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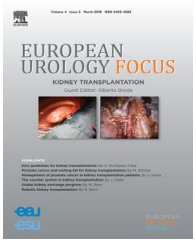

Clinical Studies Update – Penile Cancer

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

Table 1 – Abbreviated inclusion and exclusion criteria for InPACT.

Inclusion criteria
Male, aged ≥18 yr
Histologically proven squamous cell carcinoma of the penis
Stage:
Any T, N1 (ie, a palpable mobile unilateral inguinal lymph node), M0; or
Any T, N2 (ie, palpable mobile multiple or bilateral inguinal lymph nodes), M0; or
Any T, N3 (ie, fixed inguinal nodal mass or any pelvic lymphadenopathy), M0
Measurable disease according to Response Evaluation Criteria in Solid Tumours v.1.1
Eastern Cooperative Oncology Group performance status ≤2
Patient is fit to receive the randomisation options for which he is being considered
Haematological and biochemical parameters within local standards for randomisation options
eGFR >50 ml/min (patients with eGFR <50 ml/min are only eligible for the surgery alone arm or the neoadjuvant chemoradiotherapy arm, and not the neoadjuvant chemotherapy arm)
Willing and able to comply with the follow-up schedule
Able to give written informed consent
Exclusion criteria
Nonsquamous malignancy of the penis
Pure verrucous carcinoma of the penis
Presence of distant metastatic squamous cell carcinoma of the penis
Previous chemotherapy or chemoradiotherapy outside of the InPACT trial
Concurrent malignancy (other than squamous cell carcinoma or basal cell carcinoma of non-penile skin) that has required surgical or nonsurgical treatment in the last 3 yr
Patients who are sexually active and unwilling to use effective contraception (if they are not already surgically sterile)

eGFR = estimated glomerular filtration rate.

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https://doi.org/10.1016/j.euf.2019.05.010

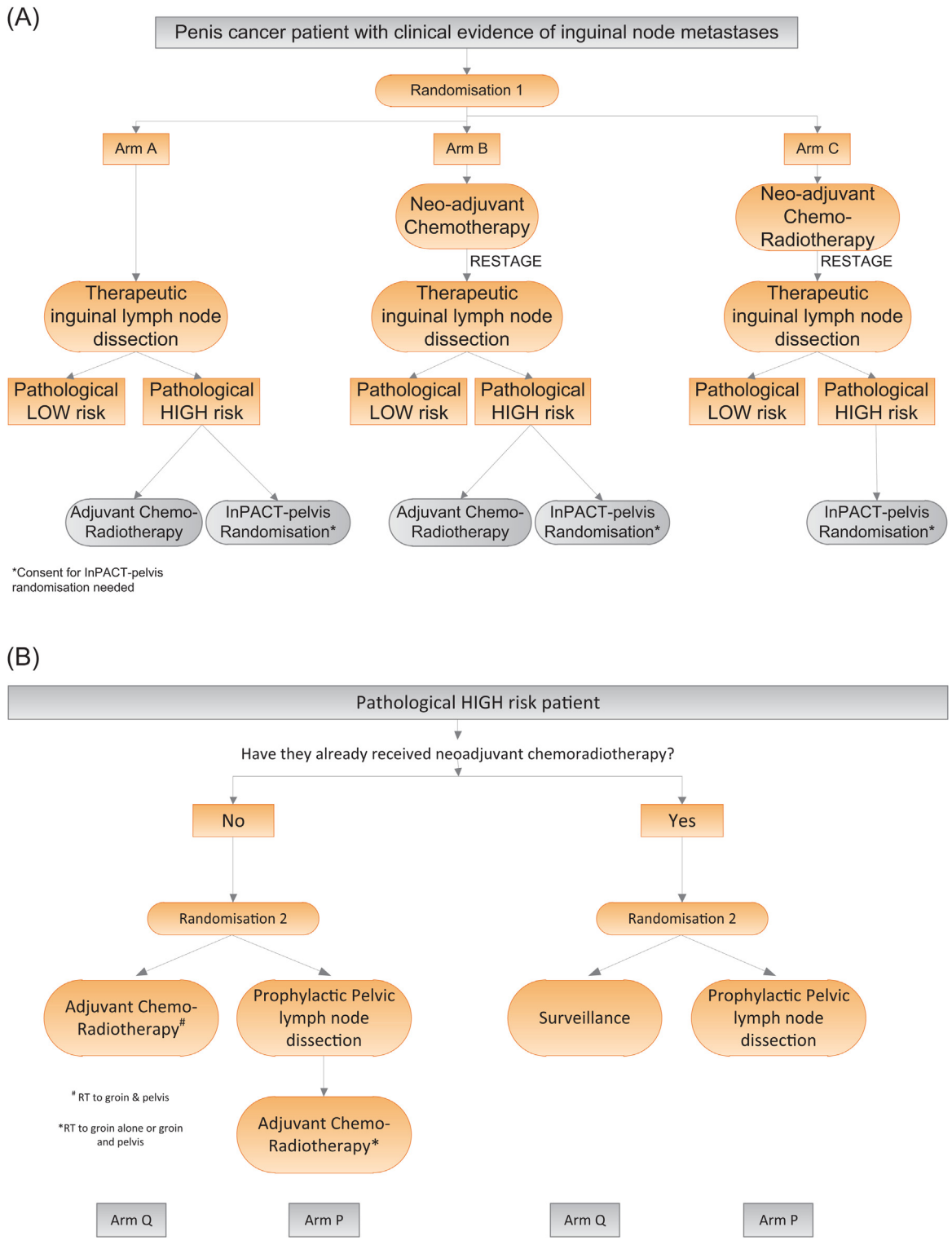

Fig. 1 – Trial design with randomisation to InPACT-neoadjuvant and InPACT-pelvis.

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) (see full InPACT protocol in supplemental material) [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

Table 2 – Burden of disease risk stratification for treatment allocation in InPACT-neoadjuvant.

Disease burden	Inclusion criteria	GFR (ml/min)	Allocation to trial arms [a]				
			A	A vs B vs C	A vs C	B vs C	C
Low	One mobile LN with no HRF-CT	Any	Trial entry	X	X	X	X
Intermediate	Two ipsilateral mobile LNs with no HRF-CT	≥50	Trial entry	Randomise	X	X	X
		<50	Trial entry	X	Randomise	X	X
	Bilateral, pelvic, or fixed LNs, or radiological evidence of ≥3 LNs involved or Presence of HRF-CT	≥50	Trial entry [b]	Randomise	X	Randomise	X
High		<50	Trial entry [b]		Randomise	X	Trial entry

LN = lymph node; HRF-CT = high-risk features on computed tomography; GFR = estimated glomerular filtration rate.
[a]Arm A = surgery; arm B = neoadjuvant chemotherapy; arm C = neoadjuvant chemoradiotherapy. X denotes allocations not permitted in the trial. No cell shading denotes first-choice treatment allocation and shading denotes allocation at investigator discretion.
[b]Not if pelvic LNs involved.

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.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: InPACT is funded by Cancer Research UK (CRUK/13/005) and supported by the National Institute for Health Research Cancer Research Network and NHS funding to the NIHR Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London. Funding for InPACT North and South America from the National Cancer Institue (5 U10 CA 180858 04) of the United States.

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

InPACT UK, Europe, and Australia

ICR-CTSU: www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/inpact

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.euf.2019.05.010.

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