed study in review for initial funding, recognising that a definitive non-inferiority trial will require a large sample size in excess of 1000 participants. We hypothesise that if water irrigation is found to be non-inferior to intravesical chemotherapy in terms of recurrence rates, its widespread usage would be strongly justified by probable gains in terms of safety, simplicity, cost, and quality of life. Furthermore, this would allow an effective intervention to be delivered in centres lacking infrastructure and expertise for the delivery of intravesical chemotherapy, as well as in low-resource settings where intravesical chemotherapy may not be easily available.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-024-04800-0.

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Author contributions ML: project development, data collection and analysis, manuscript writing and editing. RN: data collection and analysis, manuscript writing and editing. JT: project development, manuscript editing. IDD: project development, manuscript editing. SS: project development, data collection and analysis, manuscript writing and editing.

Data availability All participant data is stored securely and available on request, with appropriate agreements and safeguards for privacy.

Declarations

Conflict of interest ID Davis and S Sengupta are Board Directors (unpaid) of ANZUP trials group. ID Davis has been on advisory boards for Merck/Pfizer, MSD, Eisai, Ipsen and Bristol Myers Squibb (All invoiced by and paid to ANZUP Cancer Trials Group). SS has been a speaker or advisor for Mundipharma, Abbvie, Ipsen, Janssen, MSD and the Eastern Melbourne Primary Health Networks (All honoraria donated directly into institutional research fund). No other author has any interests to declare.

Human or animal rights Undertaken with approval from Eastern Health Human Research Ethics Committee approval (E12-2018) and informed consent provided by participants.

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