

## The International Penile Advanced Cancer Trial (InPACT): Rationale and Current Status

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Patients presenting with regional metastases from penile squamous cancer (PSC) have a potentially lethal form of the disease for which there is little prospective evidence to guide rational treatment selection. Surgery for such patients often demonstrates adverse pathological features, including extranodal extension, involvement of three or more inguinal nodes, or positive pelvic nodes. The 5-yr survival in these circumstances ranges from 0% to 42%, depending on the extent of adverse features [1–3]. It is clear that surgery alone is inadequate for patients with clinically or radiologically apparent inguinal nodes, and the dilemma is how chemotherapy and radiotherapy should be integrated to optimise patient outcomes.

Neoadjuvant chemotherapy (using the paclitaxel, ifosfamide, and cisplatin [TIP] regimen) has been explored in the phase 2 setting; clinically significant responses with the suggestion of enhanced survival were observed [4,5]. Radiotherapy with or without synchronous chemotherapy has become standard management for head and neck, vulvar, and anal squamous cancers [6–9], but its use in the perioperative setting in penile cancer remains controversial. Some retrospective series suggest a benefit in certain patient subsets, while others show none, and as a result the European Association of Urology penile cancer guideline group declined to recommend adjuvant radiotherapy in its recent review [10–13]. The aim of the International Penile Advanced Cancer Trial (InPACT; NCT02305654) is to determine prospectively the relative benefits and sequencing of surgery, chemotherapy, and chemoradiotherapy in the management of patients with penis cancer who present with palpable or radiologically evident inguinal lymph node metastases (Table 1) [14]. InPACT addresses the following questions:

- 1 Is there a role for neoadjuvant therapy and, if so, which of two options (chemotherapy or chemoradiotherapy) before surgery yields superior outcomes?
- 2 Among patients whose inguinal node histology predicts a high risk of recurrence, does prophylactic pelvic lymph node dissection (PLND) plus chemoradiation to the inguinal and pelvic fields improve survival compared to chemoradiation alone?

The trial design consists of two randomisations: InPACT-neoadjuvant and InPACT-pelvis (Fig. 1A,B). At registration, patients are stratified by disease burden (low, intermediate, or high) based on both physical examination and the proposed computed tomography scan

criteria developed by Graafland et al [15], and these criteria guide the randomisation allocation (Table 2). Patients in the low-burden group (Fig. 1A) proceed directly to surgery (they are not randomised) but may still participate in InPACT-pelvis if postoperative pathology shows high-risk features. The statistical plan uses a Bayesian approach, which is a very effective strategy for trials in rare diseases [14,15]. Prospective, unbiased, worldwide trial data will be collected for 400 patients, with a focus on the probability of selecting the superior treatment regimen rather than formal hypothesis testing [16].

The primary outcome measure for the trial is survival, with secondary outcome measures of disease-specific survival, disease-free survival, and freedom from locoregional recurrence and distant metastasis. Feasibility, toxicity, the type/extent of surgical complications, and quality of life (QoL) will be assessed as secondary endpoints for all the InPACT treatment arms. Given the potential functional impact of the different arms of the trial, QoL could be an important factor in deciding the best treatment, especially if oncological outcomes appear to be similar. Tissue will be collected from all consenting patients and will allow future correlation of clinical outcomes with molecular markers including human papillomavirus presence and other pathways that are potentially important in pathogenesis or progression [17,18].

Support and funding for the trial have been provided by Cancer Research UK/Stand Up To Cancer and the US National Cancer Institute (NCI). The trial is open and currently enrolling at sites in the UK (where there the trial is sponsored by The Institute of Cancer Research [ICR]) and the USA (sponsored by the NCI). Additional countries projected to open sites in 2019 include Canada, Mexico, and Colombia. Data from all countries will be pooled for central statistical analysis at the ICR. Trial complexity and the potential for inconsistent management of advanced disease mean that participating investigators from the disciplines of pathology, radiation oncology, radiology, and urology are required to be credentialed before starting recruitment. Additional ongoing quality assurance procedures are in place to monitor sites as patients receive therapy. Feedback suggests that credentialing procedures have not been overly burdensome but can be a source of delay if not addressed proactively by potential study sites.

The study goal is to recruit approximately 80 patients per year over 5 yr to achieve the target of 400 patients. Accrual during the first year has been lower than expected at 14 patients internationally. This is probably multifactorial and a reflection of site start-up delays related to (1) the institutional review board process, (2) credentialing requirements for surgeons, radiation oncologists, radiologists, and pathologists, and (3) difficulty in acquiring funding for the infrastructure necessary for the trial. Currently, eight of the 20 proposed study sites in North and South America are open for accrual. In the UK, two of ten potential sites are open for accrual. However, an increasing number of study sites are anticipated for 2019, with new sites in Canada, the USA, Colombia, Mexico, and the UK.

In summary, InPACT represents a novel international approach to providing high-level evidence to guide therapy for locally advanced penis cancer. It is our hope that InPACT will lay the foundation not only for future international collaborative studies but also for the growth of international centres of excellence for penile cancer management.

## **Appendix A. Links for trial information and participation**

### **InPACT North and South America information**

ECOG-ACRIN: <https://ecog-acrin.org/clinical-trials/ea8134-educational->

materials **Site participation**

Clinical trial support unit: [www.ctsu.org/pp\\_default.aspx?nodeKey=3](http://www.ctsu.org/pp_default.aspx?nodeKey=3)

### **InPACT UK, Europe, and Australia**

ICR-CTSUs: [www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/inpact](http://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/inpact)

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**Fig. 1 – Trial design with randomisation to InPACT-neoadjuvant and InPACT-pelvis.**

