A/PROF. NIRDOSH KUMAR GOGNA (Orcid ID : 0000-0003-4448-9488)

A/PROF. SANDRA TURNER (Orcid ID : 0000-0002-7669-8316)

Article type : Radiation Oncology Letter to the Editor

Dear Editor

TROG trial Phase III- Muscle Invasive Bladder Cancer trial (TROG 02.03): a moral dilemma

N. Kumar Gogna¹ FRCP FRANZCR, Gillian Duchesne² MD FRCR, FRANZCR, Peter O' Brien³ FRANZCR, Nigel Spry⁴ FRCP FRANZCR PhD, Sandra Turner⁵ FRANZCR, John Mathews⁶ FRANZCR, Martin Borg⁷ FRANZCR, Kathryn Bauman¹ B. App Sc Med Tech, Madeleine King⁸ PhD, Elizabeth Burmeister⁹ MSc.

1 Radiation Oncology Services – Mater Centre, Princess Alexandra Hospital, 31 Raymond Terrace, South Brisbane Queensland 4101 Australia, 61738403255, fax 61738403298, Kumar.Gogna@health.qld.gov.au

2 Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne Victoria, Australia

3 Radiation Oncology Department Calvary Mater Newcastle Hospital, Waratah, New South Wales, Australia

4 Radiation Oncology Department, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

5 Radiation Oncology Department, Westmead Hospital, Westmead, New South, Wales Australia

6 Radiation Oncology Department, Auckland Hospital, Grafton, Auckland, New Zealand

7 Adelaide Radiotherapy Centre, Royal Adelaide Hospital, Adelaide, South Australia, Australia

8 School of Psychology, University of Sydney, Camperdown, New South Wales, Australia

9 Princess Alexandra Hospital, Woolloongabba, & University of Queensland, Queensland, Australia

Trial funded by NHMRC 243100; Clinical Trials.gov no: NCT00330499

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/1754-9485.12752](https://doi.org/10.1111/1754-9485.12752)

This article is protected by copyright. All rights reserved

A primary tenet of conducting a randomised clinical trial is that the outcomes should be reported whether or not the null hypothesis is refuted. Despite best endeavours, some clinical trials may not meet their objectives, whether due to failure to recruit, protocol deviations, difficulties with follow-up, limited funding or being superseded by newer developments. The Trans Tasman Radiation Oncology Cancer Research Group (TROG) and USANZ Phase 3 trial, “Definitive radiation therapy with and without concurrent weekly cisplatin for muscle invasive bladder cancer trial (TROG 02.03)”, illustrates the dilemma faced by clinicians and publishers alike. The trial was designed as a logical follow-on from two previous Phase 2 studies [1] that explored the optimal way to use chemosensitisation with radiation therapy to treat muscle-invasive bladder cancer. However, recruitment fell short of target, and with a longer than expected recruitment phase before trial closure, the designed follow-up data collection fell victim to lack of ongoing funding, not allowing long-term analysis.

In essence the study compared a RT schedule of 64Gy in 32 fractions delivered to the bladder planning target volume either with concurrent weekly cisplatin at a dose of 35 mg/m² (Arm A) or without (Arm B) for patients with localised muscle-invasive bladder cancer (MIBC). The primary outcome was local control (LC) at 3 years. The secondary end points included cystoscopic complete response rates, disease-specific survival (DSS), distant relapse-free survival (DRFS) and OS at 3 years. Acute and late toxicity were also assessed and patient reported health related quality of life (HRQOL) data were collected up to 24 months post completion of treatment. The full trial design and requirements are available in the trial protocol through TROG on request.

The sample size was estimated to detect an improvement in the three-year local failure rate as the primary endpoint, from 70% in the radiotherapy alone arm to 45% in the chemo-radiation arm with a probability of 80%. Descriptive comparisons of the prevalence of acute toxicity grades between the two arms during treatment were undertaken to assess the tolerability of the concurrent CRT regimen and potential impact on protocol compliance. QOL data were scored using the EORTC QLQ-C30 scoring manual [2] and unvalidated QLQ-BLM30 guidelines [3].

59

60 A total of 68 participants entered the trial between 1 January 2003 and 31 December 2008,
61 and their characteristics are presented in Table 1, available in the electronic Appendix. The
62 median (minimum, maximum) follow-up was 48 (3, 87) months. Complete trans-urethral
63 tumour resection was only achieved in 40% suggesting majority of patients had bulky
64 tumours. Radiation therapy was completed in 91% of cases in both arms, with only 68% of
65 patients in the CRT arm completing the cisplatin therapy as prescribed. Decline in renal
66 function was the main cause of non-compliance with one dose being omitted in 5 patients
67 (13%) and further dose reductions (≤ 4 doses) necessary in 7 (20%) other cases. No grade 3
68 or 4 haematological toxicity was seen. Grade 3 acute abdomino-pelvic side effects seen
69 were: vomiting (1 CRT), proctitis (1 in each arm), and urinary (20% in both arms), which did
70 not impact on treatment delivery and resolved subsequently. (Figure 1, eAppendix). One
71 grade 4 late bowel toxicity occurred (RT arm), bowel obstruction requiring surgery. The
72 HRQOL analysis was impeded by increasing rates of missing data with both arms being
73 affected similarly, considered most likely due to failing health in the non-responders, and
74 interpretation was therefore confined to the differences between arms at specific points,
75 rather than trajectories over time. Deterioration in HRQOL was more pronounced in the CRT
76 arm (Figure 2, eAppendix), and recovery to baseline slower, with clinically significant
77 differences in the scores for fatigue at the end of treatment (mean difference >19). Urinary
78 function scales showed improvement over baseline by 3 months in both arms, sustained in
79 surviving patients to two years. This would be in keeping with the QOL assessments reported
80 on long term survivors (≥ 6 years) of the various chemoradiation protocols undertaken at the
81 Massachusetts General Hospital [4] demonstrating that satisfactory bladder function is
82 maintained in the majority.

83

84

85 None of the tumour control endpoints reached statistical significance, presumed at least in
86 part to be due to the low patient numbers. The relevant values are shown in Table 2 and
87 Figure 3 in the eAppendix. Whilst a suggestion of a better response at first check cystoscopy
88 was seen in the CRT arm (89 % vs. 80%), no difference in overall local control at 3 years was
89 seen. There is a suggestion of improved DSS and DRFS in the CRT arm compared to the RT
90 arm. This is very unlikely to be related to the systemic effects of the low dose cisplatin

regimen in reducing the distant metastatic rate per se. It is difficult to know whether its impact on local control, in turn reducing the risk of subsequent metastatic seeding, may have had some bearing on this finding. Finally no difference in OS was seen between the 2 groups. However, given the age of the patients and their co-existing comorbidities, it should be noted the results may have been confounded to some extent by the fact that 23% of patients in the CRT arm and 16% in the RT arm died of unrelated illnesses.

It is unfortunate that this trial was not able to recruit a sufficient number of patients to answer the question posed, because the optimal scheduling of cisplatin, or indeed other chemosensitising agents, with radiation therapy for MIBC has still not been resolved. TROG developed this study from basic principles, with preclinical studies suggesting improved radiosensitisation with more frequent dose administration and the prior two phase 2 TROG studies [1] showed efficacy and tolerability of the weekly schedule. The dose intensity of cisplatin in the majority of this challenging group of patients in this study was maintained close to 80% (which compares favourably with other cisplatin based phase III CRT trials reported in the literature [4,5], with violations mainly resulting from decline in GFR. The failure to complete the prescribed chemotherapy usually occurred late in the course of treatment. The weekly schedule therefore possibly allows the radiosensitisation effect to be maintained over a longer period through the treatment and potentially improving the therapeutic ratio.

In conclusion, the three TROG studies have demonstrated that a weekly CRT regimen is feasible and has an acceptable toxicity profile even in the older patients. Despite a short-term negative impact on QOL with CRT, recovery follows with the improved bladder function being sustained, a reasonable trade off if disease control is indeed improved with CRT. This foreshortened trial limits any conclusions being drawn regarding tumour control outcomes; ideally the comparative efficacy of the regimen ought to be reinvestigated in a larger cohort of patients. The main challenge however that would remain is to find eligible patients amongst the challenging cohort of patients usually referred by default for consideration of definitive RT. Similar issues have been experienced by other Phase III studies [5-6] as well including the most successful recent UK study [7]. We have therefore

presented a brief synopsis of the trial and its outcomes to ensure that it is available in the literature to support any future overview or systematic analysis.

Yours sincerely,

A/Prof N. Kumar Gogna

References:

1. Gogna NK, Mathews JH, Turner SL et al. Efficacy and tolerance of concurrent weekly low dose cisplatin during RT of localised muscle invasive bladder cancer: A report of two sequential Phase II studies from the Trans-Tasman radiation Oncology group. *Radiother Oncol* 2006; 81, 9-17.
2. Aaronson NK, Ahmedzai S, Bergman B, *et al.*, The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, 1993; 85:365-376.
3. Botteman MF, Pashos CL, Hauser RS, *et al.*, Quality of life aspects of bladder cancer: a review of the literature. *Quality of life Research*, 2003; 12(6):675-688.
4. Zietman AL, Sacco D, Skowronski U, *et al.*, Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and Quality of life study on long-term survivors. *J Urol*, 2003; 170:1772–1776
5. Shipley WU, Winter KA, Kaufman DS, *et al.*, Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*, 1998; 16:3576–3583.
6. Coppin CM, Gospodarowicz MK, James K, *et al.*; Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*, 1996; 14:2901–2907.
7. James ND, Hussain SA, Hall E, *et al.*, Radiation therapy with and without chemotherapy in muscle invasive bladder cancer. *NEJM*, 2012; 366:1477-1488.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Gogna, NK;Duchesne, G;O'Brien, P;Spry, N;Turner, S;Matthews, J;Borg, M;Bauman, K;King, M;Burmeister, E

Title:

Trans Tasman Radiation Oncology Group Cancer Research: Phase III - Muscle Invasive Bladder Cancer trial (TROG 02.03): A moral dilemma

Date:

2018-10-01

Citation:

Gogna, N. K., Duchesne, G., O'Brien, P., Spry, N., Turner, S., Matthews, J., Borg, M., Bauman, K., King, M. & Burmeister, E. (2018). Trans Tasman Radiation Oncology Group Cancer Research: Phase III - Muscle Invasive Bladder Cancer trial (TROG 02.03): A moral dilemma. JOURNAL OF MEDICAL IMAGING AND RADIATION ONCOLOGY, 62 (5), pp.668-670. <https://doi.org/10.1111/1754-9485.12752>.

Persistent Link:

<http://hdl.handle.net/11343/284601>