NETSCC, HTA

9th November 2010

Sentinel lymph node (SLN) status in vulval cancer: Systematic quantitative reviews and decision analytic model based economic evaluation

1 Clinical Background

Vulval cancer accounts for approximately 3–5% of all gynaecological malignancies and 1% of all cancers in women, with an incidence rate of 1–2/100,000.[1] In the UK, it affects approximately 1,063 women every year with a 1 in 316 lifetime risk of developing vulval cancer.[2] Mortality data from 2007 shows 384 deaths in the UK.[2] Squamous cell carcinomas (SCC) account for more than 90% of vulval cancers;[3] the other 10% include melanomas, sarcomas, basal cell carcinomas and adenocarcinomas.[4] Although its peak incidence is in the 7th decade, there has been a significant increase in rates of vulval cancer in younger women. The proportion of women diagnosed with this cancer under the age of 50 rose from 6% in 1975 to 15% in 2006.[2] This trend has been observed in many countries, and has been linked to the rising incidence of vulval intraepithelial neoplasia (VIN) in young women caused by infection with HPV.[5;6]

Vulval cancer is curable when diagnosed at an early stage. The standard treatment for squamous cell carcinoma of the vulva is radical surgery, which in all but stage Ia or superficially invasive disease includes inguinofemoral lymphadenectomy.[7] The inguinal lymph node status has been identified as the single most important factor in predicting mortality attributable to vulval cancer.[8] Overall, about a third of patients with operable disease have nodal spread.[7] Those patients with primary lesions not more than 2 cm, who are inguinal node negative have a 98% 5-year survival rate, while those with any size lesion and three or more unilateral nodes or two or more bilateral nodes associated have a 29% 5-year survival rate.[9] Morbidity from lymphadenectomy is high with significant negative impact on the Quality of Life (QoL). Nodal assessment with biopsy is currently not routinely performed in practice.

The likelihood of metastasis is related to the size and the depth of the primary tumour. In stage Ia, this likelihood is almost zero, and rises once invasion extends beyond 1 mm depth. At the time of presentation, up to 25% of patients with vulval cancer are stage I, and of these, 30% are stage Ia. In absolute terms, this means that in any one year there will be a requirement for 700 - 750 groin lymph node dissections in the UK.[10] However, only around 30% of these operated cases will have evidence of nodal involvement;[7] the rest being node negative. This project will assess if nodal biopsy can be accurately and efficiently performed to direct the need for further lymphadenectomy.

1.1 Current clinical practice

Traditionally, the management of vulval cancer involves radical surgery which includes the excision of the primary lesion and unilateral or bilateral superficial and deep inguinofemoral lymphadenectomy.[7] The efficacy of this treatment is good, with reported groin recurrence rates varying between 1% and 10%.[11] However, as only 25% - 35% of patients with early-stage disease will have lymph node metastases,[7;12] and the remaining 65% - 75% possibly do not benefit from elective inguinofemoral lymphadenectomy while risking significant morbidity.[13] In the short term, wound healing in the groin is compromised by infection and breakdown in 20% to 40% of patients.[13] In the long term, lymphoedema of the legs with increased risk for erysipelas occurs in 30% to 70% of patients.[13] These complications can be incapacitating with major impact on sexual and psychological function.[14] Patients are also subjected to groin radiotherapy if cancer metastasis is detected on histopathological examination of lymph nodes. Patients treated with both complete inguinofemoral lymph node dissection and external beam radiotherapy to groin nodes suffer the morbidity of both treatments with a higher risk of lymphoedema and cellulitis.

Despite significant surgical morbidity and a low frequency of lymph node metastases, an elective inguinofemoral lymphadenectomy is regarded as standard of care. This is because unrecognised disease in the inguinofemoral lymph nodes is nearly always fatal.[13] An accurate test is needed that could identify those patients in whom the risk of metastases is low. Such a test could help exclude the need for

lymphadenectomy and would be extremely valuable. A minimally invasive technique to detect metastasis to the groin lymph nodes has a huge potential to reduce unnecessary morbidity.

1.2 **Tests for nodal involvement**

Assessment of the nodal status by clinical palpation of the groins is inadequate; of patients with clinically normal lymph nodes, 16–24% has metastases, while 24–41% of those with clinically involved nodes are negative at histological examination.[15;16] There are several minimally and non-invasive tests available for the status of groin nodes in vulval cancer, but none are routinely used in clinical practice. These include ultrasonography with or without fine needle aspiration, computerised tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and SLN identification (using blue dye or technetium-99m-labelled nanocolloid—99mTc).[7] This call for proposals focuses on the value of sentinel node biopsy using 99mTc or blue dye.

1.3 **Sentinel lymph node (SLN) identification by lymphoscintigraphy**

SLN refers to any lymph node that receives drainage directly from the primary tumour[17] (Fig 1). The SLN will be the lymph node with the highest probability of containing metastasis. Removal of SLN should therefore allow assessment of the status of lymphatic basin without the need to remove all the lymph nodes, providing an opportunity to avoid the morbidity associated with formal lymphadenectomy. If SLN is negative the rest of the groin should be at least risk of having subclinical metastasis.[18] The removal of fewer nodes (typically 1-3/groin) also permits more focussed pathological assessment of the SLN and direct pathological resources compared to 10-20 nodes removed by inguinofemoral lymphadenectomy.[18] SLNs are identified by isosulfan blue dye or 99mTc enhanced lymphoscintigraphy alone or in combination.[18]

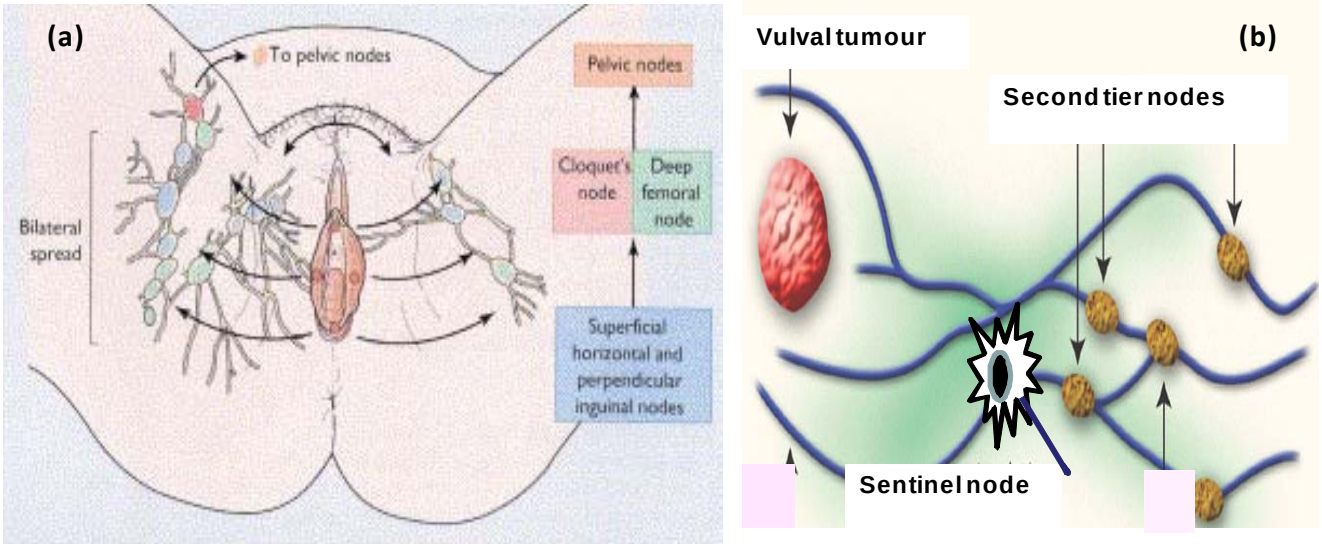


Fig 1. Lymphatic drainage of vulva (a) and radioactivity in sentinel node in vulval cancer (b)

(Adapted from Nature Biotech 2004; 22: 38-39 and Eur J Surg Oncol 2006; 32: 825-831)

Pre operatively 99mTc nanocolloid is injected around the primary tumour and dynamic images are obtained. The first site of focal accumulation is considered to be the sentinel node. During surgery a gamma probe (typically a caesium iodide scintillator) is used to confirm the location of the SLN. Once

the SLN have been removed the groin is rescanned to ensure removal of all SLNs. A background count after SLN removal of <10% of the initial value is typically used to confirm that all relevant nodes have been sampled. The signal arising from the SLN will depend on the dose of isotope used, the time lapse since injection, the number of and rate of flow within lymphatic channels and the distance between the probe and the target SLN. Where the signal from the SLN is weak, removal of the primary injection site on the vulval may be performed first, to facilitate localisation of the SLN in the absence of background signal.

99mTc enhanced lymphoscintigraphy has the advantage that in comparison to blue dye it facilitates localisation of the SLN even prior to the skin incision, potentially enabling a smaller groin incision (2 cm) to be used. The use of isotope also permits detection of sentinel nodes outside the usual basin, with the identification of aberrant drainage in those cases of clitoral involvement. Use of radiocolloid alone in vulvar carcinoma can avoid complications from blue dye (allergic reactions, permanent staining, and false oximeter readings.[19] This technique has already become well established in breast cancer where it was found to be better than blue dye in the identification of the sentinel node[20] and available data in vulval cancer would support the increased sensitivity afforded by the use of isotope.

Blue dye is injected intraoperatively around the site of primary tumour. This test is done in isolation or in combination with 99mTc enhanced lymphoscintigraphy. The use of blue dye to identify the sentinel node has the advantage that the entire test is performed under general anaesthetic at the time of the operation; hence additional preoperative assessment is not required. This technique does require a sizable skin incision to allow the surgeon dissection down to Camper's fascia and identification of the blue afferent channel to the blue / sentinel node.

1.4 Histopathological examination method of SLN

The accuracy of SLN biopsy in staging vulval cancer depends on the histopathological technique used for the examination of the sentinel nodes. Post-operative pathological assessment of the SLN may be combined with intra operative frozen section analysis.[18] Frozen section offers the advantage of performing synchronous complete lymphadenectomy and SLN biopsy if the SLNs are positive. The sensitivity of frozen section usually by single haematoxylin and eosin (H/E) staining is around 80%.[21] Apart from the concerns of accuracy with high false negative rates, there is a risk of loss of diagnostic tissue with intra operative methods. Standard pathologic examination of lymph nodes, i.e., H&E staining of a bivalved node, will sample only a fraction of the resected tissue. This sampling methodology could potentially fail to detect lymph node metastasis in the SLN producing a false negative result. Detailed analysis with serial sectioning and immunohistochemical staining can identify micrometastases that are not otherwise apparent. Enhanced pathologic analysis, termed "ultrastaging," generally involves serial sections through the node and application of specific immunohistochemical staining for epithelial antigens. Post-operative ultrastaging is labour intensive and could not be performed on the large numbers of nodes removed at formal lymphadenectomy. It has been shown to improve the sensitivity in detecting micro and macro metastatic deposits compared to routinely stained sections[22] . Whilst the biological relevance of metastases detected by ultrastaging remains controversial, groin recurrence has been identified in patients with micrometastasis only in the SLN.[18] Reverse transcriptase polymerase chain reaction (RT-PCR) has the potential to accurately detect micrometastasis.[20] Their use is limited for SLN biopsy in other tumours with very little data in vulval cancer. The therapeutic impact of stage migration due to detection of micrometastasis by the use of techniques with ever increasing sensitivity compared to standard histopathology needs further evaluation.

1.5 Role of SLN biopsy in clinical management of vulval cancer

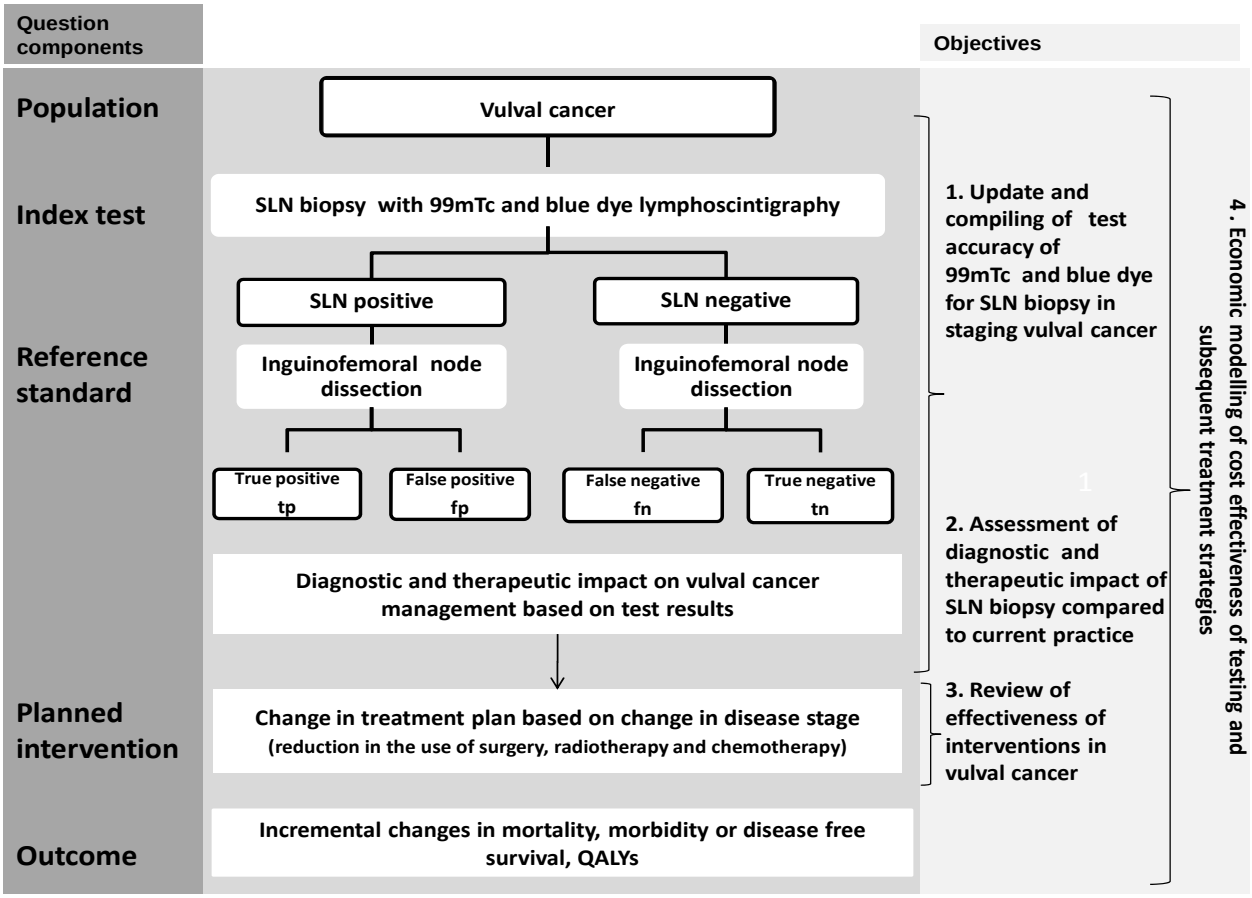
Early vulval cancer may be treated with radical excision of the primary tumour in combination with SLN biopsy. Most protocols utilise ultrastaging for assessment of the SLN. Where the SLNs are negative no further treatment is employed and the patient is observed. Where such a protocol is followed for patients with small (<4cm) tumours and no obvious preoperative metastases, the groin recurrence rate is low (3% including multifocal disease; 2.3% in unifocal vulvar disease), there is excellent disease-specific survival

rate of 97% at 3 years and minimal treatment-related morbidity.[13] If SLNs are positive for micro or macrometastasis, the patients typically undergo inguinofemoral lymphadenectomy. For those with a metastasis >5mm, more than one intranodal metastasis and/or extranodal spread, postoperative external-beam radiotherapy (50 Gy) to the groin/pelvis is recommended, possibly combined with chemotherapy. There are no randomised controlled trials (RCT) in vulval cancer that compare the effect of SLN biopsy on treatment and outcome due to the rarity of the condition. In fact, the EORTC (European Organisation for Research and Treatment of Cancer) withheld an attempt to assess SLN biopsy by an RCT as the power calculation estimated a prohibitively large sample size[21]. An ongoing study (GROINSS-V II GROningen INternational Study on Sentinel nodes in Vulvar cancer) is investigating the safety of omitting further surgery in such SLN positive patients but this is not yet within standard practice.

The performance of SLN biopsy is known to be associated with a learning curve.[23] Due to the consistent pattern of lymphatic drainage of the vulva the learning curve is considered to be much steeper for vulval cancer than other tumours. Introduction of SLN biopsy into routine practice will require quality control at each step. This multidisciplinary procedure, includes injection of radioactive tracer by either the surgeon or a nuclear medicine physician familiar with vulval anatomy, careful interpretation of lymphoscintigram, a surgeon with successful experience (sentinel node procedure followed by full lymphadenectomy) in at least 10 patients, and a pathology department experienced in ultrastaging (laterally sectioning of the nodes at 3-mm intervals and then each block cut at 400-µm intervals) of the sentinel nodes.[13]

There is a need to systematically review the comparative accuracy of 99mTc and blue dye for SLN biopsy in staging for vulval cancer. Moreover it is important to review how testing of sentinel nodes will impact on staging, therapeutic options and outcomes. Fig 2 conceptualises the role of SLN biopsy in the management of vulval cancer to be evaluated in this project.

Fig 2: SLN biopsy and treatment strategies in women with vulval cancer



2. Work leading to the proposal

An MRC Fellowship awarded to TS supervised by KSK and TR conducted systematic reviews of accuracy of tests for lymph node metastasis in gynaecologic oncology[24] (PhD awarded at University of Birmingham in 2009). We published a systematic review of accuracy of tests that evaluate node status in vulval cancer in 2005. We have also initiated a decision-analytic model based economic evaluation to determine the relative costs and effectiveness of a range of alternative preoperative tests and subsequent management strategies for inguinofemoral lymph nodes.[24] This HTA call for proposals gives us the opportunity to update the accuracy review, to use more robust statistical methods for meta analysis,[25] to complete the economic evaluation initiated, and to undertake a probabilistic sensitivity analysis on the model.

2.1 Systematic review of accuracy of tests for sentinel node status

We identified relevant literature from 1974-2005 to conduct the review using a prospective protocol and widely recommended methods.[26;27]The initial search generated 1154 citations from which 82 articles were potentially relevant. After assessment of the full manuscripts, a total of 24 articles that reported 29 tests were selected.[10] Studies included in the review were those that compared the index test to the histological evaluation of inguinofemoral lymphadenectomy specimen. Eleven studies evaluated the accuracy of 99mTc and 8 studied blue dye for SLN biopsy in staging. SLN biopsy using 99mTc had a pooled sensitivity and negative Likelihood ratio (LR-) of 97% (91–100 95% CI) and 0.12 (0.053–0.28 95% CI), respectively, and was the most accurate of the tests reviewed.[10] Blue dye alone for identification of SLN had a pooled sensitivity of 95% (82–99 95% CI) and LR- of 0.16 (0.07–0.32 95% CI).[10] This review needs updating with reassessment of the study quality, use of bivariate meta analysis and metaregression to compare 99mTc vs blue dye.

Table 1. Accuracy of studies evaluating sentinel nodes with 99mTc enhanced lymphoscintigraphy and blue dye in vulval cancer

Study (year)	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Isosulfan blue dye								
Levenback 1994	2	0	5	0	100% (63-100)	100%(48-100)	10(0.67-149)	0.18(0.01-2.31)
Levenback 1995	3	0	15	0	100%(29-100)	100%(78-100)	28(1.78-439.41)	0.13(0.01-1.73)
Ansink et al 1999	9	0	41	2	81%(48-98)	100%(91-100)	66.5(4.17-1061)	0.21(0.07-0.64)
Echt 1999	2	0	7	0	100%(16-100)	100%(59-100)	13.3(0.87-204.7)	0.18(0.01-2.25)
Molups 2001	2	0	6	0	100% (16-100)	100% (54-100)	11.6 (0.77-176.84)	0.18 (0.01-2.27)
Levenback 2001	10	0	45	0	100%(69-100)	100%(92-100)	88(5.6-1387)	0.05(0.003-0.69)
Puig-Tintore 2003	5	0	24	0	100% (48-100)	100% (86-100)	45.8 (2.92-720.2)	0.08 (0.006-1.21)
Moore 2003	3	0	16	0	100% (29-100)	100% (79-100)	29.75 (1.89-456.0)	0.13 (0.01-1.72)
Summary	**36**	**0**	**159**	**2**	**95%(82-99)**	**100% (98-100)**	**27.4(10.4-72.2)**	**0.16 (0.07-0.32)**
99mTc identification								
DeCesart 1997	10	0	0	0	96%(68-100)	50%(6-95)	---	---
De Hullu 1998	2	0	8	0	100%(16-100)	100%(63-100)	15(.96-232)	0.18(0.014-2.23)

De Cicco 2000	8	0	29	0	100%(16-100))	100%(88-100)	50(3.06-817.98)	0.17(0.013-2.13)
De Hullu 2000	27	0	68	0	100%(87-100)	100%(95-100)	135.54(8.6-2146)	0.018(0.001-0.28)
Sideri 2000	13	0	31	0	100%(75-100)	100%(89-100)	61.7(3.94-867.23)	0.04(0.002-0.52)
Molpus 2001	2	0	6	0	100%(16-100)	100%(54-100)	11.7(0.78-176.84)	0.18(0.01-2.27)
Tavares 2002	3	0	12	0	100%(29-100)	100%(73-1000)	22.8(1.46-353.43)	0.13(0.01-1.74)
Boran 2002	4	0	11	2	67%(22-96)	100%(71-100)	15.4(0.97-245.88)	0.37(0.14-1.01)
Sliutz 2002	9	0	17	0	100%(66-100)	100%(80-100)	34.2(2.22-527.99)	0.05(0.003-0.76)
Moore 2003	9	0	22	0	100%(66-100)	100%(85-100)	43.7(2.81-680.31)	0.05(0.003-0.76)
Puig-Tintore 2003	5	0	25	0	100%(48-100)	100%(86-100)	47.7(3.03-749.83)	0.08(0.006-1.21)
Summary	**91**	**0**	**229**	**2**	**97%(91-100)**	**100%(98-100)**	**33.4(14.-79.8)**	**0.12(0.053-0.28)**

2.2 Prospective observational study of SLN biopsy in early vulval cancer (GROINSS-V GROningen INternational Study on Sentinel nodes in Vulvar cancer)

PB was the principal UK investigator of the GROINSS-V study and is now the chief investigator for the UK in the follow-on GROINSS-V II study. GROINSS-V was a large, prospective, multicentre observational study on SLN detection using radioactive tracer and blue dye in patients with early vulval cancer.[13] The study demonstrated that for appropriately selected patients, sentinel node dissection appears to be safe, reliable and associated with reduced morbidity as compared to formal inguinofemoral lymphadenectomy. The accuracy of SLN biopsy has been verified by two different reference standards. When SLN was found to be negative, inguinofemoral lymphadenectomy was omitted, and the patient was observed with follow-up for 2 years at intervals of every 2 months for groin recurrences. There is a risk of bias with this differential verification. Nevertheless GROINSS-V is the largest single well conducted study (n=403) to date compared to other studies evaluating SLN biopsy. Furthermore it offers prospective data to evaluate the actual therapeutic impact of the alternate strategy of performing SLN biopsy without routine inguinofemoral lymphadenectomy.

2.3 Review of outcomes following inguinofemoral lymphadenectomy

We systematically reviewed the literature (1974-2005) for relevant clinical outcomes, Quality Adjusted Life Years (QALYs) and early and late complication rates following inguinal femoral lymphadenectomy.[24] The 5 year survival rate was estimated from published studies for node negative and node positive patients, the range of survival depending on the size of primary vulval lesion and the number of positive lymph nodes. For those with negative lymph nodes as point estimate for five year survival was 84% (70-98%) and for node positive patients 42.5% (25-60%). QALYs are the preferred outcome taking into account both the quantity and quality of life.[24] We failed to identify any studies that had used QALY data. As patients suffering for breast cancer also suffer similar lymphoedema a review of that literature was undertaken, but this also failed to provide relevant data. The data on complication rates came from studies specifically reporting on complications of lymphadenectomy excluding the radical vulvectomy procedure and from those that used a triple incision approach to the management of vulval cancer[28]. Two studies reported immediate post operative complication rates ranging from 44% to 66%.[29] A literature review of long term complications found variation in rates from 12 – 51% with an average point estimate for the model of 34%.[30-32] The duration of inpatient stay was taken from local hospital statistics (Birmingham Women's Hospital NHS foundation Trust). We will obtain updated data from current inpatient statistics from the Pan Birmingham gynaecological cancer centre and the Addenbrookes NHS trust for this project. This review needs updating with recent searches and where published data are not available, we will contact the individual specialist centres to provide more information. This will

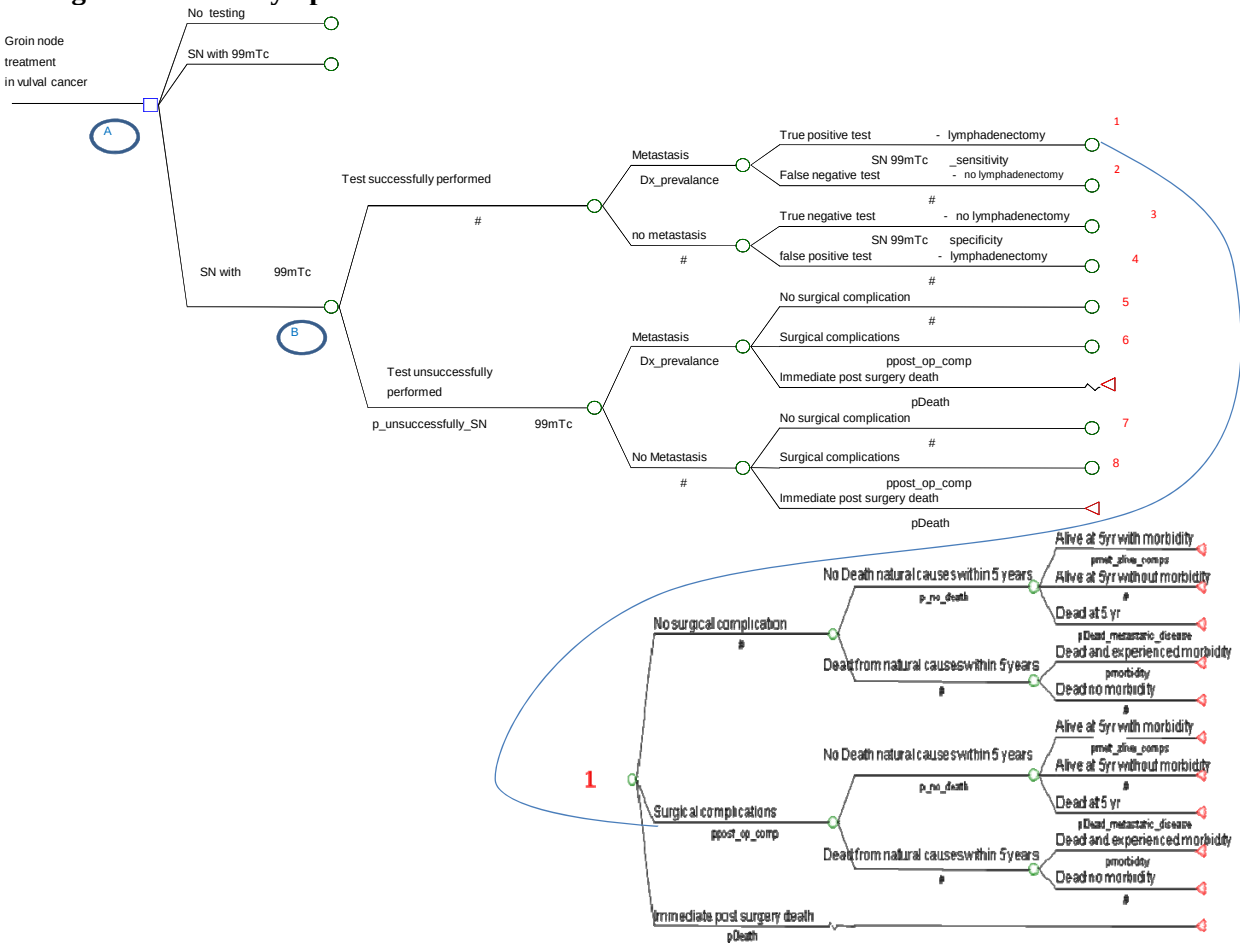
enable us to evaluate the diagnostic and therapeutic impact of performing SLN biopsy over inguinofemoral lymphadenectomy.

2.4 Model based cost effectiveness analysis of testing for sentinel nodes

We initiated an economic evaluation using a decision analytic model to compare strategies that used the results from various pre operative tests to determine the need for performing inguinofemoral lymphadenopathy in women over 70 years of age with vulval cancer.[24] This work is not prepared for publication as there are several areas for improvement identified below. Fig 3 shows a subset of the model to illustrate the approach developed.

The outcomes were cost per morbidity free 5 year survival and cost per death avoided at 5 year. Absence of relevant data prevented the estimation of cost per QALY. The strategy of inguinal femoral lymphadenectomy for all patients with vulval cancer without pre operative lymph node testing was the most expensive and not the most effective in avoiding death. It was the least effective in providing morbidity free survival. The most effective strategy for both was that of pre operative SLN biopsy. This had an annual Incremental cost effectiveness ratio (ICER) of £33,079 for the outcome of death avoided and an ICER of £100,888 for morbidity free survival. Both ICERs were above the willingness to pay threshold set by NICE of £30,000. Through this exploratory work we have identified the following areas of additional work for a robust evaluation through this project. We will construct the model for women with vulval cancer of all age groups. We will evaluate the development of late complications in those women suffering early complications and incorporate data on inpatient stay. We will perform probabilistic sensitivity analysis. With this exhaustive evaluation we hope to have reliable answers to guide practice.

Fig 3. Branch of the decision tree model used in cost effectiveness analysis of treatment strategies for inguinal femoral lymph nodes in women with vulval cancer



3 Research Objectives

The commissioning brief is for an evidence synthesis of the added value of 99mTc enhanced lymphoscintigraphy for SLN biopsy in staging for women with vulval cancer in comparison to the current practice of inguinofemoral lymphadenectomy. Our project will follow the key steps involved in health technology assessment of tests[33] and will meet the commissioned brief by fulfilling the following objectives:

Objectives	Plan of Research
1. To determine the accuracy of SLN biopsy with 99mTc enhanced and blue dye lymphoscintigraphy compared to the histopathology of inguinofemoral lymphadenectomy specimen in vulval cancer through systematic review, bivariate meta analysis and metaregression analysis.	Section 5.1
2. To assess through systematic review the diagnostic and therapeutic impact of lymphoscintigraphy for SLN biopsy in a) changing disease staging b) changing planned treatment c) reducing complications associated with lymphadenectomy d) improving morbidity and disease free survival	Section 5.1
3. To determine the effectiveness of various interventions (surgery, radiotherapy, chemotherapy) in the management of vulval cancer	Section 5.2
4. To evaluate the cost-effectiveness of lymphoscintigraphy directed treatment vs current treatment strategy in terms of both human and financial costs using decision-analytic modelling.	Section 5.4

The relationship of our objectives to the clinical process is shown in Fig 2.

4 Relevance to commissioning brief

The title of the HTA commissioning brief (09/112) refers to 'The value of adding 99mTc enhanced lymphoscintigraphy for SLN biopsy to current methods of staging of vulval cancer'. It goes on to include the following in the scope of the work to be carried out: effect of staging on treatment planned, reduction in the need for lymphadenectomy, decision analysis and cost effectiveness of added value of 99mTc enhanced lymphoscintigraphy compared to blue dye and current practice of inguinofemoral lymphadenopathy. From this, we take it that the scope of the work is to be broad.

We have published systematic review of the diagnostic accuracy of 99mTc enhanced and blue dye lymphoscintigraphy directed SLN biopsy in the staging of vulval cancer in 2006.[10] We shall update the search to incorporate the findings of the primary studies published in the last 5 years. The brief has specified inguinofemoral lymph node dissection as the gold standard. It also asks researchers to 'ensure data is included from the latest clinical trials and identify to what extent this will lead to a change in staging of the cancer and the subsequent treatment and quality of life of patients'. The largest and recent trial in this area, GROINSS-V, uses different reference standards - inguinofemoral lymph node dissection (if SLN positive) and follow up for groin recurrence (if SLN negative).[13] We have broadened our search and selection criteria to include studies that confirm SLN status by either inguinofemoral lymph node dissection or follow up and accounted for this variation in study design in our analysis and modelling.

In order to determine the value of SLN biopsy with 99mTc, information on diagnostic accuracy alone will not be sufficient. We will evaluate the potential of SLN biopsy in correctly identifying the sentinel node (localisation or mapping failure rates), the impact of surgeon and team's experience and skills on the

accuracy, the impact of variation in disease characteristics, index test protocols and histopathological examination methods on the accuracy. In addition information on diagnostic impact, therapeutic and patient outcomes will be needed. Thus, it is crucial to review effectiveness of various interventions in patients with vulval cancer in addition to accuracy of 99mTc enhanced and blue dye lymphoscintigraphy directed SLN biopsy compared to inguinofemoral lymphadenopathy in staging of vulval cancer to inform decision analytic modelling. Through this project we will update the structure of our existing decision analytic model, will update the probability and cost input data, and will perform probabilistic sensitivity analysis.

We believe that it is feasible to undertake this work within the time scale with the resources we have requested. Our team has the necessary experience and expertise for fulfilling all the requirements in the HTA brief. We have a very strong, internationally renowned, group knowledgeable in systematic reviews of diagnostic and effectiveness data and in economic modelling. Through our MRC training fellowship project, we have the expertise to undertake and update systematic reviews on SLN status in vulval cancer.[24]

5 Plan of research

The plan of research will be to update systematic reviews of the accuracy of 99mTc enhanced and blue dye lymphoscintigraphy for sentinel lymph node biopsy in vulval cancer and to undertake systematic reviews of the effectiveness of treatments for vulval cancer. Simultaneously a previously developed decision analytic model will be refined and additional rapid systematic reviews will be undertaken as necessary to populate the emerging model.

We will address the following structured question:

Population: Women with early stage vulval cancer

Index Tests: 99mTc enhanced and blue dye lymphoscintigraphy for SLN biopsy

Reference standard: Histopathology of inguinofemoral node dissection
Follow up for groin recurrence

Interventions: Current practice of surgery with routine inguinofemoral lymphadenectomy compared to interventions based on SLN status with or without groin node dissection; radiation, or chemotherapy

Outcomes:

- Test accuracy: Accuracy of 99mTc enhanced lymphoscintigraphy compared to blue dye in identifying potentially curable disease
- Diagnostic impact: change in staging after 99mTc enhanced lymphoscintigraphy compared to blue dye or current practice
- Therapeutic impact: change in treatment plan including avoidance of full inguinofemoral lymphadenectomy after 99mTc enhanced lymphoscintigraphy compared to blue dye and current practice by response to treatment that permits continuation or alteration of treatment or decision on clinical follow up only
- Patient outcomes: mortality, morbidity free survival, Quality of Life
- Economic outcome: Use of resources, cost per death avoided, cost per complication free survival, cost per quality adjusted life years (costs per QALY)

Study design:

- Test accuracy studies
- Prospective cohort studies of outcomes of patients tested
- Studies investigating diagnostic and therapeutic impact with or without concurrent assessment of test accuracy.
- Randomised controlled trials and non randomised controlled studies assessing effectiveness of interventions.
- Economic evaluations

Exclusions:

- Advanced stage vulval cancer, inoperable tumours, tumours with diameter > 4cm or those unsuitable for primary surgery
- Clinical suspicion of metastases with palpable inguinofemoral lymph nodes, enlarged lymph nodes (>1.5 cm) on imaging or cytologically proven inguinofemoral lymph node metastases.
- Patients with multifocal tumours

Systematic reviews of test accuracy, diagnostic and therapeutic impact, and effectiveness will be updated / carried out using established methodology in line with the recommendations of the NHS Centre for Reviews and Dissemination and the Cochrane Collaboration including those of Cochrane Methods Working Group on Screening and Diagnostic tests.[26;34] Inclusion, data extraction and quality assessment will be carried out in duplicate with differences resolved by consensus and/or arbitration involving a third reviewer.

5.1 Reviews of test accuracy and impact of testing

Evidence on the accuracy of SLN biopsy with 99mTc and blue dye lymphoscintigraphy will be reviewed. Alongside this we will review the impact of SLN biopsy on staging and treatment in vulval cancer. Studies will be identified from a database of published and unpublished literature which will be assembled. We have published a systematic review of literature on diagnostic accuracy of SLN biopsy and have identified 24 relevant studies.[10] We will rerun our search strategy and update the accuracy review, seeking studies on diagnostic and therapeutic impact in addition.

5.1.1 Study identification and selection

Evidence on the accuracy of sentinel node biopsy using 99mTc and blue dye and their diagnostic and therapeutic impact in early vulval cancer will be identified from sensitive searches of published and unpublished sources. Language restrictions will not be applied to electronic searches. The following databases will be searched: MEDLINE, EMBASE, Science Citation Index, MEDION and Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including Clinical Trials.com and UK Clinical Research Network Portfolio. A draft MEDLINE strategy is included in appendix 1. Electronic searches will be supplemented by hand searching, contacting manufacturers and consultation with experts in the area. In addition authors of included studies will be contacted for information on relevant published or unpublished studies. The preliminary search undertaken to update our published accuracy review has yielded additional 142 citations with 85 on test accuracy. Citations identified by the search will be selected for inclusion in the review in a two-stage process using predefined and explicit criteria regarding populations, index tests, reference standard, outcomes and study design. These criteria have been piloted in our previous review.

5.1.2 Study quality assessment and data extraction

Methodological quality of the selected primary studies of test accuracy will be assessed based on elements of study design, conduct and analysis included in a validated assessment tool, QUADAS, which will be adapted to the topic area.[35] Existing studies of diagnostic and therapeutic impact are likely to be concurrent test accuracy studies evaluating SLN biopsy with either groin dissection or clinical follow up[13] as reference standards. There are no validated assessment tools for studies that evaluate the impact of testing. We shall adapt the QUADAS criteria to evaluate the studies on impact adjusting for test, reference standard, treatment and outcome characteristics. Data extraction will be performed using pre-designed, piloted data extraction forms, drawing on existing pro-formas used by the project team in previous, completed reviews in the topic area.[10] Missing information will be obtained from investigators if is crucial to subsequent stages of analysis and modelling. To avoid introducing bias, unpublished information will be treated in the same fashion as published information. In addition to using double data extraction to ensure the reproducibility of the overview, sensitivity analyses around important or questionable judgements regarding quality assessment and data extraction will be performed.

5.1.3 Data synthesis

Sensitivity, specificity and LRs for individual studies comparing 99mTc and blue dye with inguinofemoral lymphadenopathy will be derived.
It is anticipated that the following will be important sources of variation in test accuracy estimates:

-Population characteristics: Stage of vulval cancer, size of lesion, location of lesion, method of diagnosis of vulval cancer (clinical diagnosis, excision or punch biopsy)
-Index test characteristics: Type of sentinel node biopsy, reporting of test execution and interpretation, number, training and expertise of the persons reading and executing the test, healthcare setting (secondary or tertiary)
-Reference test: readers of histopathology of nodes from inguinofemoral lymphadenectomy blind to the index results, clinical follow up for groin recurrence in test negative patients
-Study quality: study design (prospective or case-control) and study quality (high: meeting all assessment criteria; medium: meeting at least one assessment criteria; low: meeting no quality criteria). High quality studies will be used as the reference category to determine whether medium and low quality studies have biased estimates of test accuracy.

Based on an investigation of heterogeneity summary estimates of sensitivity, specificity and summary ROC curves will be derived using bivariate method for meta-analysis.[25;36-38] LRs are considered more clinically meaningful as measures of test accuracy and they allow estimation of probabilities for economic modelling. Post test probabilities can be used to tailor the absolute effectiveness estimates according to test results. Presence of a threshold effect will be examined by plotting sensitivity against 1-specificity in a receiver operating-characteristic analysis (ROC analysis) and by calculating Spearman correlation coefficients.[39]

Heterogeneity of results between studies will be investigated qualitatively by examining the distribution of sensitivities and specificities in (ROC) space and variability of estimates of diagnostic odds ratios (DOR) across studies using the forest plot.[39] In addition, heterogeneity will be investigated quantitatively using meta-regression and subgroup analyses. Quantitative investigation will be undertaken based on variables defined a priori and including population characteristics, index and reference test characteristics and study quality.[40] Metaregression will allow us to test the hypothesis as to whether 99mTc is more accurate than blue dye or not. We will perform sensitivity analysis to assess the effect of study design and quality including those with differential reference standard on the overall accuracy, diagnostic and therapeutic impact. This data will be utilised in the development of the decision analytic model.

The risk of publication and related biases is expected to be high in reviews of test accuracy. Publication bias will be investigated using funnel plots of DOR against corresponding variances.[41;42] Qualitative investigation will be based on the premise that large gaps in the funnel indicate possible 'missing' publications. These omissions are usually due to small studies showing limited accuracy and are unlikely

to be missing at random. Statistical investigation of publication bias will be undertaken in STATA based on templates of commands and instructions already developed by the project team.

5.2 Review of effectiveness of interventions

For evidence on the effectiveness of treatments for vulvar cancer we will begin by searching for existing systematic reviews. Any existing reviews will be examined for relevance and currency in order to inform further searching for primary studies. Existing reviews will be assessed for their quality and currency follow existing guidelines QUOROM and PRISMA.[43] Through this process we will identify gaps where reviews do not exist and where they need updating.

5.2.1 Study identification and selection

Where necessary effectiveness reviews of RCTs of treatments for vulval cancer will be undertaken following existing guidelines[27] ensuring the output complies with the QUOROM statement.[43] Searches for further primary studies will be performed. The following databases will be searched: MEDLINE, EMBASE, Science Citation Index and the Cochrane Library (all databases). On-going studies will be sought by searching Clinical Trials.com and the UK Clinical Research Network portfolio. Draft searches for MEDLINE are included in Appendix 1. Studies will be selected for inclusion in the review in a two-stage process using predefined and explicit criteria regarding populations, interventions and outcomes using procedures similar to the ones outlined in the previous section 5.1.1

5.2.2 Study quality assessment and data extraction

The quality of included reviews will be assessed against a validated tool and a reporting checklist, QUOROM.[43] Methodological quality of randomised and non-randomised trials will be assessed based on accepted criteria. Information on the adequacy of randomisation, sequence generation, concealment, blinding, description of withdrawals, and follow-up rates would be sought as these are elements most likely to have a direct relationship to bias in a RCT.[44] Procedures for obtaining missing information and resolving disagreements will be similar to the ones outlined in section 5.1.2.

5.2.3 Data synthesis

Revman and Stata softwares will be used to conduct analyses. Heterogeneity of results between studies and investigation for publication bias will be statistically and graphically assessed using established methods. The decision to proceed to meta-analysis will depend on the degree of heterogeneity in the data set. It is anticipated that the following will be important sources of variation in the estimates of effectiveness:

-Population characteristics: Stage of vulval cancer, age of patient, number of lymph node metastases, morphology of the nodes (size, extracapsular involvement)
-Treatment characteristics: Type of intervention (surgery, radiotherapy or chemo radiotherapy), duration of therapy, healthcare setting (secondary or tertiary), timing of intervention
-Outcome measures: Mortality, morbidity, Quality of life

Conclusions regarding the typical estimate of an effect size of the intervention will be interpreted cautiously if there is significant heterogeneity. Where uncertainty exists, the output from data syntheses will be employed following triangulation against subjective probability estimates, judiciously in decision analytic modelling.

5.3 Eliciting subjective probabilities

In anticipation of small numbers of effectiveness studies subjective probabilities will be elicited, using a group interview, from between 10 and 15 clinical experts in the fields of gynaecological cancer and oncology with no conflict of interest in the area, identified by clinicians in the project team and project advisors. The aim of the elicitation process will be to gather subjective views about the size and

probability of diagnostic and therapeutic impact of SLN biopsy using 99mTc to current practice in the staging of vulval cancer and reduction in the need for lymphadenectomy.

A face-face group interview (behavioural aggregation) will be used in preference to individual interviews as this facilitates a common understanding of the problem and task from experts and will allow us to benefit from group discussion and interaction leading to a consensus of opinion. The expert group will be facilitated by both a clinical and non-clinical expert drawn from the project team with sufficient statistical expertise to provide probabilistic training to experts, validate their results and provide feedback. The interview will take place over two half days and will, briefly, comprise of:

-Training of experts (probability, probability distributions, judgement heuristics and biases)

-Practicing elicitations

-Eliciting probabilities

-Presentation of results back to experts

-Repeat elicitation of probabilities to check face validity and if necessary ensure a joint probability distribution.

Findings from the elicitation process will be triangulated with findings from the systematic reviews and probability distributions will assist with populating the decision analytic model. As well as expertise within the project team[45] we have access to experts in the field, based at the University of Birmingham.[46] Furthermore the use of this method in the HTA funded project PET-CT imaging in restaging recurrent cervical cancer (HTA No 09/29/02) will help us to develop and refine the questionnaire for this project.

5.4 Model based economic evaluation

The objective of the economic evaluation will be to compare the relative cost effectiveness of undertaking SLN biopsy compared to current practice of intervention involving inguinofemoral lymphadenectomy without testing.

5.4.1 Perspective and data collection

If SLN biopsy is shown to be an accurate and effective alternative to the standard practice in staging vulval cancer then it is likely that important cost implications will be seen for the health care sector. For example, SLN biopsy may detect additional evidence of the extent of metastasis compared to standard investigations which could increase the number and extent of subsequent tests and treatment required by the individual. But the additional costs associated with more accurate staging of the cancer may lead to a reduction in costs associated with unnecessary or ineffective subsequent treatments and also prolong the life of the woman. Thus, if available data allow, the economic evaluation will be based on an outcome of cost per QALY and/or Cost per morbidity free 5 year survival (this latter is an outcome we have used in our previous analysis[24] due to the paucity of quality of life data)/or cost per 'death due to recurrent cancer' avoided. The analysis will adopt the perspective of the NHS.

Therefore data collection required for the model based economic evaluation will at least include:

- The equipment, other resource use and costs associated with SLN biopsy
- knock on costs associated with additional further tests and treatments that are required as a result of the staging
- equipment, resource use and costs associated with current practice
- Accuracy of the SLN biopsy and current practice package compared to the accuracy of current practice tests alone
- Effectiveness of alternative intervention pathways that are followed as a result of the diagnosis
- Outcomes such as quality of life associated with vulval cancer at various disease stages

Cost data will be collected from two principal sources. First, once the clinical evidence has been synthesised into the main strategies of diagnosis and treatment, relevant studies will be examined for their data on costs and resource use. These data will be subject to relevant quality criteria. Additional cost data

will be available from other sources such as the National Schedule for Reference Costs. If necessary primary cost and resource data will be collected from Pan Birmingham Cancer network and Addenbrookes Hospital to complete any gaps in the information required for the modelling process.

Additional searches will be undertaken to help populate the decision model. The Information Officer will work in close liaison with the health economist to identify the model questions. Information to answer these questions will be provided by focused searching of appropriate databases, including reference cost databases, statistical sources and other sources of relevant information. The evidence found in the clinical accuracy and effectiveness reviews will provide the majority of the parameters required to carry out the economic evaluations of alternative test and treat packages. Additional data on early complications predisposing to late complications, and psychosexual problems will be systematically obtained by searching the relevant literature. Where there is paucity of evidence, we will elicit subjective probabilities as detailed above. The costs for lymphoedema and district nurse input will be gathered by liaising with the lymphoedema service and the centres.

5.4.2 Model and analysis

The economic evaluation will involve the development of an existing decision analytic simulation model as a framework for conducting cost-effectiveness analyses.[24] The economic evaluations will inform current treatment policy in this clinical area. A modelling framework is ideally suited to demonstrate and explore the importance of the inherent uncertainty. We will develop the model including women with vulval cancer of all age groups. This will be a development of the existing model which focuses only on women 70 years and older.

An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from current practice to alternative test and treatment strategies. Using discounting, adjustments will be made to reflect the differential timing of costs and outcomes in terms of the extension to the length of life extend associated with the test and treat strategies. The base-case analysis will follow Treasury recommendations for public sector projects.

5.4.3 Presentation of results and sensitivity analysis

The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

In addition to probabilistic sensitivity analysis on our base-case model, we shall include a range of alternative analyses to explore the robustness of these results to plausible variations in key assumptions and variations in analysis, and to consider generalisability of the results.

6 Expertise in the team

The applicants have a wide and appropriate range of expertise in systematic reviews, gynaecological oncology, clinical pathology, clinical epidemiology, health measurement, economic evaluation, medical statistics, information science and health technology assessment.

The team (KSK, ST, SS, TR, AF) has recently been awarded a HTA grant to undertake systematic review and economic modelling of clinical effectiveness of PET-CT imaging in restaging recurrent cervical cancer (HTA No 09/29/02). KSK and TR have successfully completed many HTA projects on systematic reviews of test and treatments including systematic reviews of tests for pre-eclampsia, intrapartum rapid tests for Group B streptococcus infection and preterm labour.[47-49] In addition KSK has experience of the process of eliciting subjective probabilities. His former student and current colleague TS was awarded MRC research training fellowship to undertake systematic reviews of accuracy of tests and treatment in

gynaecologic cancer including vulval cancer and for undertaking decision analytic modelling and economic evaluation.[24] KSK has also led a grant on the methodology of evaluation of tests without gold standards by the NHS Research Methodology Programme. ST has undertaken many systematic reviews on tests and treatment in with pre-eclampsia, preterm labour and epilepsy. TS has conducted systematic review of accuracy of sentinel node biopsy with tests including 99mTc and blue dye in vulval cancer. She has been awarded PhD by the University of Birmingham for her work 'Non invasive and minimally invasive diagnosis and treatment of lymphadenopathy in gynaecologic cancer. Systematic review of evidence'[24]

SS and PB are both gynaecologic oncologists involved in managing women with vulval cancer. They are members of the gynaecological cancer clinical studies group of the NCRI (National Cancer Research Institute) – the national group responsible for selecting national trials for inclusion in the NCRI portfolio and supporting and directing clinical research in gynaecological cancer. PB is a former trial group member of the large GROINSS-V prospective study investigating the role of SLN biopsy in early vulval cancer. His is also the Chief Investigator in the UK in the ongoing prospective multicentre international study GROINSS-V II which is evaluating the safety of omitting surgery in selected SLN positive patients. PB represents the study at the vulval subgroup of the NCRI. RG is a Consultant Histopathologist involved with Pan Birmingham Cancer network and Associate Director of Birmingham Cytology Training Centre (CTC). KB is a Consultant in Nuclear Medicine and has expertise in 99m Tc and blue dye lymphoscintigraphy for SLN biopsy. He will provide expert input into the issues that arise regarding the techiques used for SLN and variation in the interpretation of findings. This input will especially be valuable by providing clinical input into the decision analytic model where necessary. AF (information specialist) has extensive experience as an information specialist in providing support to a diagnostic and effectiveness technology assessments as a member of the West Midlands Health Technology Assessment Collaboration and the Aggressive Research Intelligence Facility (ARIF) based at the University of Birmingham. She is currently working on an HTA assessing the value of PET-CT for recurrent breast cancer and her expertise in devising the search strategy and database management will be of benefit to this proposal. Hilary Jeffries is a retired Lead cancer nurse and McMillan community nurse specialist with extensive experience of interaction with patients with vulval cancer. ME is a member of the Consumer liaison group, NCRI.

7 Contribution to Collective Research Effort

This systematic review on the value of SLN biopsy with 99mTc enhanced lymphoscintigraphy compared to blue dye and the current management of groin node dissection in vulval cancer and the cost effectiveness analysis of SLN biopsy using the above methods in comparison to current management fits comfortably with previously published HTA evaluations of sentinel node biopsy in other cancers. This research application complements existing National cancer research network portfolio research in gynaecological cancer. The ongoing GROINSS-V II study evaluates if inguinofemoral lymph node dissection can be omitted in the presence of a positive SLN and the treatment of groins with radiotherapy or chemoradiotherapy instead. This project will augment the current published evidence acquired through the MRC training fellowship on SLN biopsy in vulval cancer through update of the review and further comprehensive development of the decision analytic model.[24]

Due to the multiple methods employed by the proposed evidence synthesis the project team expect that the outputs of the work would be of interest to a broad research and clinical community including experts in the areas of evidence synthesis and in particular synthesis of test accuracy, gynaecological cancer, and decision making. Outputs would be submitted for presentation at national and international conferences such as Health Technology Assessment international, Medical Decision Making, European Society of Gynaecological Oncology (EGSO) and Society of Gynaecological Oncology (SGO). Similarly the outputs of this work would be of interest to a variety of peer reviewed journals and the project team would aim for a minimum of 3 peer reviewed publications in addition to publication as an HTA monograph. The project team have involved members of the NCRI consumer liaison group and VACO (Vulva Awareness Campaign Organisation), an international support group dedicated to women with vulval cancer. Users will be represented in study conduct and planning of dissemination strategies. The

team will benefit from the HJ in an advisory role who has worked closely with women with vulval cancer. She has recently published a qualitative study on the experiences of women with vulval cancer as part of her PhD.[50] Experience from previous research conducted by the team has already indicated that publication and dissemination needs careful consideration from the outset.[47-49] Publication strategy will also need to anticipate early the need for versions of the report, which can be, used by women themselves. For this we will seek input from relevant consumers.

8 Details about any related (planned or active) grants held by members of the research team

KSK (as supervisor) and TS were awarded MRC research training fellowship to undertake systematic reviews of accuracy of tests in gynaecologic cancer including vulval cancer. The resulting PhD has recently been awarded.[24] Information from the accuracy of tests in vulval cancer will be updated and the analysis will be refined. We have also developed a decision analytic modelling structure for tests in vulval cancer that will be improved upon. ST, KK, TR and SS have been successful in obtaining HTA grant for conducting systematic review and developing an economic model to evaluate the clinical effectiveness of PET CT in recurrent cervical cancer. (HTA No. 09/29/02) SS has a PhD student funded by the department of Health investigating the epigenetic changes induced by HPV in cervical cancer. PB holds a CRUK award to support the ongoing GROINSS-V II study. The expertise of SS and PB in gynaecologic oncology will be of use in providing subjective probabilistic estimates for test accuracy and effectiveness. AF (information specialist) is currently working on an HTA assessing the value of PET-CT for recurrent breast cancer and her expertise in devising the search strategy and database management will be of benefit to this proposal.

9 Summary for the non expert

Vulval cancer accounts for approximately 3–5% of all gynaecological cancers. In the UK, the lifetime risk of developing vulval cancer is 1 in 316. Although the peak incidence of this cancer is in the 7th decade, the proportion of women diagnosed with vulval cancer under the age of 50 has risen from 6% in 1975 to 15% in 2006. Vulval cancer is curable when diagnosed in an early stage. The current treatment for early stage vulval cancer is extensive removal of the vulval tumour and excision of the groin nodes to check for spread of cancer. Cancer in the groin nodes has been identified as the single most important factor in predicting survival. Removal of the groin nodes is associated with complications in the short term (infection, wound breakdown) and long term (lymphoedema, cellulitis, sexual dysfunction) with significant negative impact on the Quality of Life. Only about a third of patients with operable disease have nodal spread and the rest are unlikely to benefit from routine removal of groin nodes. Despite the risk of significant complications and low probability of cancer spread to the nodes, groin nodes are routinely removed as missed cancer in the groin nodes is nearly always fatal. A test that could accurately identify those patients in whom cancer has spread to the groin nodes without extensive removal of all groin would be extremely valuable. There are several methods to check for involvement of the groin nodes, but none are routinely used in clinical practice. This HTA proposal focuses on the value of testing the groin node (sentinel node) with biopsy by locating them with radioactive substance (99m Technetium) or blue dye.

The sentinel node (SLN) refers to any node that receives lymphatic drainage directly from the vulval tumour and therefore has the highest probability of containing cancer cells. If the sentinel node is free from cancer, the rest of the groin should be at least risk of having spread of cancer. Identification and removal of the SLN(s) avoids the significant complications associated with complete groin dissection. In those patients negative for cancer in the sentinel nodes where extensive groin dissection was omitted, studies suggest that the risk of future disease in the groin is low, the survival rate is excellent (97% at 3 years) and that there are few complications associated with this smaller operation. If the SLN is negative no further treatment is therefore required and the patient will be followed up in the clinic.

There is a need to systematically review the accuracy of SLN biopsy with 99mTc and blue dye in identifying the spread of cancer to the groins. Moreover it is important to review how testing of SLN will have an impact on the extent of cancer spread, treatment decisions, clinical and cost outcomes.

For the proposed project our objectives are as follows:
In women who have been diagnosed to have vulval cancer, to systematically review the literature

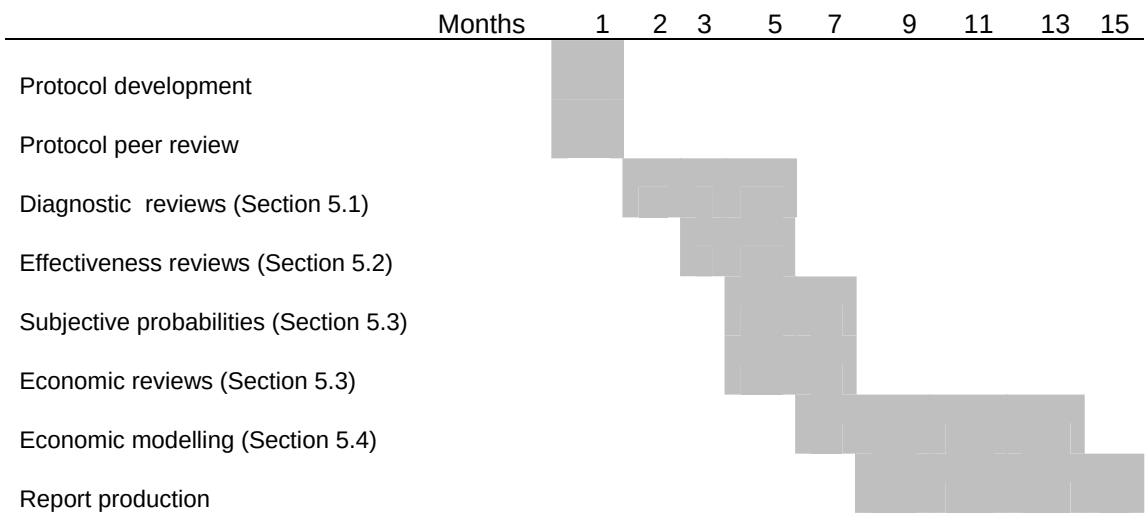
- To assess if SLN biopsy with 99mTc or blue dye can accurately diagnose spread of cancer to the groins compared to current practice of routine extensive removal of all groin nodes
- To evaluate if the use of SLN biopsy results in change in (re)staging i.e. extent of disease compared to current practice
- To assess the impact of performing SLN biopsy on the typical standard treatment
- To summarise the effectiveness of available treatments in women with vulval cancer
- To estimate the impact of SLN biopsy results on patient outcomes and the costs associated with its routine use in this patient group.

We plan to fulfil the above objectives by systematically identifying the available evidence on the diagnostic accuracy of SLN biopsy with 99mTc and blue dye in vulval cancer compared to the accuracy of existing practice of groin dissection used in this patients group and the effectiveness of treatments for vulval cancer. The evidence found will be used in an economic evaluation comparing existing testing and treatment strategies with SLN biopsy guided treatment strategies. This evaluation will inform current treatment policy in this clinical area and highlight future research need.

10 Project Timetable and Milestones

Fig 3 shows the project timetable and milestones for the accuracy and effectiveness reviews and economic modelling. We have carefully evaluated the ongoing work and the level of staffing within our departments and feel that we would be able to commence the work in Oct 2010 for a period of 15 months, if funded.

Fig 3: Timetable



11 Justification for the support required

Staff:

- Supervisor, also providing support for researchers, for example: double data extraction, assisting with inclusion decisions and being the lead for producing the final report – 1 day per week for the duration of the project.
- Researcher to perform systematic review of accuracy and effectiveness studies and to identify additional epidemiological and background information for input into the modelling exercise – 1 wte for 15 months.

- Health economist to perform systematic review of cost-effectiveness literature and modelling – 1wte for 12 months.
- Information support for searching and document retrieval –20 days.

Equipment and consumables:
- two standard specification computers, printing cartridges, paper and photocopying,
- telephone and fax calls, postage,
- estimated 200 interlibrary loans.

Support:
- Meeting room, refreshments and travel for the project team and consultants based on 4 face to face meetings over 12 months.
- Meeting room, refreshments and travel for consumer group representatives
- Administrative support, for steering group and preparation of final report –10 days over 12 months.

We are in an excellent position to gauge the level of resources required to deliver this type of project (systematic review and cost-effectiveness analysis) with several years experience in their delivery. We are able to draw on additional in-house expertise if necessary. Travel costs have included the cost of travel of experts and non experts for obtaining probabilistic estimates.

Appendix 1: Search strategy for electronic database identification of diagnostic studies for preoperative tests of lymph node status and therapeutic studies of interventions in vulval cancer

Test accuracy search – proposed MEDLINE strategy

Ovid MEDLINE(R) 1950 to November Week 3 2009
1 technetium.tw. (12014)
2 (radionuclide adj imag$).tw. (1508)
3 technetium/ (18834)
4 radionuclide imaging/ (23714)
5 sentinel lymph node biopsy/ (5545)
6 99m tc$.tw. (3979)
7 99mtc$.tw. (16283)
8 (sentinel adj2 lymph adj2 node$).tw. (4422)
9 or/1-8 (62808)
10 vulvar neoplasms/ (6493)
11 ((vulva or vulval or vulvar) adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (4197)
12 or/10-11 (7219)
13 9 and 12 (192)

Effectiveness search (systematic reviews) – proposed MEDLINE strategy

Ovid MEDLINE(R) 1950 to November Week 3 2009>
1 vulvar neoplasms/ (6493)
2 ((vulva or vulval or vulvar) adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (4197)
3 or/1-2 (7219)
4 limit 3 to "reviews (specificity)" (32)

Effectiveness search (RCTs) – proposed MEDLINE strategy

Ovid MEDLINE(R) 1950 to November Week 3 2009>
1 vulvar neoplasms/ (6493)
2 ((vulva or vulval or vulvar) adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (4197)
3 or/1-2 (7219)

4 limit 3 to "therapy (optimized)" (91)

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