

Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Testicular/Penile)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected testicular or penile cancer. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference.

Limited relevant studies were identified during literature searches. This document includes evidence on the following topics:

- Symptoms and Investigations
- Risk Stratification

Background

In males in the UK, testicular cancer is the 17th most common cancer, with around 2,400 new cases every year (2017–2019)¹. Scotland data by stage on either testicular or penile cancer is not publicly available. In England in 2018, 92% of testicular cancers were diagnosed at early stage (stage 1 or 2). 1-year survival for those who are diagnosed at the earliest stage is 100%, compared to 83% at Stage 3 (stage 4 data not available due to small numbers, England, 2016–2020)².

As a reproductive cancer, it is important to consider additional barriers along the pathway for people who are transgender. A systematic review aimed to investigate prevalence of reproductive cancers in those who are transgender, but the overall evidence quality was low³. Further research is required in a symptomatic context to determine prevalence in this cohort and potential barriers to diagnosis they may face.

Search Strategy

¹ Based on the average annual number of new cases of testicular cancer (ICD10 C62) diagnosed in men in the United Kingdom in the years 2017–2019. Similar statistics are available here: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer#heading-Zero>.

² Cancer Research UK (2022). Early Diagnosis. [online] [crukcanerintelligence.shinyapps.io](https://crukcanerintelligence.shinyapps.io/EarlyDiagnosis/). Available at: <https://crukcanerintelligence.shinyapps.io/EarlyDiagnosis/>.

³ Joint, R., Chen, Z. and Cameron, S. (2018b). [Breast and reproductive cancers in the transgender population: a systematic review](#). *BJOG: An International Journal of Obstetrics & Gynaecology*, 125(12), pp.1505–1512. doi:<https://doi.org/10.1111/1471-0528.15258>.

Search terms: PubMed search for combinations of the following terms: testicular cancer, penile cancer, risk, testicular cancer symptoms, testicular cancer PPV, testicular cancer investigation, scrotal mass, orchitis, phimosis, ultrasound, ultrasound, stage, presentation, recognition, referral, primary care, transgender, inequality

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from [NICE NG12 Evidence Review document](#).

Peer-reviewed literature

Topic: Symptoms and Investigations			
Summary:			
<p>There has been one UK based study published since 2015 investigating PPVs of individual symptoms or symptom combinations for testicular cancer. There are some symptom combinations, particularly those including testicular pain in those aged <50 years, which have relatively high PPVs and are not currently included in SRG:</p> <ul style="list-style-type: none"> • Testicular pain and abdominal pain: 6.1% • Testicular pain and groin pain: 3.7% • Testicular pain and raised inflammatory markers: 3.7% <p>Testicular pain has been reported as a common symptom in those diagnosed with testicular cancer, and paper 3 reported an association between testicular pain and longer diagnostic intervals (in comparison with symptoms included in previous NICE suspected cancer referral guidelines, 2005). This symptom is not included in current SRG.</p> <p>No UK based studies have been published investigating PPVs for individual symptoms or symptom combinations for penile cancer. Penile cancer has a much wider symptom signature than testicular cancer. LUTS are the most commonly reported symptoms for penile cancer (in paper 2, of all patients diagnosed with penile cancer, 46% experienced LUTS), which are not included in SRG. These symptoms are challenging to incorporate into guidelines, as they often present for benign conditions as well as potential cancers, making it difficult to differentiate.</p>			
Paper number	Study	Summary	Notes

<p>1</p>	<p>Shephard EA, Hamilton WT. Selection of men for investigation of possible testicular cancer in primary care: a large case-control study using electronic patient records. British Journal of General Practice. 2018 Jul 2;68(673):e559-65.</p>	<p>This study aimed to identify clinical features of testicular cancer and to quantify their risk in primary care.</p> <p>Of 31 symptoms and 22 investigations, 9 remained significant in the multivariable final model:</p> <p>Symptoms (Odds Ratio, 95% CI):</p> <ul style="list-style-type: none"> • Testicular swelling (280, 110-690) • Testicular lump (270, 100-740) • Testicular pain (38, 22-68) • Abdominal pain (2.5, 1.5-4.0) • Scrotal swelling (170, 35-800) • Groin pain (6.8, 3.3-14.0) • Orchitis/epididymis (13, 7.8-23.0) • Hydrocele (28, 7.7-100) <p>Investigations</p> <ul style="list-style-type: none"> • Raised inflammatory markers (4.3, 2.5-7.5) <p>PPVs were calculated for those aged <50 years:</p> <p>Individual symptoms:</p> <ul style="list-style-type: none"> • Testicular lump: 2.5% • Testicular swelling: 2.3% • Hydrocele: 1.1% • All other symptoms: <1% <p>Combinations of symptoms (and investigations):</p> <ul style="list-style-type: none"> • Testicular lump and abdominal pain: 6.1% • Testicular lump and testicular pain: 10% • Testicular lump and scrotal swelling: 3.7% • Testicular lump and testicular swelling: 17% 	<p>Matched case-control study using Clinical Practice Research Datalink (CPRD) dataset.</p> <p>Included those aged >17 years, and diagnosed between 2000-2012 across the UK</p> <p>N= 1398 cases, n= 4956 matched controls</p> <p>Limitations: despite the large sample size in this study, some of the symptoms, particularly combinations of symptoms had very small sample sizes. Many combinations could not determine PPVs due to this, particularly in those aged >50 years.</p>
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2	<p>Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. British Journal of Cancer [Internet]. 2024 Feb 1 [cited 2024 Feb 1];130(2):297–307.</p>	<p>This study aimed to (1) examine the relative frequency of presenting symptoms by cancer site (the ‘symptom signature’ of each cancer site), and (2) to examine the relative frequency of cancer sites by presenting symptom (the ‘cancer site case-mix’ of each symptom), among incident cancer cases.</p> <p>The mean number of symptoms present at penile or testicular cancer diagnosis was 1.2.</p> <p>Of all patients diagnosed with testicular cancer, the proportion that experienced x symptom are as follows: Testicular lump: 64%</p>	<p>Data from 2018 National Cancer Diagnosis Audit (England) N=55,122 (total cohort)</p> <p>Limitations: this is a case-only analysis (only patients with diagnosis of cancer were included), so cannot make inferences about PPV</p>

		<p>Testicular pain: 32%</p> <p>Other symptom, abdominal pain: 2%</p> <p>Weight loss, distention, lower abdominal pain, pelvic pain, loin pain, LUTS, back pain: 1%</p> <p>Of all patients diagnosed with penile cancer, the proportion that experienced x symptom are as follows:</p> <p>LUTS: 46%</p> <p>'Other' symptom: 18%</p> <p>Dysuria, back pain: 5%</p> <p>Haematuria: 4%</p> <p>Bruising/petechiae, pruritus, local lymphadenopathy, ulceration, UTI, erectile dysfunction: 3%</p> <p>Weight loss, thyroid lump/mass, leukoplakia, oral ulcer, clubbing, loin pain, bone pain, testicular pain: 1%</p>	
3	<p>Din NU, Ukoumunne OC, Rubin G, Hamilton W, Carter B, Stapley S, et al. Age and Gender Variations in Cancer Diagnostic Intervals in 15 Cancers: Analysis of Data from the UK Clinical Practice Research Datalink. Katoch M, editor. PLOS ONE. 2015 May 15;10(5):e0127717.</p>	<p>This study aimed to quantify the relationship between diagnostic interval and age, gender and presenting symptom in 15 cancers.</p> <p>Mean diagnostic intervals were shortest for testicular cancer (54.5 days) out of all cancers included.</p> <p>There was evidence that the diagnostic interval was longer for non-NICE* symptoms for testicular cancer (mean difference in diagnostic interval: 36.7 days; 95% CI: 17.0–56.4)</p> <p>*NICE symptoms were defined as those specifically cited in the NICE Guideline for Urgent Referral of Suspected Cancer (2005) for urgent investigation or specialist assessment.</p> <p>NICE symptoms: Painless lump/swelling in testis</p>	<p>Retrospective analysis, using Clinical Practice Research Datalink (CPRD) dataset for England and Wales.</p> <p>Included were cancers diagnosed between 2007–2010</p> <p>N= 18,618, n=161 for testicular</p>

		<p>Non-NICE symptoms: pain in testis, anaemia, anorexia, fatigue, weight loss</p>	<p>Limitations: despite this study including a large sample size, the sample size for testicular cancer only is relatively small, which may limit the representativeness of these results.</p>
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Topic: Risk Stratification			
<p>Summary:</p> <p>Testicular cancer risk factors have not been conclusively identified, but include age, family history and cryptorchidism (also known as undescended testicle/s). See here for Cancer Research UK’s webpages about testicular cancer risk. Male infertility and testicular microlithiasis (calcium deposits in testes, diagnosed via ultrasound) associated with infertility have been shown to increase the risk of testicular cancer.</p> <p>Penile cancer risk is higher in those diagnosed with either HIV, HPV or phimosis (inability to retract the foreskin over the glans). See here for Cancer Research UK’s webpages about penile cancer risk. Douglawi (2017) provides an overview of risk factors for penile cancer, which includes additional risk factors such as obesity, but notes the evidence is quite sparse. It also includes circumcision as a known protective risk factor.</p> <p>It may help primary care health professionals recognise potential testicular/penile cancer earlier if they are aware of these risk factors.</p>			
Paper number	Study	Summary	Notes
4	Del Giudice, F., Kasman, A.M., De Berardinis, E., Busetto, G.M., Belladelli, F. and Eisenberg, M.L. (2020). Association between	This study aimed to assess the available evidence on the association between impaired male fertility* with the risk of developing male-related malignancies (testicular and prostate).	Systematic review and meta-analysis Studies published up to 2019 were included

	<p>male infertility and male-specific malignancies: systematic review and meta-analysis of population-based retrospective cohort studies. Fertility and Sterility, 114(5), pp.984–996. doi:https://doi.org/10.1016/j.fertnstert.2020.04.042.</p>	<p>All four studies investigating testicular cancer reported a positive association with impaired male fertility, a range of relative risk (RR) estimates from 1.55–3.0.</p> <p>While the risk of subsequent testicular cancer is higher for infertile men, the absolute risk of cancer remains low (<1% for either cancer).</p> <p>*defined as 1 year of unsuccessfully attempting to conceive</p>	<p>N=6 studies included 4 conducted in USA, 2 in Europe (Denmark and Sweden)</p> <p>Limitations: none of the studies were conducted in the UK, which may limit applicability to UK context</p>
5	<p>Barbonetti, A., Martorella, A., Minaldi, E., D’Andrea, S., Bardhi, D., Castellini, C., Francavilla, F. and Francavilla, S. (2019). Testicular Cancer in Infertile Men With and Without Testicular Microlithiasis: A Systematic Review and Meta-Analysis of Case-Control Studies. Frontiers in Endocrinology, 10. doi:https://doi.org/10.3389/fendo.2019.00164.</p>	<p>This study aimed to systematically evaluate whether, and to what extent, testicular microlithiasis (TM: calcification present on ultrasound) is associated with a significantly higher prevalence of testicular cancer in infertile males.</p> <p>Pooled unadjusted estimate in this review indicated that the presence of TM is associated with a ~18-fold higher odd for having testicular cancer (OR: 18.11, 95% CI: 8.09–40.55; P<0.0001) in infertile men, compared to infertile men without TM. The adjusted estimate was lower but still considerably greater odds (adjusted OR: 16.42, 95% CI: 7.62–35.37; P<0.0001)</p>	<p>Systematic review</p> <p>N=8 studies included from across the world. 1 study is from the UK</p> <p>Limitations: meta-analysed studies included very few patients with TM (n=180) and very few cases (n=14 testicular cancers in cases and n=20 in controls), resulting in wide confidence intervals. Additionally, it is uncertain whether health professionals would have access to information about TM in primary care medical records.</p>

Suspected Testicular/Penile Cancer Referral Guidelines: NICE NG12 and SRG

NICE NG12	SRG
<p>Testicular cancer</p> <p>Consider a suspected cancer pathway referral for testicular cancer in men if they have a non-painful enlargement or change in shape or texture of the testis.</p> <p>Consider a direct access ultrasound scan for testicular cancer in men with unexplained or persistent testicular symptoms.</p> <p>Penile cancer</p> <p>Consider a suspected cancer pathway referral for penile cancer in men if they have:</p> <ul style="list-style-type: none"> • a penile mass or ulcerated lesion, when a sexually transmitted infection has been excluded as a cause, or • a persistent penile lesion after treatment for a sexually transmitted infection has been completed. <p>Consider a suspected cancer pathway referral for penile cancer in men with unexplained or persistent symptoms affecting the foreskin or glans.</p>	<ul style="list-style-type: none"> • Non painful enlargement or change in shape or texture of the body of the testis • Suspicious scrotal mass found on imaging • Men considered to have epididymo-orchitis or orchitis which is not responding to treatment • Any non-healing lesion on the penis or painful phimosis