

The first International Penile Advanced Cancer Trial (InPACT) opens in Canada! Why additional centers are needed

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Penile cancer is rare in Canada and the Western world. For this reason, penile cancer lags well behind most other malignancies in development of evidence-based guidelines for management. When patients present late, with clinical involvement of inguinal nodes, the prognosis can be especially poor. Surgery in these cases is seldom curative but the role of neoadjuvant and adjuvant treatment is poorly defined. Neoadjuvant chemotherapy has demonstrated efficacy for bulky lymph node metastases in single-arm clinical trials, particularly, the paclitaxel, ifosfamide, and cisplatin (TIP) regimen.¹ Chemoradiation therapy has become the care standard for initial management in patients with locally advanced squamous cell carcinomas in other sites, particularly the head and neck, anal canal, and vulva, based on phase 2 and 3 trials²⁻⁴ but evidence for application in penile cancer is lacking.

This dilemma was the basis for the international cooperation to develop InPACT: the **I**nternational **P**enile **A**dvanced **C**ancer **T**rial (NCT02305654) sponsored by both the National Cancer Institute (lead by ECOG-ACRIN Cooperative Group) and Cancer Research of the United Kingdom (CRUK). The aim of InPACT is to determine prospectively the potential benefits of chemotherapy or chemoradiation, in addition to lymph node dissection, in patients with clinical evidence of inguinal lymph node metastases.

InPACT poses two questions. **InPACT neoadjuvant** focuses on groin management, randomizing patients according to disease burden⁵ to inguinal lymph node dissection (ILND) preceded or not by neoadjuvant chemotherapy or chemoradiation. **InPACT pelvis** is open to those patients with adverse pathological features after ILND to determine if survival is improved by pelvic LND followed by chemoradiation, as compared to chemoradiation alone (Fig. 1).

The primary endpoint of the study is overall survival, but secondary endpoints include disease-specific survival, treatment-related toxicity, surgical complications, feasibility of on-schedule treatment delivery, and quality of life (QoL).

Participating centers undergo credentialing for the multiple disciplines involved, including radiology, pathology, surgery, and radiation oncology, to ensure consistent standards. Initially, accrual aimed for 400 patients over five years, with 50% coming from supra-regional high-volume centers in the U.K. and the remaining 50% from an anticipated 20 centers in the U.S. and Canada.⁶

InPACT initially opened in a few sites in 2017 but has faced challenges related to the credentialing process of the multiple disciplines involved, institutional review board approvals, and research slowdowns due to COVID-19. Nonetheless, 65 patients have been accrued worldwide, the majority (71%) from 16 sites in the U.S. The National Cancer Institute of Canada-Clinical Trials Group (NCIC CTG) manages the trial in Canada (PNC-1), and British Columbia is the first Canadian site to open to accrual, but others in Quebec, Ontario, and Alberta are in the process.

Review of the Bayesian design⁷ and statistical assumptions has permitted a reduction in the accrual target to a total of 200 patients, while still meeting study objectives. We hope to meet this accrual within two years, averaging five patients per center. We, and our colleagues in the uro-oncology community, feel it is essential that this effort succeed. The truth is that no single center sees enough of these patients to make it “worthwhile” to open this trial. Therefore, we are dependent on a sense of obligation, on appreciation of the need to do better with this disease.

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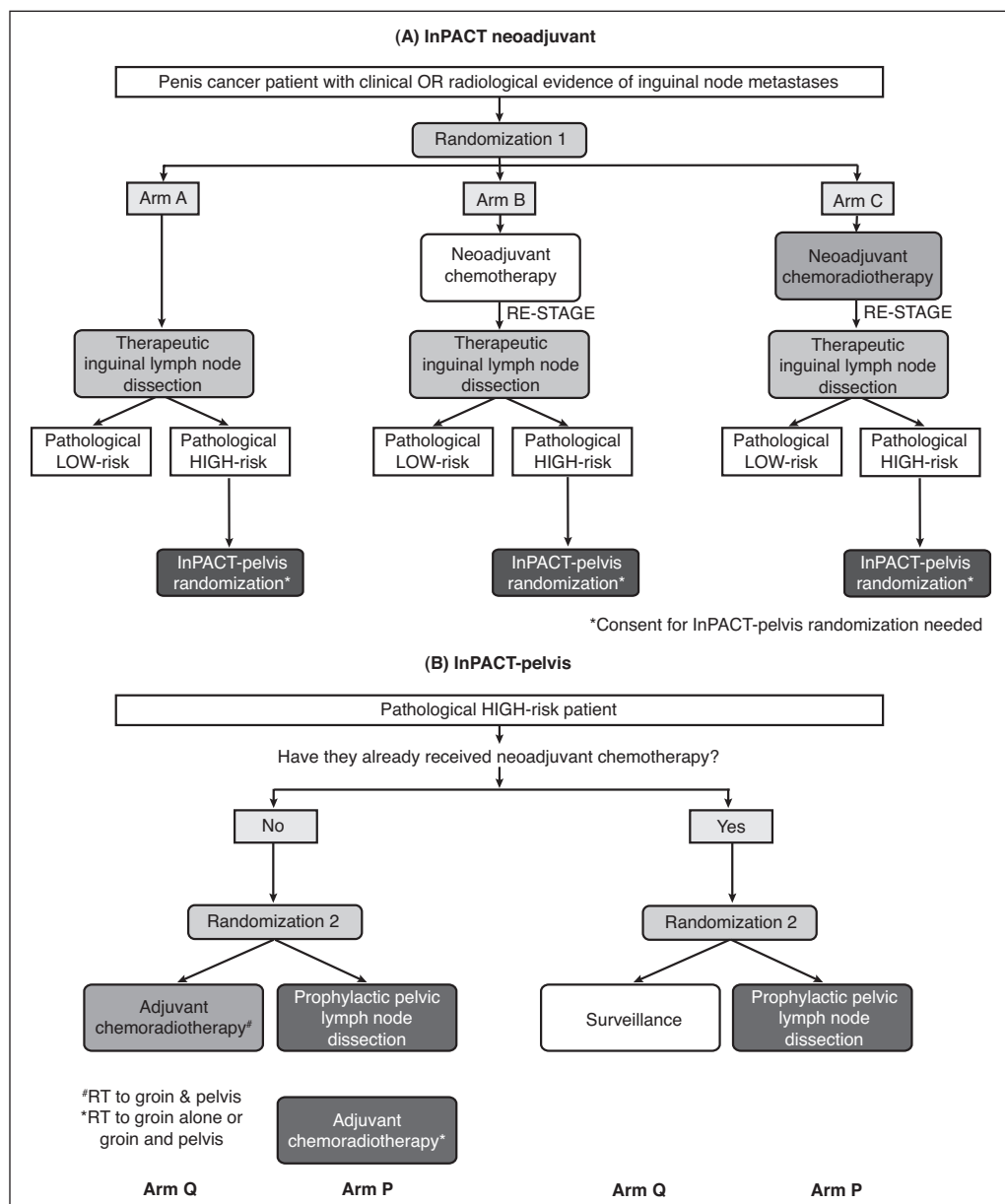


Fig. 1. Trial schema for **(A)** InPACT neoadjuvant study; and **(B)** InPACT pelvis study. RT: radiation therapy.

InPACT will shed some light on how to improve management of node-positive penile cancer. We sincerely hope that other Canadian centers will join this historic effort to improve outcomes in this rare disease.

References

- Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: A phase 2 study. *J Clin Oncol* 2010;28:3851-7. <https://doi.org/10.1200/JCO.2010.29.5477>
- Montana GS, Thomas GM, Moore DH, et al. Preoperative chemoradiation for carcinoma of the vulva with N2/N3 nodes: A Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys* 2000;48:1007-13. [https://doi.org/10.1016/S0360-3016\(00\)00762-8](https://doi.org/10.1016/S0360-3016(00)00762-8)
- Ang K, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35. <https://doi.org/10.1056/NEJMoa0912217>
- Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: Results of a phase 3 randomized intergroup study. *J Clin Oncol* 1996;14:2527-39. <https://doi.org/10.1200/JCO.1996.14.9.2527>
- Graafland NM, Teertstra HJ, Besnard AP, et al. Identification of high-risk pathological node positive carcinoma: Value of preoperative computerized tomography imaging. *J Urol* 2011;185:881-7. <https://doi.org/10.1016/j.juro.2010.10.058>
- Canter DJ, Nicholson S, Watkin N, et al; InPACT Executive Committee. The International Penile Advanced Cancer Trial (InPACT): Rationale and current status. *Eur Urol Focus* 2019;5:706. <https://doi.org/10.1016/j.euf.2019.05.010>
- Bogaerts J, Sydes MR, Keat N, et al. Clinical trial designs for rare diseases: Studies developed and discussed by the International Rare Cancers Initiative. *Eur J Cancer* 2015;51:271-81. <https://doi.org/10.1016/j.ejca.2014.10.027>

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