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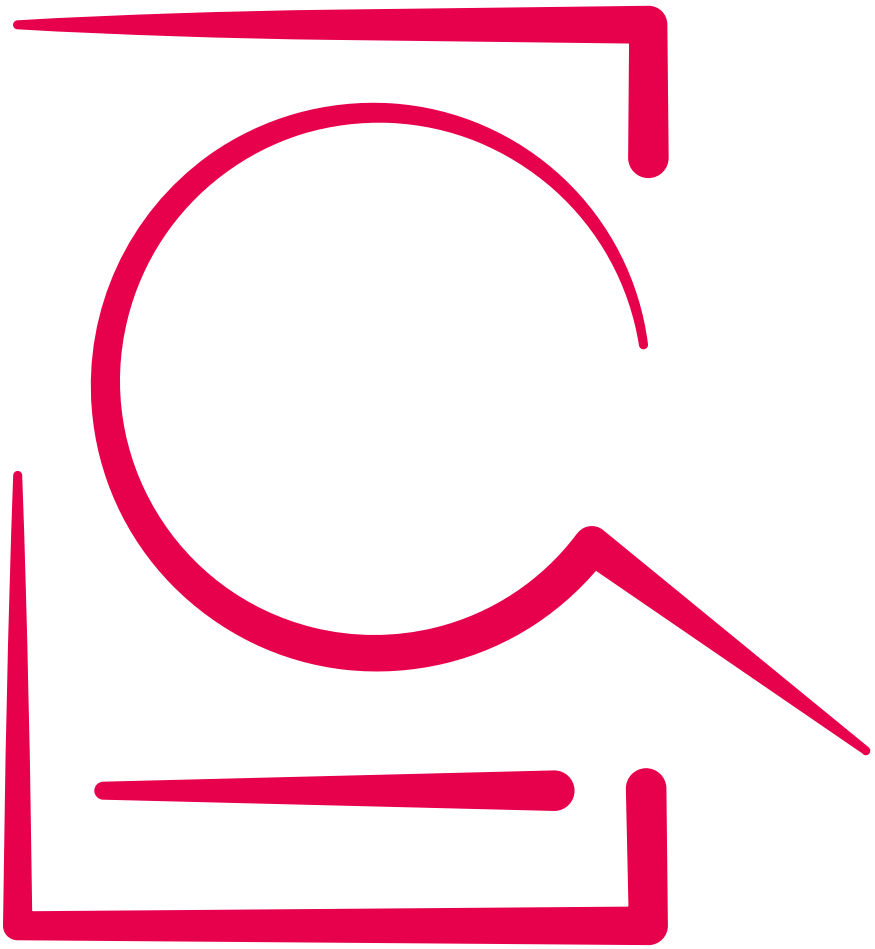
Evidence-based Interventions
Clinical guidance

Release 4 – Urology



Evidence-based Interventions

Clinical guidance
Release 4 — Urology

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Introduction

Medicine is constantly evolving, and the Evidence-based Interventions (EBI) programme is an initiative led by the Academy of Medical Royal Colleges designed to capture that evolving understanding to help us improve the quality of care.

Backed by both doctors and patients, the programme is designed to ensure patients get the most appropriate test, treatment, or procedure for them. This might mean carrying out fewer interventions across the NHS or it may sometimes mean carrying out different interventions to achieve the same or better outcome for a patient. Prescribing a course of physiotherapy as opposed to surgery is a good example of this approach.

Since its inception in 2018, the programme has been supported by four partners: NHS England, NHS Confederation, the Patients Association and the National Institute for Health and Care Excellence (NICE).

As well as improving outcomes and reducing patient harm or exposure to risk, prioritising evidence-based care means we can improve outcomes and minimise unwarranted variation in service provision. It also frees up valuable resources for use elsewhere in the NHS. This is more important than ever as the NHS recovers from the impact of COVID-19 and reduces the backlog of patients.

The programme reviews, with a panel of expert clinicians, existing interventions where the evidence indicates that they are inappropriate for some patients in some circumstances where specific criteria are not met. The programme produces best practise clinical guidance based on that work.

The recommendations set out here have been developed with expert clinicians from the British Association of Urological Surgeons (BAUS), the Primary Care Urology Society, Integrated Care Boards (ICBs) from England and patient representatives from the Academy of Medical Royal Colleges Patient and Lay Committee. Expert opinion has also been sought from other specialist societies, specialist charities and patient representative groups. Their feedback has been considered, and where appropriate, incorporated in the development of these recommendations.

The panel is overseen by an Expert Advisory Committee (EAC) which evaluates the evidence and ensures only those proposals which meet strict criteria are progressed. The EAC reports to a Programme Board, comprising programme partners, senior clinicians, and NHS system leaders. It is this group that makes the ultimate decision on whether a change to the clinical guidance can be made.

PSA Testing for men aged 80 years and above

These recommendations aim to maximise shared decision making between men who are 80 years old or older and primary care clinicians in relation to the investigation and diagnosis of prostate cancer. By developing a clear understanding of the potential outcomes to PSA testing for this group it will begin to address the harm associated with overdiagnosis and overtreatment and the wide variance in care delivery across the country. It provides clarity and guidance to primary care providers on when it is appropriate to refer a concerned patient aged over 80 to a secondary specialist care following a PSA test.

This guidance relates to those who have a prostate, this includes:

- Cismen (men who identify as male and were assigned male at birth)
- Trans women (women who identify as female and were assigned male at birth)
- Non-binary people who were assigned male at birth
- Some intersex people.

The information has been developed based on guidance and evidence in men. If you are a trans woman, male-assigned non-binary or intersex, some of this information is still relevant to you — but your experience may be slightly different.

Please note for the purposes of this document and to align with the evidence when we use 'men' it refers to all those with a prostate.

Summary of current practice

Prostate cancer is common, up to 1 in 8 men are diagnosed during their lifetime with over 45,000 cases diagnosed each year in England and Wales[1,2]. It is a common cause of cancer-related death globally[3]. In the UK, prostate cancer diagnosis typically begins in primary care with a blood test for serum prostate specific antigen (PSA) and/or a digital rectal examination. A PSA test may be performed in asymptomatic patients concerned about the risk of prostate cancer or in individuals with symptoms localised to the urinary tract or indicative of metastatic disease, who are defined as 'symptomatic' in national guidance[4]. The PSA level that should prompt specialist referral is defined at a fixed threshold for asymptomatic men[5] and at age-specific thresholds for 'symptomatic' men[4]. An age-specific PSA threshold is not defined for men aged over 80 in NICE guideline

NG12 due to the lack of evidence in this group; instead 'clinical judgement' is advised[4]. In the absence of specified value for this age-group, individual cancer alliances have devised their own numerical thresholds with significant regional variation[6]. Screening and monitoring PSA levels in men over 80 can create health anxieties and unnecessary hospital visits. Simple numerical cut-offs can miss the bigger picture, including what a referral for suspected prostate cancer is likely to involve, and what factors are important in treatment decisions.

PSA testing of men over 80 is often offered to men with lower urinary tract symptoms (LUTS) in line with national guidance, although LUTS are not a reliable indicator of localised prostate cancer and are common in this age-group due to other causes[7]. In fact, prostate cancer confined to the prostate gland often does not have any symptoms[8]. Many of these men could be considered 'asymptomatic' with the PSA test therefore constituting a form of screening. PSA testing is known to have a poor specificity in this age-group, meaning many with a raised test will not have cancer. This can result in over-investigation, including prostate biopsy, which carries significant risk. The need for a biopsy has partly been mitigated by the introduction of multi-parametric prostate magnetic resonance imaging (MRI), but this is resource intensive.

Evidence shows there is a particular risk of over-diagnosing prostate cancer and over-treating prostate cancer in men over 80 where the prevalence of cancer is highest, but the proportion of cancers which are clinically significant is lowest. For many patients although they may have cancer, it will not cause symptoms in their lifetime or impact their life expectancy. Tests and treatments may in fact expose the patient to additional risks and unnecessary anxiety. Studies have shown that men aged between 50-70 years old are most likely to benefit from PSA testing[8]. Individuals would need to have a further life expectancy of at least 10 years to benefit from radical treatment for localised prostate cancer. This will not be true for many, with the median life expectancy at only 8 years for a man turning 80 in the UK[9]. The diagnosis and radical treatment of prostate cancer carries a significant risk of side effects that can negatively impact quality of life and it is important that these are avoided where treatment will not improve quality of life or survival[10,11]. Active surveillance can be a safe and effective for managing patients with prostate cancer and localised disease, giving more time for men to make decisions on radical treatment. Clinicians and patients are both poor predictors of life expectancy, meaning that some patients with slow growing cancers but a high level of comorbidity are 'overtreated'[12].

PSA testing is a highly complex and contentious area, and it is important that primary care clinicians and patients are appropriately supported to allow shared decision making together.

This guideline aims to complement NICE guideline NG12[4] by providing detail on the principles that should inform a shared decision making process in men over 80 who are considering, or who have had, a PSA test.

These recommendations aim to ensure:

- Localised prostate cancer is diagnosed in all individuals who would benefit from radical treatment.
- Over-diagnosis and overtreatment are minimised in those who don't have cancer or have clinically insignificant prostate cancer where radical treatment is unlikely to be of benefit and could cause harm.
- Men with metastatic prostate cancer are identified and offered treatment where appropriate.
- Improving the quality of life for men over 80 with slow growing prostate cancer.
- Support shared decision making between primary care clinicians and patients in relation to PSA testing.

Recommendations

Scope

This guideline aims to support primary care clinical decision making in men aged over 80 where PSA testing is being considered or where a PSA test has been performed.

NICE guideline NG12[4] advises that primary care clinicians should use 'clinical judgement' when deciding whether to refer 'symptomatic' men over 80 who have an elevated PSA test.

Recommendations

PSA testing: Framework for shared decision making prior to testing

1. Before a PSA test is performed a shared decision-making process[13] should take place between the patient and the primary care clinician where the limitations of the test and the possible consequences of an abnormal result are discussed[14]. The clinician should consider discussing the following points:

About the PSA test

1.1. PSA can commonly be raised in the absence of prostate cancer (false positive) and occasionally be normal where cancer is present (false negative).

About localised prostate cancer

1.2. Prostate cancer confined to the prostate gland is typically asymptomatic — Lower urinary tract symptoms (LUTS) are not a reliable symptom of localised prostate cancer for men over 80 years old.

1.3. Prostate cancer confined to the prostate gland is common, but many cancers diagnosed in this age-group will be clinically insignificant meaning they won't cause symptoms in an individual's lifetime or shorten their life expectancy.

1.4. An individual must live for at least 10 years to benefit from radical treatment of prostate cancer when it is confined to the prostate gland. However, radical treatment can be associated with side effects (e.g. incontinence and erectile dysfunction) that impact quality of life[15].

About metastatic prostate cancer

1.5. When prostate cancer has spread outside the prostate gland there are effective treatments that may help reduce symptoms (but not cure the disease).

PSA testing: Clinical recommendations on testing

1.6. In men over 80, PSA testing should be encouraged where there are symptoms suggestive of metastatic prostate cancer (such as bone pain, unintended weight loss and fatigue).

1.7. In men over 80 without signs of metastatic disease the benefit of PSA testing is uncertain. A PSA test should only be performed in men who want one after an appropriate shared decision-making process (see above). The potential benefits are greater in those with a life expectancy of more than 10 years.

PSA testing: Interpreting test results

1.8. For men ≥80 years of age who have had a PSA test, offer referral via a suspected cancer pathway if:

- the PSA >20 ng/mL;

OR

- the PSA >7.5 ng/mL AND there are symptoms suggestive of metastatic disease (bone pain and/or fatigue and/or significant unintended weight loss).

1.9. If the initial PSA test is between 7.5 – 20 ng/L and there are no symptoms suggestive of metastatic disease, repeat PSA **ONCE** after 6 months in primary care, prior to any secondary care referral.

1.10. When the PSA is repeated, offer referral via the suspected cancer pathway if:

— either criteria in recommendation 1.8 being met;

OR

— PSA has increased significantly (more than doubled), and the patient has a performance status of 0 or 1.

1.11. If patients do not fit the above criteria but concerns remain, seek appropriate support via 'advice and guidance'.

Rationale for recommendations

The panel discussed current NICE guidance on PSA testing in 'symptomatic' men and the lack of evidence on the predictive accuracy of age-specific thresholds in this group was acknowledged. The panel considered there was a lack of guidance to support primary care clinicians with 'clinical judgements' on PSA testing and on actioning abnormal results. Panel members underlined how individual cancer alliances have introduced local age-specific thresholds to help address this uncertainty but that this has led to significant regional variation in referral patterns[6]. The panel agreed there was a need for unified recommendations covering men in this age group and these would benefit from considering the evidence on prostate cancer treatment, and outcomes rather than simply focussing on the predictive accuracy of the PSA test in isolation. The panel's opinion that a more holistic view would help mitigate some of the risks associated with over-investigation and overtreatment and have important resource implications.

The panel noted that prostate cancer is a common diagnosis in older men. More than 75% of all prostate cancers are diagnosed in men aged over 65[16] and it is estimated that approximately 50% of men over 50 years have histological evidence of prostate cancer, rising to almost 80% in men aged over 80[17]. The panel noted that for most men, prostate cancer is slow growing and does not cause symptoms during an individual's lifetime and/or affect life expectancy[17,18,19]. The panel noted that there is a particular risk of over-diagnosing and overtreating prostate cancer in men over 80 where the prevalence of cancer is highest, but the proportion of cancers that are clinically significant is lowest.

The role of PSA testing in over-diagnosis was discussed. The panel noted that PSA testing can advance the time of diagnosis, but this may not confer treatment benefits where cancers are indolent, or life expectancy is limited[20]. It was noted that the long-term prognosis for older men with PSA-detected prostate cancer is excellent, including

those treated conservatively[21]. Studies looking at prostate cancer-specific mortality after radical treatment of localised disease were reviewed, and the panel agreed that those with a life expectancy less than 10 years are unlikely to derive benefit from radical treatment[22,23,24,25,26,27,28]. The difficulties with predicting life expectancy were noted[29]. Evidence was presented that patients and clinicians do this poorly[30,31,32] and that clinicians often fail to appropriately adjust for comorbidities, leading to a tendency to overestimate survival[12,29]. The panel concluded that early diagnosis, in certain cases, may expose patients to harm through treatments that do not benefit quality of life or survival[20].

The panel discussed the utility of the World Health Organization (WHO) performance scale — which is simple, widely used, and has good inter-rater reliability — in helping identify those who might benefit from early diagnosis and treatment. The panel considered that only individuals with a performance status under 2 should be offered radical treatment of localised prostate cancer given how long the benefits of treatment take to be realised. It was therefore agreed that performance status would be used as one criterion for screening patients for onwards referral. It was the view of the panel that patients would need to be provided with clear information on the rationale behind the decision-making process and that 'advice and guidance' should be used by primary care where there was clinician or patient uncertainty.

The panel acknowledged that the benefit of radical treatment in men over 80 with the highest performance status will be equivocal and relate, among other things, to the precise histological features of an individual's cancer. These individuals stand to benefit from a histological diagnosis, which can then be used as part of risk prediction algorithms such as Predict Prostate to individualise treatment decisions. The panel noted that even among this group, only approximately 10% of patients receive radical treatment (predominantly radiotherapy) [National Cancer Registration and Analysis Service 2013-2019]. A consensus expert view was taken that the PSA cut-off for the lower 70-79 age group should be used as a threshold for PSA monitoring in primary care, and that men should be referred where their PSA is rapidly rising.

There was considerable discussion on the value of LUTS as a symptom of prostate cancer and it was noted that LUTS continue to form an important part of national guidelines and media health campaigns. Evidence evaluating the diagnostic utility of LUTS was reviewed and the negative association between LUTS and localised prostate cancer diagnosis in screening studies was noted[7]. The findings of a 2013 Cochrane review, which concluded that *'the presence of LUTS, typically due to benign prostatic obstruction, are very common in the ageing male and are not considered to increase prostate cancer risk'*, were felt to be significant[24]. PSA for LUTS was noted to be an important factor contributing to over-investigation and overdiagnosis and the panel agreed that this issue should be addressed explicitly in the guidance.

The panel considered the benefits of early hormonal treatment for localised disease in those not fit enough for radical treatment. It was noted that the current evidence only supports early hormonal treatment in those with a baseline PSA > 50 ng/ml and/or a

PSA doubling time < 12 months[33]. An age-specific PSA threshold of 20 and repeating PSA measurement in those with a PSA>7.5 at six months (to pick up individuals where PSA is rapidly rising), was considered adequate to ensure all individuals potentially benefitting from early hormonal treatment were seen in secondary care.

The panel agreed on the importance of ensuring all men with suspected metastatic disease are offered referral to secondary care. The panel came to a consensus on the typical symptoms of metastatic disease (bone pain, fatigue, and unintended weight loss) and agreed that even a mildly raised PSA in these individuals should prompt a high index of suspicion of metastatic cancer. A PSA above the age-specific threshold for the 70-79 age group was agreed upon as a reasonable referral threshold where possible symptoms of metastatic disease exist. The appropriate PSA threshold for detecting metastatic disease in asymptomatic patients was also considered. The available evidence indicates that a PSA threshold of 20ng/ml has a high sensitivity for detecting asymptomatic metastatic disease[34,35].

Patient information

What is a PSA test?

The prostate, which is a gland about the size of a ping pong ball located just below your bladder, produces the protein PSA. If the levels of PSA in your blood are raised it can be an indicator of cancer.

The Prostate-specific antigen (PSA) test is a blood test used to help detect prostate cancer. It is normally carried out by your GP or clinician at your local surgery. Your blood sample will be sent to a laboratory to measure its PSA level.

When should a PSA test be carried out?

A PSA test should be performed on a case-by-case basis, when finding and treating early prostate cancer would help improve a person's life expectancy or quality of life.

It is entirely normal for you to have a small amount of PSA in your blood. However, you may have raised PSA levels for other reasons including diet, sexual activity, vigorous exercise, recent infection, or if you are taking some medications. The amount of PSA tends to increase as you age because the prostate gets bigger over time — a larger prostate releases more protein.

A raised PSA might also be due changes in your urine flow, known as lower urinary tract symptoms (LUTS). For example, you may find it difficult to begin to pee, or your flow may stop and start when you are peeing. You may need to take a pee more urgently or during

the night. As men age, they can experience LUTS due to age-related enlargements in the prostate. Generally, LUTS are not a sign of prostate cancer, and should not automatically mean you need a PSA test.

Should everyone be tested?

The test itself may not be suitable for everybody. For men over 80, before having a PSA test we recommend talking with your doctor about what the test involves and the implications for you. This will help you decide together, what is best for you. If you choose to have the test, this guidance can also help decide if a referral to a specialist doctor such as a urologist is likely to be beneficial.

References

1. HQIP. *Annual report 2021 – Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2019 to 31 March 2020 and the Impact of COVID-19 in England during 2020*. January 2022.
2. Prostate Cancer UK. *About prostate cancer*. June 2022.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68: 394-424.
4. NICE. *NICE guideline [NG12]. Suspected cancer: recognition and referral*. Published: 23 June 2015, Last updated: 15 December 2021.
5. GOV.UK. Prostate cancer risk management programme: overview. 1 Jan 2015.
6. Light A, Burns-Cox N, Maccormick A, John J, McGrath J, Gnanapragasam VJ. The diagnostic impact of UK regional variations in age-specific prostate-specific antigen guidelines. *BJU Int.* 2021 Sep;128(3):298-300. doi: 10.1111/bju.15484. Epub 2021 Jun 13. PMID: 34014596.
7. Gnanapragasam VJ, Greenberg D & Burnet N. Urinary symptoms and prostate cancer—the misconception that may be preventing earlier presentation and better survival outcomes. *BMC Med* 20, 264 (2022).
8. De Vos, I. et al (2023) 'A Detailed Evaluation of the Effect of Prostate-specific Antigen–based Screening on Morbidity and Mortality of Prostate Cancer: 21-year Follow-up Results of the Rotterdam Section of the European Randomised Study of Screening for Prostate Cancer,' European Associate of Urology, 84(4), pp. 426–434

9. ONS. *National life tables – life expectancy in the UK: 2018 to 2020*. 23 Sept 2021.

10. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, Martin RM, Young GJ, Walsh EI, Bryant RJ, Bollina P, Doble A, Doherty A, Gillatt D, Gnanapragasam V, Hughes O, Kockelbergh R, Kynaston H, Paul A and Paez E. (2023). Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *New England Journal of Medicine*. doi:https://doi.org/10.1056/nejmoa2214122

11. Tikkinen KAO, Dahm P, Lytvyn L, Heen A F, Vernooij RWM, Siemieniuk RAC et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline *BMJ* 2018; 362.

12. Daskivich TJ, Chamie K, Kwan L, Labo J, Palvolgyi R, Dash A, Greenfield S, Litwin MS. Overtreatment of men with low-risk prostate cancer and significant comorbidity. *Cancer.* 2011 May 15;117(10):2058-66. doi: 10.1002/cncr.25751. Epub 2010 Nov 29. PMID: 21523717.

13. NHS England. *Shared decision-making*. *22 Dec 2022.*

14. NHS. *Should I have a PSA test? - Prostate cancer*. 18 Oct 2021.

15. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, Blazeby JM, Peters TJ, Holding P, Bonnington S, Lennon T, Bradshaw L, Cooper D, Herbert P, Howson J, Jones A, Lyons N, Salter E, Thompson P, Tidball S, Blaikie J, Gray C, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Davis M, Turner EL, Martin RM, Neal DE; ProtecT Study Group*. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*. 2016 Oct 13;375(15):1425-1437. doi: 10.1056/NEJMoa1606221. Epub 2016 Sep 14. Erratum in: N Engl J Med. 2023 Jun 8;388(23):2208. PMID: 27626365; PMCID: PMC5134995.

16. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022.

17. Sakr WA, Grignon DJ, Haas GP, Heilbrun LK, Pontes JE, Crissman JD. Age and racial distribution of prostatic intraepithelial neoplasia. *Eur Urol*. 1996;30(2):138-44. doi: 10.1159/000474163. PMID: 8875194.

18. Holman CD, Wisniewski ZS, Semmens JB, Rouse IL, Bass AJ. Mortality and prostate cancer risk in 19,598 men after surgery for benign prostatic hyperplasia. *BJU Int.* 1999 Jul;84(1):37-42. doi: 10.1046/j.1464-410x.1999.00123.x. PMID: 10444122.

19. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol*. 1984 Sep;132(3):474-9. doi: 10.1016/s0022-5347(17)49698-4. PMID: 6206240.

20. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schröder FH, de Koning HJ. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst*. 2003 Jun 18;95(12):868-78. doi: 10.1093/jnci/95.12.868. PMID: 12813170.

21. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, Barry MJ, Zietman A, O'Leary M, Walker-Corkery E, Yao SL. Outcomes of localized prostate cancer following conservative management. *JAMA*. 2009 Sep 16;302(11):1202-9. doi: 10.1001/jama.2009.1348. PMID: 19755699; PMCID: PMC2822438.

22. Mottet N, Cornford P, van den Bergh R.C.N.,Briers , Expert Patient Advocate (European Prostate Cancer Coalition/Europa UOMO), Eberli D, De Meerleer G, De Santis M, Gillessen S, GrummetJ, Henry A.M., van der Kwast T.H., van Leenders G.J.L.H., Mason M.D, O'Hanlon S, van Oort I.M, Oprea-Lager D.E, Ploussard G, Rouvière O, Schoots I.G , Stranne J, Tilki D, Wiegel T, Guidelines Associates: Van den Broeck T, Farolfi A, Gandaglia G, Grivas N, Lardas M, Liew M, Linares E, Espinós, Willemse P-P.M. 2023. *EAU - EANM - ESTRO - ESUR - ISUP – SIOG Guidelines on Prostate Cancer*. European Association of Urology 2023.

23. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, Aronson WJ, Brawer MK. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. *N Engl J Med*. 2017 Jul 13;377(2):132-142. doi: 10.1056/NEJMoa1615869. PMID: 28700844.

24. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. *Cochrane Database Syst Rev*. 2013 Jan 31;2013(1):CD004720. doi: 10.1002/14651858.CD004720.pub3. PMID: 23440794; PMCID: PMC8406915.

25. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, Nordling S, Häggman M, Andersson SO, Bratell S, Spångberg A, Palmgren J, Steineck G, Adami HO, Johansson JE; SPCG-4 Investigators. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011 May 5;364(18):1708-17. doi: 10.1056/NEJMoa1011967. PMID: 21542742.

26. Johansson E, Bill-Axelson A, Holmberg L, Onelöv E, Johansson JE, Steineck G; Scandinavian Prostate Cancer Group Study No 4. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. *Eur Urol*. 2009 Feb;55(2):422-30. doi: 10.1016/j.eururo.2008.08.054. Epub 2008 Sep 2. PMID: 18783877.

27. Bill-Axelson A, Holmberg L, Filén F, Ruutu M, Garmo H, Busch C, Nordling S, Häggman M, Andersson SO, Bratell S, Spångberg A, Palmgren J, Adami HO, Johansson JE; Scandinavian Prostate Cancer Group Study Number 4. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst*. 2008 Aug 20;100(16):1144-54. doi: 10.1093/jnci/djn255. Epub 2008 Aug 11. PMID: 18695132; PMCID: PMC2518167.

28. Bill-Axelson A, Holmberg L, Ruutu M, Häggman M, Andersson SO, Bratell S, Spångberg A, Busch C, Nordling S, Garmo H, Palmgren J, Adami HO, Norlén BJ, Johansson JE, Scandinavian Prostate Cancer Group Study No. 4. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005 May 12;352(19):1977-84. doi: 10.1056/NEJMoa043739. PMID: 15888698.

29. Chase EC, Bryant AK, Sun Y, Jackson WC, Spratt DE, Dess RT, Schipper MJ. Development and validation of a life expectancy calculator for US patients with prostate cancer. *BJU Int*. 2022 Oct;130(4):496-506. doi: 10.1111/bju.15740. Epub 2022 Apr 24. PMID: 35373440; PMCID: PMC9474626.

30. Walz J, Gallina A, Perrotte P, Jeldres C, Trinh QD, Hutterer GC, Traumann M, Ramirez A, Shariat SF, McCormack M, Perreault JP, Bénard F, Valiquette L, Saad F, Karakiewicz PI. Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer. *BJU Int.* 2007 Dec;100(6):1254-8. doi: 10.1111/j.1464-410X.2007.07130.x. PMID: 17979925.

31. Wilson JR, Clarke MG, Ewings P, Graham JD, MacDonagh R. The assessment of patient life-expectancy: how accurate are urologists and oncologists? *BJU Int*. 2005 Apr;95(6):794-8. doi: 10.1111/j.1464-410X.2005.05403.x. PMID: 15794785.

32. Allen LA, Yager JE, Funk MJ, Levy WC, Tulsky JA, Bowers MT, Dodson GC, O'Connor CM, Felker GM. Discordance between patient-predicted and model-predicted life expectancy among ambulatory patients with heart failure. *JAMA*. 2008 Jun 4;299(21):2533-42. doi: 10.1001/jama.299.21.2533. PMID: 18523222; PMCID: PMC3623529.

33. Studer UE, Collette L, Whelan P, Albrecht W, Casselman J, de Reijke T, Knönagel H, Loidl W, Isorna S, Sundaram SK, Debois M, EORTC Genitourinary Group. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). *Eur Urol.* 2008 May;53(5):941-9. doi: 10.1016/j.eururo.2007.12.032. Epub 2007 Dec 27. PMID: 18191322.

34. Gleave ME, Coupland D, Drachenberg D, Cohen L, Kwong S, Goldenberg SL, Sullivan LD. Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. *Urology.* 1996 May;47(5):708-12. doi: 10.1016/s0090-4295(96)80016-1. PMID: 8650870.

35. Manohar PR, Rather TA, Khan SH. Determination of the optimal cut-off value of serum prostate-specific antigen in the prediction of skeletal metastases on technetium-99m whole-body bone scan by receiver operating characteristic curve analysis. World J Nucl Med. 2020 Jul 1;19(3):255-259. doi: 10.4103/wjnm.WJNM_77_19. PMID: 33354181; PMCID: PMC7745856.

Investigation and onward referral of women with recurrent urinary tract infections (rUTIs)

These recommendations aim to reduce variation in care experienced by women with recurrent urinary tract infections (rUTI) by providing guidance for primary care clinicians on when to refer individuals to specialist urology. These recommendations aim to limit harm to patients by reducing harmful and invasive investigative procedures when other alternatives are more appropriate and effective which can be conducted before specialist referral.

This guidance relates to:

- Ciswomen (women who identify as female and were assigned female at birth)
- Some transgender people
- Non-binary people who were assigned female at birth.
- Some intersex people.

The information has been developed based on guidance and evidence in women. If you are transgender, female-assigned non-binary, or intersex, some of this information is still relevant to you — but your experience may be slightly different.

Please note for the purposes of this document and to align with the evidence when we use 'women' it includes all those above.

Summary of current practice

Urinary tract infections (UTI) are extremely common in women with over half experiencing at least one in their lifetime[1]. Many women experience recurrent infection, defined as at least 3 UTIs in one year or 2 UTIs in six months[2,3]. Recurrent UTIs affect approximately 1 in 1,000 women under the age of 65[4] and can significantly impact quality of life[5,6].

Urinary infections can affect the lower urinary tract or the upper urinary tract. Recurrent upper tract infections are uncommon, and these individuals should be reviewed in secondary care. For the remainder of this proposal, we use recurrent UTI (rUTI) to refer to recurrent lower tract infections only.

In the UK, most women with rUTIs present initially to primary care. Recommendations covering the primary care management of rUTIs are outlined in NICE guideline NG112[3] — it also specifies when clinicians should refer or seek specialist advice in those patients where malignancy is suspected or where 'the underlying cause of rUTI is unknown'.

Specialist urological input (this term includes specialists with an interest in female functional urology and/or urogynaecology) is important for identifying and treating women with structural or functional abnormalities of the urinary tract that predispose to bacterial persistence (so-called 'complicated' rUTIs). These abnormalities are often identified through specialist tests, including cystoscopy, which allows direct visualisation of the lower urinary tract. Other tests performed in secondary care include urodynamic studies and imaging such as computed tomography or ultrasound.

Women with 'complicated' UTIs only make up a small fraction of those with recurrent infection and most will not benefit from additional investigations and could even experience harm, including new infection and bleeding, from invasive tests[7]. Identifying the subset of individuals that will benefit from specialist referral is critical in maximising patient benefit while ensuring resources are used judiciously. NICE guideline NG112[3] does not define the clinical features that suggest a complicated aetiology, which are included in other international guidelines. In addition, it does not define the findings on renal tract ultrasound — a test commonly performed in primary care in the work-up of rUTI — that should prompt specialist referral.

These recommendations aim to complement NICE guideline NG112[3] by providing guidance for primary care clinicians on when to refer women with rUTIs to specialist urology services and the investigations that should be performed prior to referral.

A list of important definitions used in this guideline is provided below.

- Urinary tract infection (UTI) is defined as:
    - Typical symptoms of infection (such as dysuria, nocturia, change in urine appearance or odour) with a clinical response to antibiotics, even in the absence of microbiological confirmation.
    - Typical symptoms of infection with a positive urine dipstick (positive for nitrite or leukocyte and red blood cells).
    - Typical symptoms of infection with a positive urine culture.
- Recurrent lower urinary tract infection (rUTI) — 2 or more symptomatic lower UTIs in six months or 3 or more symptomatic lower UTIs in one year.
- Relapsed urinary tract infection — where the same organism is identified in the urine within two weeks of appropriate antimicrobial treatment. Relapsed or persistent infections should not be counted as 'new' infections when defining a woman with rUTIs. If the same organism is identified more than two weeks after completion of antibiotic therapy, this should be counted as a new infection.

— Asymptomatic bacteriuria — the presence of bacteria in the urine of a person without signs or symptoms of UTI. It should not be routinely screened for, or treated, in women who are not pregnant[8]. It does not count as a urinary tract infection.

— Complicated urinary tract infection — a UTI that occurs in an individual with predisposing structural or functional abnormalities of the genitourinary tract or host factors that put them at increased risk of pyelonephritis or urosepsis[9].

Recommendations

Scope

These recommendations provide referral guidance for primary care clinicians when **managing non-pregnant women over the age of 18 with recurrent lower UTI.**

The recommendations do not cover the management of:

— Suspected malignancy [gynaecological cancer; urological cancer].

— Acute UTI, which is covered by NICE guideline NG109[8].

— Recurrent or persistent asymptomatic bacteriuria. This is common[10] and should not prompt further investigation or treatment, unless it is a persistent finding in pre-menopausal women.

Recommendations

1. All women with recurrent UTIs should be offered a **kidneys, ureters and bladder ultrasound** (KUB USS) in primary care. This should include measurement of a **post-micturition residual volume** as standard.

Specialist referral

2. Specialty urology referral should be offered to women where **ANY** of the following clinical criteria are met:

   2.1 Prior urinary tract surgery, pelvic organ prolapse surgery or trauma.

   2.2. Prior abdominopelvic malignancy.

   2.3. Visible and non-visible haematuria after resolution of infection (this should be managed as per NICE suspected cancer guidance — gynaecological cancer; urological cancer).

2.4. Urea-splitting bacteria on culture (e.g. Proteus, Yersinia) in the presence of a stone, or atypical infections (e.g. tuberculosis, anaerobic bacteria)

2.5. Bacterial persistence or on-going lower urinary tract symptoms after sensitivity-based therapy.

2.6. Pneumaturia or faecaluria.

2.7. Voiding symptoms (straining, weak stream, intermittency, hesitancy).

OR if any of the following features are present on renal ultrasound:

2.8. Hydroureter or hydronephrosis.

2.9. Bladder OR ureteric OR obstructive renal stones (for non-obstructive renal stones please use advice and guidance).

2.10. Post-micturition residual volume greater than 150ml.

3. Women who do not meet the above criteria for speciality referral should be managed in primary care where possible. Management will differ depending on menopausal status, may include lifestyle modifications, non-antibiotic, and antibiotic based treatments, and should follow the recommendations set out in NICE guideline NG112[3].

4. If concerns persist, or symptoms remain uncontrolled despite optimal primary care management, primary care clinicians should use 'advice and guidance' to seek specialist advice in the first instance, prior to referral.

Rationale for recommendations

The panel accepted the definition of rUTI used in all the international guidelines reviewed: 2 or more symptomatic urinary tract infections in six months or 3 or more symptomatic infections in one year.

The panel considered international guidelines on rUTI[11]. These broadly agree that most women with rUTIs do not require further investigation with cystoscopy or imaging in the absence of specific 'risk factors'[2,12,13,14]. The panel noted that guidelines differ in what 'risk factors' they consider significant. Of the guidelines reviewed, the Canadian urological guidelines are the most detailed[15] and the panel was of the opinion that this list should be adapted for use in our recommendations.

The 'risk factors' from the Canadian guidelines were discussed individually. Voiding dysfunction was discussed in detail and the panel decided that this should remain in

the 'symptom list' as abnormal post-residual volume may not identify all patients with functional issues. There was a discussion about whether the presence of stones should prompt referral. The consensus view was that patients with bladder stones, or stones causing obstruction should be referred. Non-obstructive renal stones and stones <5mm are unlikely to be significant in rUTI but the panel considered that primary care should be provided with the explicit option of seeking a specialist opinion via advice and guidance in these cases. Regarding diabetes, it was agreed that this should be removed from the list as a standalone factor. In these cases, the focus should be on optimisation of diabetic control (directed by primary care, and endocrinology, where appropriate) with no added benefit provided by urology in the absence of other complicating factors.

The panel considered the evidence underpinning international recommendations relating to the utility of further investigations in women with rUTIs. The most comprehensive evidence summary is provided by a recent systematic review that includes data from seven published research studies[16,17,18,19,20,21,22]. The panel discussions are summarised below.

Cystoscopy

In the pooled analysis from the systematic review:

- 23% of cystoscopies performed for recurrent UTI were abnormal but most abnormalities were incidental with inflammation being the main 'abnormality' found.
- Only 1 out of 656 cystoscopies performed (0.15%) revealed a potentially life-threatening finding (carcinoma).
- There were few other findings of consequence in cystoscopies performed (18 out of 656 or 2.74%). Of the findings deemed significant, 17 out of 18 could have been identified via other means such as through clinical history (colovesical fistula and suture material), by ultrasound (ureterocele), and from flow studies (stricture).

The panel noted the author's conclusions that *'there is no evidence for performing cystoscopy for recurrent UTI'*.

The panel acknowledged that cystoscopy is currently considered part of the standard work-up of rUTI in secondary care. Based on the available evidence the panel considered that most women are unlikely to derive additional benefit from cystoscopy and specialist referral should not be routinely justified so this test can be performed. It was the panel's view that women with high-risk clinical features are more likely to have significant pathology and that referral to secondary care (with the understanding that most patients will undergo cystoscopy) is still justified in these cases.

Urodynamics

- The panel noted that this is the area with least published literature with only two studies[23,24] with extractable data in the systematic review and significant heterogeneity in findings.
- The data presented indicated about 50% of women with rUTI have impaired urine flow and 35% have a positive post void residual but the studies included did not consistently define what was meant by a 'positive' post-void volume.
- The pragmatic view of the panel was that all women with rUTI should have a post-void residual measured. This can be performed easily in the community as part of a standard urinary tract ultrasound without the need for additional resource. There was limited data to support the volume of the post-void residual deemed significant and a value was agreed upon based on expert opinion.
- Urodynamics require specialist equipment and given the limited data available, the panel's view was that it is reasonable to reserve further urodynamic testing for women with high-risk clinical features, particularly those with a high post-void residual or symptoms suggestive of significant voiding dysfunction.

Imaging

- Most studies included in the systematic review focussed on Intravenous urography (IVU) which is a historical test and no studies reported specifically on CT.
- Only two studies reported specifically on ultrasound[19,20]. Of 785 imaging studies only 10 (1.3%) showed serious findings requiring urgent management and only 30 (3.8%) showed findings requiring some form of follow-up. Of the serious findings, most were detected on US, but missed on IVU and abdominal radiograph.
- The authors of the systematic review considered that imaging was 'unlikely to be of value in the absence of symptoms of upper tract disease or gynaecological problems'.
- The panel considered this data in the context of current UK practice, where ultrasound is commonly obtained in primary care prior to referral. The expert view of the panel was that ultrasound could serve as a valuable screening test for significant pathology and given its low cost and accessibility, should form part of the standard work-up of all women with rUTI prior to specialist referral. The fact that ultrasound does not use ionizing radiation or intravenous contrast was considered to further support its use as a screening tool over other imaging modalities.
- In the absence of robust data, the panel came to an expert consensus on what ultrasound features should warrant specialist review.

Patient information

Cystitis is inflammation of the bladder, often caused by a urinary tract infection (UTI). It is also used as a general term for bladder infection. Recurrent UTIs (rUTIs) are defined as at least 3 infections in one year or 2 infections in six months. Recurrent UTIs affect approximately 1 in 1,000 women under the age of 65[4] and can significantly impact quality of life[5,6].

This guidance is for non-pregnant women over 18 years old who experience rUTIs. It supports primary care clinicians (usually GPs) in deciding whether referring a patient to a hospital-based urologist is the best course of action for them. This guidance should be used alongside existing national guidance produced by the National Institute of Clinical Excellence (NICE).

We recommend that:

- Most women should be treated in primary care (usually by your GP) according to the steps set out in NICE guidance NG112[3].
- All women with rUTIs should have an ultrasound scan of their kidneys, bladder, and ureters (the tubes that connect the kidneys to the bladder).
- Women should only be referred to a hospital-based specialist in kidney and urinary tract diseases (urologist) if they have symptoms, medical conditions or findings on their ultrasound that suggest a problem with the structure or function of their urinary system.

GPs always have the option of seeking advice from hospital-based urology specialists if they have additional concerns in cases that don't meet the criteria for automatic referral.

A small number of women with rUTIs will have problems with the structure and function of the urinary system. These individuals tend to have clues in their medical history and/or abnormal ultrasound findings and may therefore benefit from specialist treatments to reduce the number or severity of infections they get. Additional investigations (usually performed by hospital-based urologists) are typically needed to diagnose these conditions after someone is referred. One common test is called a flexible cystoscopy. This involves inserting a thin flexible tube called a cystoscope through the opening into the bladder to examine its lining. This procedure is relatively safe but can be painful, cause bleeding and/or a new infection (in between 1% to 10% of cases[7]). For most women with rUTIs nothing significant is found as a result of this test (less than 3% of cystoscopies). Therefore it is important that additional invasive investigations are only performed if they are likely to reveal issues or signs of disease.

References

1. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. (2003) *Dis.Mon* Feb;49(2):53-70. doi: 10.1067/mda.2003.7. PMID: 12601337.

2. Bonkat et al. (2022) EAU Guidelines on Urological Infections. EAU. 2022.

3. NICE. *Guideline [NG112] Urinary tract infection (recurrent): antimicrobial prescribing*. 31 October 2018

4. Suskind AM, Saigal CS, Hanley JM, Lai J, Setodji CM, Clemens JQ; Urologic Diseases of America Project. Incidence and Management of Uncomplicated Recurrent Urinary Tract Infections in a National Sample of Women in the United States. *Urology.* 2016 Apr;90:50-5. doi: 10.1016/j.urology.2015.11.051. Epub 2016 Jan 26. PMID: 26825489; PMCID: PMC4822518.

5. Foxman B. The epidemiology of urinary tract infection. *Nat Rev Urol*. 2010 Dec;7(12):653-60. doi: 10.1038/nrurol.2010.190. PMID: 21139641.

6. Renard J, Ballarini S, Mascarenhas T, Zahran M, Quimper E, Choucair J, Iselin CE. Recurrent Lower Urinary Tract Infections Have a Detrimental Effect on Patient Quality of Life: a Prospective, Observational Study. *Infect Dis Ther.* 2014 Dec 18;4(1):125–35. doi: 10.1007/s40121-014-0054-6. Epub ahead of print. PMID: 25519161; PMCID: PMC4363217.

7. Cusumano JA, Pharm D and others. Evaluation of post–flexible cystoscopy urinary tract infection rates. *American Journal of Health-System Pharmacy*, Volume 77, Issue 22, 15 November 2020, Pages 1852–1858.

8. NICE. *Guideline [NG109] Urinary tract infection (lower): antimicrobial prescribing* Published, 31 October 2018.

9. Campbell Meredith F et al. (2007) Campbell-Walsh urology 9th edition. W.B. Saunders.

10. Lindsay E. Nicolle and others, Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. *Clinical Infectious Diseases*. Volume 40, Issue 5, 1 March 2005, Pages 643–654.

11. Kwok M, McGeorge S, Mayer-Coverdale J, Graves B, Paterson DL, Harris PNA, Esler R, Dowling C, Britton S, Roberts MJ. Guideline of guidelines: Management of recurrent urinary tract infections in women. *BJU Int*. 2022.

12. Anger J, Lee U, Ackerman L, Chou R, Chughtai B, Clemens JQ, Hickling D, Kapoor A, Kenton KS, Kaufman MR, Rondanina MA, Stapleton A, Stother L, and Chai TC (2019) Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. *Journal of Urology Adult Urology.* 1 Aug 2019 pg 282-289.

13. Arnold JJ, Hehn LE, Klein DA. Common Questions About Recurrent Urinary Tract Infections in Women. *Am Fam Physician*. 2016 Apr 1;93(7):560-9. PMID: 27035041.

14. Kranz J, Schmidt S, Lebert C, Schneidewind L, Mandraka F, Kunze M, Helbig S, Vahlensieck W, Naber K, Schmiemann G, Florian M. Wagenlehner FM. The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients: Part 1. *Urol Int* 18 April 2018; 100 (3): 263–270.

15. Dawson S, Danson JT and Kapoor A. Guidelines for the diagnosis and management of recurrent urinary tract infection in women. *Can Urol Assoc J*. 2011 Oct; 5(5): 316-322.

16. Pagano MJ, Barbalat Y, Theofanides MC, Edokpolo L, James MB, Cooper KL. Diagnostic yield of cystoscopy in the evaluation of recurrent urinary tract infection in women. *NeurourolUrodyn*. 2017; 36: 692- 696.

17. Howles S, Tempest H, Doolub G, Bryant RJ, Hamdy FC, Noble JG, Larré S. Flexible cystoscopy findings in patients investigated for profound lower urinary tract symptoms, recurrent urinary tract infection, and pain. *J Endourol*. 2012 Nov;26(11):1468-72. doi: 10.1089/end.2012.0139. Epub 2012 Jul 30. PMID: 22612791.

18. Lawrentschuk N, Ooi J, Pang A, Naidu KS, Bolton DM. Cystoscopy in women with recurrent urinary tract infection. *Int J Urol*. 2006 Apr;13(4):350-3. doi: 10.1111/j.1442-2042.2006.01316.x. PMID: 16734849.

19. van Haarst EP, van Andel G, Heldeweg EA, Schlatmann TJ, van der Horst HJ. Evaluation of the diagnostic workup in young women referred for recurrent lower urinary tract infections. *Urology*. 2001 Jun;57(6):1068-72. doi: 10.1016/s0090-4295(01)00971-2. PMID: 11377307.

20. Nickel JC, Wilson J, Morales A, Heaton J. Value of urologic investigation in a targeted group of women with recurrent urinary tract infections. *Can J Surg*. 1991 Dec;34(6):591-4. PMID: 1747838.

21. Mogensen, P. and Hansen, L.K. Do Intravenous Urography and Cystoscopy Provide Important Information in Otherwise Healthy Women with Recurrent Urinary Tract Infection? *British Journal of Urology*. 1983, 55: 261-263.

22. Engel G, Schaeffer AJ, Grayhack JT, Wendel EF. The role of excretory urography and cystoscopy in the evaluation and management of women with recurrent urinary tract infection. *J Urol*. 1980 Feb;123(2):190-1. doi: 10.1016/s0022-5347(17)55849-8. PMID: 7354514.

23. Hijazi S, Leitsmann C. Clinical significance of video-urodynamic in female recurrent urinary tract infections. *Int J Womens Health*. 2016 Jan 19;8:31-4. doi: 10.2147/IJWH.S94956. PMID: 26855600; PMCID: PMC4725692.

24. Raz R, Gennesin Y, Wasser J, Stoler Z, Rosenfeld S, Rottensterich E, Stamm WE. Recurrent urinary tract infections in postmenopausal women. *Clin Infect Dis*. 2000 Jan;30(1):152-6. doi: 10.1086/313596. PMID: 10619744.

25. Harding C, Chadwick T, Homer T, Lecouturier J, Mossop H, Carnell S, King W, Abouhajar A, Vale L, Watson G, Forbes R, Currer S, Pickard R, Eardley I, Pearce I, Thiruchelvam N, Guerrero K, Walton K, Hussain Z, Lazarowicz H, Ali A. Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. *Health Technol Assess*. 2022 May;26(23):1-172. doi: 10.3310/QOIZ6538. PMID: 35535708.

Transurethral resection of bladder tumour (TURBT) single post instillation of mitomycin C (SPI-MMC)

These recommendations target improvements in how care is delivered to patients with bladder cancer, aiming to reduce cancer recurrence, improve patient experience and reduce unwarranted variation by setting out best practice.

Summary of current practice

These recommendations outline how mitomycin C (MMC) is best administered post-transurethral resection of bladder tumour (TURBT). The need for prompt administration is guided by best evidence as well as a drive to deliver more TURBTs as day cases where this is clinically appropriate, improving patient experience and optimising the use of resources.

Mitomycin C (MMC), a chemotherapy agent, has been in use in urology practice for a decade and is recommended as part of the treatment of non-muscle invasive bladder cancer (NMIBC) to reduce recurrence. It is theorised that MMC kills cancer cells floating in the bladder, cells at the resection site and any missed tumours[1]. This reduces recurrence and the need for further invasive and expensive interventions. Mitomycin C is instilled into the bladder after transurethral resection of bladder tumour (TURBT), a process which is termed 'single post TURBT instillation of mitomycin C' (SPI-MMC).

There is a wide variation in clinical practice relating to SPI-MMC. The Getting It Right First Time (GIRFT) urology programme[2] identified variation in the proportion of patients being offered SPI-MMC, and when offered, variation in the timing and clinical setting in which it was administered. Exemplar units had functioning pathways that allowed installation of MMC in the operating theatre or recovery area, maximising the chance of a day case pathway for the patient. Where MMC was not given in theatre, patients were often reliant on administration on the ward and this could often lead to delays or, in some cases, missed doses. The most common reason cited for not being able to perform SPI-MMC in theatre related to local pharmacy guidelines on chemotherapy. Training was occasionally an issue, though this was usually easier to overcome.

Single dose MMC is used after first TURBT to reduce the likelihood of tumour recurrence. Some patients having subsequent TURBTs are also prescribed SPI-MMC but those patients are outside the scope of this guidance. It is important that patients are consented for the administration of MMC prior to their first TURBT procedure and those with known intolerance or allergy to MMC do not receive it. At the time of the procedure, SPI-MMC

should be administered where the operating surgeon identifies a bladder tumour that does not invade the muscle layer and there are no contraindications (perforation of the bladder, need for deep resection or need for irrigation due to ongoing gross haematuria). Histological examination of the tumour specimen is used to assess whether further intravesical chemotherapy may be required, but these subsequent procedures are not covered in this guideline.

Single dose MMC works best when delivered soon after TURBT. Best practice is for the operating surgeon / suitably qualified healthcare professional to administer the dose of chemotherapeutic agent in theatre as it reduces the risk of MMC being missed, minimises the need for patients to stay overnight and likely increases clinical efficacy. MMC is also administered in other locations including the recovery unit and the inpatient ward. In the 'non-theatre' setting, any appropriately trained medical practitioner can administer single dose MMC; in practice, this is normally a urology nurse specialist or a ward nurse with urology experience.

Recommendations

Scope

This recommendation applies to all patients undergoing their initial TURBT for a new non-muscle invasive bladder cancer, who meet the clinical criteria for single dose mitomycin C administration as outlined in NICE guideline NG2[3].

It excludes patients with contraindications, such as allergies/intolerance to mitomycin C, bladder perforation/deep resection or significant post-operative bleeding.

Recommendations

1. Single dose mitomycin C should be administered within the theatre or theatre recovery setting for all eligible patients following TURBT.
2. Where this is not possible, single dose mitomycin C should be administered within 6 hours of the TURBT procedure being completed.
3. Mitomycin C should only be administered by appropriately trained practitioners.
4. The use of closed systems (e.g. Mito-In or similar) is preferable for the delivery of mitomycin C.

These recommendations are in line with the GIRFT best practice day case TURBT pathway[2].

Rationale for recommendations

The panel considered the evidence supporting the use of intra-vesical chemotherapy, including MMC, in reducing the recurrence of NMIBC after TURBT. The panel discussed the findings of three systematic reviews[4,5,6] relevant to the clinical question that provided data on recurrence rates and adverse effects. The key conclusions considered by the panel are summarised in table below.

Study	Number of randomised controlled trials	Total patients	Median follow up (years)	NMIBC recurrence rates	Adverse effects
Sylvester et al. (2004)[5]	7	1,476	3.4	267 of 728 patients (36.7%) receiving 1 postoperative instillation of epirubicin, mitomycin C, thiotepa or (2'R)-4'-O-tetrahydropyranyl-doxorubicin (pirarubicin) had recurrence compared to 362 of 748 patients (48.4%) with trans-urethral resection alone, a decrease of 39% in the odds of recurrence with chemotherapy (OR 0.61, p <0.0001).	Mild storage symptoms (10%) Allergic skin reaction (1-3%) Systemic toxicity was extremely rare

Study	Number of randomised controlled trials	Total patients	Median follow up (years)	NMIBC recurrence rates	Adverse effects
Sylvester et al. (2015)[6]	13 IPD from 11 trials	2,384 IPD=2,278	6	A single instillation reduced the risk of recurrence by 35% (hazard ratio [HR]: 0.65; 95% confidence interval [CI], 0.58-0.74; p<0.001) and the 5-yr recurrence rate from 58.8% to 44.8%. A single instillation did not reduce recurrences in patients with a prior recurrence rate of more than one recurrence per year or in patients with an European Organization for Research and Treatment of Cancer (EORTC) recurrence score ≥5.	Not reported
Perlis et al. (2013)[4]	13	2,548	Not reported	Intra-vesical chemotherapy prolonged recurrence-free interval by 38% (HR: 0.62; 95% confidence interval [CI], 0.50-0.77; p<0.001; I(2): 69%), and early recurrences (recurrence within 12 months) were 12% less likely in the intervention population (ARR: 0.12; 95% CI, -0.18 to -0.06; p<0.001, I(2): 0%). The number needed to treat to prevent one early recurrence was 9 (95% CI, 6-17 patients).	No documented serious adverse events in any study (9 studies)

Regarding the timing of MMC instillation the panel considered the recommendations from international guidelines. Recently updated guidance from the European Association of Urology states[7]:

'Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by the extracellular matrix'.

'To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre.'

Similarly, guidelines from the American Urological Association/Society of Urologic Oncology state[8]:

'In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g. gemcitabine, mitomycin C) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy.'

Scotland's Quality Performance Indicators Programme also recommends administration within 24 hours following the initial TURBT (Scotland's Quality Performance Indicators Programme[9]). This aligns with NICE guidance NG2 which says:

'Offer people with suspected bladder cancer a single dose of intravesical mitomycin C given ***at the same time as the first TURBT.****'*

As well as NICE quality standards for bladder cancer [QS106] which states:

'Adults with suspected bladder cancer are offered a single dose of intravesical mitomycin C, given at the same time as the first transurethral resection of bladder tumour (TURBT).'

The panel discussed the differences between recommendations, especially the EUA guidelines, which advise MMC is delivered 'within the first few hours after TURBT' (as opposed to within 24 hours). The panel noted that most clinical trials evaluating MMC used a 24-hour limit as this was more pragmatic in terms of trial design. However, the panel discussed how the EUA guidelines reflect a belief among the urological community that early delivery is preferable as tumour cells become firmly implanted and covered by the extracellular matrix in the first few hours after TURBT.

The panel also considered qualitative feedback from GIRFT site visits (one panel member was the GIRFT urology lead) and its relevance to when and where MMC is delivered. Not administering MMC in theatre or recovery was identified as important driver of missed

chemotherapy doses following TURBT by GIRFT. It was also flagged as a key contributor to delayed discharge and unnecessary overnight admissions. Units with optimal practice were discussed, including how barriers limiting the use of chemotherapy in theatre were overcome.

Taking the clinical and operational evidence together, the panel considered there was a clear rationale for delivering MMC as soon as possible after TURBT and that exemplar units had demonstrated that this was feasible. The panel was therefore of the opinion that that MMC be delivered in theatre or recovery, or within a 6-hour period of completing TURBT where this was not possible.

Evidence demonstrating the cost effectiveness of immediate (within 24 hours) vs delayed (within 2 weeks) MMC instillation was noted by the panel[10] with one study demonstrating a mean saving of 1,350 euros per patient over a 3-year period. The panel agreed that further cost savings were achievable by maximising the day case rate, and that this would also help to improve patient experience (where wasn't another clinical reason for admission). This was felt to further justify the recommendation that MMC should be administered as soon as possible after TURBT, rather than simply within 24 hours.

Patient information

A transurethral resection of bladder tumour (TURBT) is the usual treatment for bladder cancer when it is diagnosed early. A thin tube called a cystoscope is inserted through your urethra (the tube through which you urinate) into the bladder. The cystoscope is used by your doctor to locate and remove cancerous tumours from your bladder.

Cancerous tumours can sometimes recur. To reduce the chance of tumours coming back, the chemotherapy drug mitomycin C can be administered directly into the bladder as part of the TURBT procedure. These drugs kill tumour cells effectively because they are targeted at the site of the cancer.

Mitomycin C should be administered as close to the TURBT as possible to maximise benefit. Evidence shows that patients who receive chemotherapy into the bladder immediately after a TURBT have an estimated 12-14% less chance of bladder cancer recurrence at five years.

Mitomycin C is **not** associated with the same adverse effects of conventional chemotherapy, such as hair loss or nausea. Occasional side effects (seen in 1-10% of patients) include mild skin in reactions and the temporary sensation of needing to pee more frequently.

This guidance aligns with the European Association of Urology and American Urological Association / Society of Urologic Oncology recommendations that mitomycin-C is routinely

administered within 6 hours of a patient undergoing their first TURBT procedure, where the clinical criteria is met and in the appropriate relevant setting. By doing this within 6 hours after surgery it can maximise the clinical benefits of mitomycin-C and minimise the chance that a patient must stay unnecessarily in hospital when there are no other reasons for doing so.

References

1. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, De Nunzio C, Okamura K, Kaasinen E, Solsona E, Ali-El-Dein B, Tatar CA, Inman BA, N'Dow J, Oddens JR, Babjuk M. Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? *Eur Urol*. 2016 Feb;69(2):231-44. doi: 10.1016/j.eururo.2015.05.050. Epub 2015 Jun 16. PMID: 26091833.

2. GiRFT. *Urology: Towards better care for patients with bladder cancer A practical guide to improving bladder cancer management*. 2022 January.

3. NICE. *Bladder cancer: diagnosis and management NICE guideline [NG2]* Published, 25 February 2015.

4. Perlis N, Zlotta AR, Beyene J, Finelli A, Fleshner NE, Kulkarni GS. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. *Eur Urol*. 2013 Sep;64(3):421-30. doi: 10.1016/j.eururo.2013.06.009. Epub 2013 Jun 19. PMID: 23830475.

5. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol*. 2004 Jun;171(6 Pt 1):2186-90, quiz 2435. doi: 10.1097/01.ju.0000125486.92260.b2. PMID: 15126782.

6. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, De Nunzio C, Okamura K, Kaasinen E, Solsona E, Ali-El-Dein B, Tatar CA, Inman BA, N'Dow J, Oddens JR, Babjuk M. Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? *Eur Urol*. 2016 Feb;69(2):231-44. doi: 10.1016/j.eururo.2015.05.050. Epub 2015 Jun 16. PMID: 26091833.

7. Gontero P (Chair), Compérat E, Dominguez Escrig JL, Liedberg F, Mariappan P, Masson-Lecomte A, Mostafid AH, van Rhijn BWG, Rouprêt M, Seisen T, Shariat SF, Xylinas EN. Patient Advocates: Gürses Andersson I, Wood R. 2021. Guidelines Associates: Capoun O, Pradere B, Rai BP, Soria F, Soukup V, Guidelines Office: Bezuidenhout C. *EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)*. European Association of Urology.

8. Chang SS, Boorjian SA, Chou R et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol*. 2016; 196: 1021.

9. Scottish Cancer Taskforce. *National Cancer Quality Steering Group Bladder Cancer QPIs* (19th April 2022). Healthcare Improvement Scotland.

10. Hentschel AE, Blankvoort CJ, Bosschieter J, Vis AN, van Moorselaar RJA, Bosmans JE, Nieuwenhuijzen JA. Trial-based Cost-effectiveness Analysis of an Immediate Postoperative Mitomycin C Instillation in Patients with Non-muscle-invasive Bladder Cancer. *Eur Urol Open Sci*. 2022 Jan 17;37:7-13. doi: 10.1016/j.euros.2021.12.008. PMID: 35243387; PMCID: PMC8883187.

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