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Introduction

Lymph node involvement remains the single most important prognostic factor in squamous cell carcinoma of the penis (SCCp) [1]. Survival rates are negatively correlated with lymph node status and patients with pN3 disease have the poorest outcomes [2].

The role of lymph node dissection (LND) and adjuvant chemotherapy in managing high risk node SCCp is well recognised [3-5]. However, there remains limited evidence on the use of adjuvant radiotherapy in these patients [6-7]. A recent systematic review of adjuvant radiotherapy highlighted the lack of evidence, which is in part attributable to studies with small numbers, heterogeneity of subject inclusion and retrospective analysis [7]. The authors concluded there was insufficient evidence to demonstrate a beneficial or harmful effect of adjuvant radiotherapy. This is reflected in the 2019 EAU penile cancer guideline, which does not recommend radiotherapy except as palliation. This is a change from previous iterations which advocated consideration of adjuvant radiotherapy in selected patients with extracapsular nodal extension (ENE) [6,8].

Patients and Method:

A retrospective audit (registration number: CADB002410) approved by the St George's Hospital audit committee was conducted using prospective databases held at two UK centres. The databases included all SCCp cases discussed at the specialist multidisciplinary meeting (sMDM) over this time period. We identified all pN3 (TNM 8) SCCp patients include those with inguinal ENE as well as those with pelvic involvement with or without ENE between January 2009 and December 2017 at St George's and January 2002 to December 2016 at Leeds. All patients with a Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or better were deemed suitable for adjuvant radiotherapy by the sMDM. All

patients who started treatment, including those who did not complete it were included in the analysis.

Surgical protocols:

All clinically involved inguinal nodes were treated with radical inguinal lymphadenectomy (iLND). Surgical management of the clinically negative nodes (cN0) and pelvic nodes varied. Dynamic sentinel lymph node biopsy (DSNB) has been used since 2003 at St George's for nodal sampling in all cN0 inguinal basins. Superficial iLND was used in Leeds up to 2014 after which DSNB was introduced for all CN0 inguinal basins. Ipsilateral pelvic lymph node dissection (PLND)was performed in the presence of metastasis in two or more inguinal nodes or inguinal ENE over the study period at St George's and adopted in Leeds from 2014. This is in line with EAU guidance [8].

Adjuvant radiotherapy protocols:

The policy of both St. Georges and Leeds Hospitals has been to recommended adjuvant radiotherapy for all pN3 men fit to receive treatment after completion of nodal surgery. The treatment decision is subject to confirmation of no metastatic disease with cross-sectional imaging and ECOG performance status of 0,1 or 2. The supra-network MDT protocol mandates irradiation of the ipsilateral inguinal basin in the presence of ENE. The ipsilateral pelvis is irradiated if pelvic ENE is present or if pLND was not performed. A radiotherapy dose of 54Gy in 27 fractions has been used as standard since 2016. Prior to this, with no national guideline for SCCp, dosing was decided by clinician preference. Doses of 50-54 Gy in 25 – 27 fractions were the preferred regime over the various radiotherapy sites in the St George's network, whereas Leeds routinely administered 45Gy in 20 fractions (single radiotherapy site). A weekly low dose platinum-based chemo-sensitisation agent was

typically given in combination with radiation therapy. This was recommended and routinely given as part of the adjuvant treatment protocol however, some patient did not receive this due to concomitant co-morbidities.

During this period, no patients in this cohort received neoadjuvant or adjuvant chemotherapy. Palliative chemotherapy was offered to patients with disease recurrence.

Follow up protocol:

The follow up protocol was aligned with EAU guidance and similarly assessed at both centres by clinical examination and CT thorax/abdomen/pelvis (TAP) during 5 years of follow up. The protocol was 3 monthly CT TAP for 3 years followed by 6 monthly CT TAP for years 4 and 5 [6].

Outcomes:

Primary outcomes were recurrence free survival (RFS), cancer specific survival (CSS) and overall survival (OS). These end points were calculated from the date of last nodal surgery. Recurrence was defined as any measurable disease in a previously disease-free patient who had received adjuvant treatment. This was as per the response evaluation criteria in solid tumours (RECIST) protocol [9]. CSS and OS were obtained from death certificates, hospital notes, palliative care, and communication with primary care physicians.

Secondary outcomes assessed were time to delivery of radiotherapy, calculated from last nodal surgery to delivery of first treatment, the frequency of in field recurrence and site and side of disease recurrence.

Data Quality:

Both centres held prospective databases of SCCp patients from sMDM but retrospective data entry was required to complete our database where incomplete. Radiotherapy was carried out at agreed partner centres in the St Georges supra-network. Standardised toxicity

reporting was not routinely collected as part of the prospective databases. Due to variations in surgical practice and adjuvant treatment listed above, we analysed our data to assess correlations between these factors and RFS, CSS and OS. We also analysed the impact of chemo- sensitisation, time to radiotherapy and radiation dose delivered.

Statistical analysis:

We used basic descriptive statistics to summarise the patient cohort.

Kaplan Meier curves were used to calculate RFS, CSS, and OS with Log rank test used for p values to establish statistical significance between groups. All analyses were performed using Prism 8.2.1.

Results:

Records of 146 patients were analysed (Table 1). The median (interquartile range [IQR]) age at presentation was 59 (54 - 70) years. Radiotherapy was started on 125 of 146 patients after sMDM. Radiotherapy was completed as intended in 121 of 146 (82.9%). Treatment was stopped in 4 of 146 (2.7%), due to a severe cerebral vascular event in (1 of 4), frailty (1 of 4) and rapid disease progression (2 of 4). Treatment was intended but never started in 21 of 146 (14.4 %). In these 21 patients this was due to rapid disease progression (n = 12), issues with wound healing (n = 2), sudden death (n = 2), declined (n = 2), previous radiotherapy for anal cancer (n = 1) and undocumented reason in (n = 2) (Fig. 1). 71 of 146 (48.6%) patients with two or more involved nodes and/or ENE did no undergo pLND as this was prior to taking up of EAU guidance at one of the institutions. However, 65 of these 71 (91.5%) patients still went on to receive adjuvant radiotherapy to the inguinal and pelvic sites. Among the 75 of 146 who had pLND, 38 (51%) had positive pelvic histopathology. Of these 38 patients, 36 had ENE and 2 did not (Table 1). Chemo-sensitisation was delivered in

41% of patients and, where the chemotherapy schedule was recorded, 89% received a platinum-containing regimen (Table 2).

Primary Outcomes:

Our analysis of patients who started adjuvant radiotherapy (n = 125) demonstrated a probability of RFS at 5 years of 51 % (Fig 2), CSS at 5 years of 51 % (Fig 3) and OS at 5 years of 44 %, (Fig 4).

Secondary Outcomes:

The median (IQR) time to delivery of adjuvant radiotherapy from final nodal surgery was 75 days (48 - 106) days.

55 of 125 patients experienced a recurrence, including 52 who completed adjuvant radiotherapy and 3 who did not complete treatment. 30 of the 55 had recurrence in the inguinal and/or pelvic basins only. 26 of 55 of the recurrences were purely in an irradiated field (Table 3) and 4 of the 55 patients had an inguinal or pelvic nodal recurrence. These were in a non-irradiated nodal station. 2 patients experienced inguinal and 1 patient pelvic recurrence in the contralateral side to a previously irradiated groin and pelvis. 1 patient who received unilateral inguinal radiotherapy only developed a recurrence in the ipsilateral pelvis. In 7 of the 55 who experienced recurrence, this occured in both nodal and visceral sites. These were all out of field recurrences. A further 18 of 55 recurres were in visceral sites only (Table 4). Despite a similar number of overall recurrences (nodal and visceral), in a comparison performed according to radiation dose delivered, we observed a twofold higher risk of in-field recurrence for patients treated with < 50Gy vs patients treated with a dose > 50Gy (19/60 patients [31.6%] vs 7/49 [14.2%]; Fig. 5). However, this was not statistically

significant (p = 0.13). Table 5 shows a breakdown of the most frequently used radiation dose and fraction.

Data Quality:

We did not receive outcome data from 2 centres for a total of 7 pN3 patients. Of the 125 patients included in the analysis, 16 [12.8 %] had incomplete information on timing, site and dosing of adjuvant radiotherapy as well as site of disease recurrence. 18 of 125 (11.6%) did not have complete data on use of chemo-sensitisation or the agent used. The cause of death was ascertained as SCCp specific in while in 4 patients the cause of death was unrelated to SCCp; with 3 dying from sepsis and 1 from a rectal cancer. There was no statistically significant difference in RFS (p = 0.2) , CSS (p = 0.4) and OS (p = 0.6) between the two centres. We did see some evidence of a poorer overall survival with chemo sensitisation however the difference between the groups did not reach statistical significance (p = 0.065) (Fig 5). There was also no statistically significant effect of time to radiotherapy delivery (p = 0.13).

Discussion:

There is a paucity of evidence on best practice in the management of pN3 SCCP [10,11]. In such a rare disease, small patient numbers over multiple treatment centres and variations in treatment have all proven challenges to establishing robust evidence-based practice. Centralisation of cancer services in the UK since 2002 has been important, enabling specialist centres to build up experience and inform future management strategies. Data

from our 2 centres comes from a combined referral population of 18 million and aims to inform future management of this rare disease.

Outcomes in pN3 SCCp are poor, CSS at 5 years is quoted at 20 to 34 % without adjuvant treatment and up to 42% with treatment [2,12,13]. This reflects patients with inguinal or pelvic ENE, which carries the worst prognosis [13]. ENE was present in 99% of our cohort, 74% inguinal and 25% pelvic.

Radio sensitivity of SCCp and a likely response to therapy is supported with long-term data demonstrating RFS of 65 - 67% at 10 years after radiotherapy for all stages of the primary tumour [14-15]. In nodal pN3 disease, a cohort of 36 patients with ENE in a cohort of 70 SCCp patients treated with adjuvant radiotherapy demonstrated a 5-year CSS of 42% [2]. Franks et al published their experience of adjuvant radiotherapy in a smaller cohort of patients with ENE some of whom are included in this study and concluded it was associated with higher OS [16]. Tang et al also demonstrated improved OS and decreased incidence of recurrence with adjuvant radiotherapy after pelvic node dissection in their own cohort of patients [17]. Conversely, in a larger series of 93 patients, adjuvant chemotherapy and inguinopelvic radiotherapy was associated with improved OS and reduced recurrence only in patients without ENE [13]. In that cohort in patients with ENE (including 49% who had ENE in the pelvis), radiotherapy did not confer an OS or local recurrence benefit (median follow up of 10.6 months) but was associated with an improvement in CSS [13]. A systematic review by Robinson et al failed to demonstrate a beneficial or harmful effect of adjuvant radiotherapy in node positive SCCp [7]. Level 1 evidence however supports the benefits of adjuvant radiotherapy in other squamous cell cancers e.g. head and neck, cervical and anal SCC [18]. In these SCCs, higher doses of adjuvant radiotherapy improve CSS and reduce loco regional recurrence [19]. The InPACT trial testing the role of chemotherapy vs

chemoradiotherapy vs upfront surgery in SCCp may yet give further information as to the role of adjuvant radiotherapy in this high-risk group [20].

Adjuvant chemotherapy is recommended as part of the EAU guidance and has been shown to improve outcomes in patients with node positive SCCp [6]. However, as with radiation studies, studies in such patients tend to have small patient numbers and are heterogenous in their inclusion of different nodal stages encompassing both pN2 and pN3 patients [6]. Intuitively, inclusion of pN2 patients who have better outcomes than pN3 patients would improve overall outcomes in these studies. In a comparable study of adjuvant chemotherapy for solely pN3 disease, Sharma et al report their 3 and 5-year OS rates of 42% and 35% respectively [21]. Similarly, Nicolai et al reported RFS and CSS of 20% at 20 months in their cohort of pN3 patients treated with adjuvant chemotherapy [22]. None of the patients included in the present study had adjuvant chemotherapy. Addition of adjuvant chemotherapy to radiotherapy may improve outcomes in this group of patients.

We observed that of the 125 patients who completed radiotherapy, 70 (56 %) remained recurrence free. 26 of 125 (20.8 %) experienced recurrence in a radiation field. In field recurrences may relate to insufficient doses used or variable radio sensitivity. Johnstone et al reported an 82% rate of in field relapse in this high-risk group, using 50 Gy in 25 fractions [13]. Our relatively high rate of in-field recurrence may be explained by historical use of radiotherapy doses now considered too low. The most common dose used in our cohort prior to 2014 was 45 Gy in 20 fractions for which the equivalent dose in 2Gy fractions (EQD2) is 45 Gy (a/b 10 Gy) compared to an EQD2 of 55 Gy for 54 Gy in 25 fractions, the dose now used in both supra-networks and the International InPACT trial (NCT02305654) [20]. Nodal disease control may be improved by dose escalation. Our data shows there

were fewer infield recurrences with doses over 50Gy (31.6% vs 14.2%). We hypothesize that a lower rate of recurrence will be seen when 54 Gy in 25 fractions is delivered. We also believe that a low rate of recurrence in the non-irradiated side (4 of 125 patients) also supports our current treatment standard of offering therapy to the pathologically involved, or presumed involved, nodal stations only in cases where pLND is not performed.

Other variables may impact on RFS after therapy. The median time to recurrence in our cohort was 6 months. In other series, median time to recurrence was found to be 5.7 months which is consistent with that in our overall cohort of patients (including those not receiving adjuvant therapy) [23]. Paradoxically, time to radiotherapy did not predict RFS or CSS in the present series. Intuitively we would expect some patients to experience a local recurrence before therapy with delays of 2-3 months. Graafland et al reported 11 of 26 inguinal recurrences occurred before radiotherapy had started [23]. In our cohort, 21 patients progressed with nodal or distant disease prior to starting adjuvant radiotherapy. Delayed wound healing, prolonged drain use in some instances up to 6 weeks, limitations due to service capacity, referrals to the local radiotherapy unit and time for radiotherapy planning; (usually 3 weeks) all contributed to the delay to commencing therapies. Minimisation of time to radiotherapy may yet be important for improving outcomes given the rapid relapse and mortality rate observed in the first 12 to 24 months. Patients who recurred (both nodal [inguinal/pelvic] or viscerally) after adjuvant radiotherapy died soon after disease recurrence despite palliative treatment as demonstrated by similar RFS and CSS. These patients tend to have a poor outcome and timely administration of radiotherapy to maximise local control and hence reduce the risk of nodal recurrence may improve long term patient survival.

The present study has some limitations. It was a retrospective study but this design is somewhat compensated for by a largely prospective data collection and the absence of significant changes in adjuvant management policy directed by sMDM and regularly reviewed as part of an annual peer review process. Adjuvant radiotherapy at both centres was administered to an involved inguinal or pelvic nodal basin. Where pLND was not performed, adjuvant radiotherapy was also administered to the ipsilateral pelvis of the involved inguinal nodes. None of the patients in our cohort received adjuvant chemotherapy, which may improve outcomes further. However, surgical and supportive management varied over the 15 years. Not all patients had pelvic node staging owing to poor ECOG PS or as a result of centre practice at the time; current EAU guidance recommends pelvic staging [6]. This creates some inevitable heterogeneities but reflects the spread in demographics of the referral population and clinical practice. We were unable to obtain a small number of results with regard to radiation dosing and addition of chemo-sensitisation. Surprisingly, we did not find an improvement in OS with the addition of chemo-sensitisation and indeed patients who had chemosensitisation had a poorer outcome, however this was not statistically significant. This may be explained by offering chemo sensitisation to patients with the most aggressive disease. In most squamous cancers, addition of chemo-sensitisation (usually cisplatin) to adjuvant radiotherapy has been shown to be superior to radiotherapy alone for managing ENE [24-25]. This may contribute to the number of in field recurrences in SCCp in our cohort of 21% (26 of 125). Quality of Life (QoL) and morbidity related to radiotherapy such as toxicity remain important outcomes and should be the subject of further study. We have no data on QoL outcomes or the side effect and toxicity profiles of radiotherapy administration for the cohort that had treatment as there was no standardised collection or reporting of toxicity.

Retrospectively collecting this data with the inherent risk of recall bias would not provide robust data on toxicity or QoL outcomes to inform this paper. We did however observe that 121 of 146 (82.8 %) of our patients completed radiotherapy. 4 of 146 did not complete their treatment with only two patients unable to complete all fractions due to frailty and a cerebral vascular event. Given the high completion rate of treatment, radiotherapy may be tolerable for patients. In a systematic review of adjuvant radiotherapy after lymphadenectomy, Robinson et al failed to identify any robust evidence on the added toxicity of radiotherapy [7]. Approximately 50% of the same cohort did not receive concomitant chemo sensitisation because of underlying co-morbidities such as poor renal function and performance status [7]. Our collective experience has demonstrated an incremental risk of genital and lower limb lymphoedema with the addition of radiotherapy to surgery. This has proven to have the most significant impact on patients QoL.

Despite the study limitations, we believe this data on a large cohort of men with exclusively pN3 disease treated with adjuvant radiotherapy is important for clinicians treating penile cancer.

Conclusion:

Application of a standard radiotherapy protocol within a centralised supra-network setting has achieved survival outcomes that would appear to be superior to those previously documented for either radiotherapy or chemotherapy in a solely pN3 cohort. The addition of adjuvant chemotherapy may improve these outcomes further. This data suggests that adjuvant radiotherapy has a role to play in the management of men with pN3 SCCp. Further prospective multi centre studies with a strict protocol on inclusion and exclusion criteria or a

randomised control trial comparing surgery only vs surgery and chemotherapy vs surgery and radiotherapy would add further valuable information to the management of this rare cancer.

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Conflicts of interest

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