Enhanced cystoscopy for bladder cancer

Clinical Policy ID: CCP.1295

Recent review date: 3/2022

Next review date: 7/2023

Policy contains: Blue light or fluorescent cystoscopy; hexaminolevulinate; non-muscle invasive bladder cancer; photodynamic diagnosis.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Photodynamic diagnosis (also called blue light or fluorescent cystoscopy) is clinically proven and, therefore, medically necessary for the cystoscopic detection of non-muscle invasive bladder cancer when all of the following criteria are met (Chang, 2016; European Association of Urology, 2020; National Comprehensive Cancer Network, 2020; National Institute for Health and Care Excellence, 2019; U.S. Food and Drug Administration, 2010b):

- Performed after white light cystoscopy.
- Use of the fluorescence agent hexaminolevulinate, marketed in the United States as Cysview® (Cato Research Ltd., Durham, North Carolina) in combination with the Karl Storz D-Light C Photodynamic Diagnostic system (Karl Storz Endoscopy-America Inc., El Segundo, California).
- For either of the following clinical indications:
    - At the time of the first three-month cystoscopy in all patients with a history of intermediate- to high-risk non-muscle invasive bladder cancer.
        - Exception: patients with low-risk single small non-recurrent low-grade papillary cancers (stage Ta), as the expected three-month recurrence rate is less than 15%.
    - To guide transurethral resection.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

Contraindications to hexaminolevulinate include porphyria, gross hematuria, intravesical immunotherapy, or chemotherapy within 90 days, or known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives (U.S. Food and Drug Administration, 2010b).

Repetitive administrations of hexaminolevulinate are not medically necessary (U.S. Food and Drug Administration, 2010b).

Photodynamic diagnosis using 5-aminolevulinic acid is considered an off-label use and not medically necessary.

Alternative covered services

- Cytology with urinalysis.
- Random bladder biopsies.
- Upper urinary tract imaging.
- White light cystoscopy.

Background

Bladder cancer is the fourth most common cancer in men, but it is less common in women (American Cancer Society, 2020). About half of all bladder cancers are found while the cancer is non-invasive or *in situ* and still confined to the inner layer of the urothelium. About one in three bladder cancers have invaded into deeper layers but are still only in the bladder. High recurrence rates are associated with bladder cancer, often requiring repeat treatment and lifelong surveillance (Zlatev, 2015).

The most common tests used to detect bladder cancer are cytology with urinalysis and transurethral intravesical illumination using white light cystoscopy with biopsy (Lopez, 2014; Zlatev, 2015). Cytology detects morphological changes in intact, exfoliated cells. It can identify high-risk disease reliably but tends to miss low-grade or early-stage tumors. White light cystoscopy is unreliable for determining low- and high-grade cancer, assessing level of invasion, differentiating non-papillary and flat malignant lesions (e.g., carcinoma *in situ*) from inflammation, detecting smaller or satellite tumors, and visualizing submucosal tumor margins during transurethral resection. These limitations can lead to incomplete tumor resection and under-staging, which can increase the risk of cancer persistence, recurrence, and progression (of high-grade cancer) to more lethal disease.

Photodynamic diagnosis in urology applies the principle of fluorescence under ultraviolet light to distinguish suspicious lesions from non-cancerous mucosa (Lopez, 2014; Zlatev, 2015). Innovations in transurethral intravesical illumination using fluorescent markers, which show selective absorption by malignant cells, provide additional contrast enhancement. The goal of these modifications is to improve optical diagnosis beyond standard white light cystoscopy, resulting in more effective use of both bladder sparing management for low-grade cancer and more aggressive treatment for high-grade cancer.

Clinical application of photodynamic diagnosis of bladder cancer involves two agents: the heme precursor 5-aminolevulinic acid and its derivative hexaminolevulinate. The U.S. Food and Drug Administration (1999) has approved 5-aminolevulinic acid for topical use in dermatology; intravesical evaluation of the bladder is an off-label use. Hexaminolevulinate is available in the United States as Cysview performed in combination with the Karl Storz D-Light C Photodynamic Diagnostic system for the cystoscopic detection of non-muscle invasive bladder cancer in patients suspected or known to have lesion(s) on the basis of a prior white light cystoscopy (U.S. Food and Drug Administration, 2010a, 2010b). Approval highlights the importance of performing a thorough white light examination first, as some lesions may be missed with Cysview/blue light. Cysview/blue light cystoscopy may be used during an endoscopic examination of the bladder and during resection of bladder cancer.

Findings

We found five systematic reviews/meta-analyses, three evidence-based guidelines, and no cost-effectiveness analyses for this policy. Moderate quality evidence from randomized controlled trials, nonrandomized controlled trials, and cross-sectional studies comprised the majority of the evidence in the secondary analyses (Burger, 2013; Chou, 2015; Di Stasi, 2015; Gakis, 2016; Lee, 2015). Studies enrolled persons with known or suspected bladder cancer. They compared photodynamic diagnosis using hexaminolevulinate and, to a lesser extent, 5-aminolevulinic acid as an adjunct to white light cystoscopy during initial diagnosis and transurethral resection. The role of photodynamic diagnosis as a replacement for white light cystoscopy has not been evaluated.

Most studies reported data by lesion, which may hyperinflate estimates of diagnostic accuracy, as opposed to analysis by patient (i.e., intention-to-treat analyses) that is generally more relevant to assess clinical effectiveness. Cystoscopies were performed in a hospital inpatient setting. Since applying photodynamic diagnosis with 5-aminolevulinic acid during cystoscopy is considered an off label use, this policy will restrict discussion to photodynamic diagnosis using hexaminolevulinate.

Photodynamic diagnosis is a reasonably safe procedure, as no serious side effects were noted. The harms associated with any cystoscopy procedure are discomfort, subsequent dysuria and bleeding, and the possibility of urinary tract infection or acute retention. Hexaminolevulinate is contraindicated in patients with porphyria, gross hematuria, intravesical immunotherapy or chemotherapy within 90 days, or known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives, as false-positive results may occur from inflammatory lesions, previous biopsy sites, or in patients previously treated with bacillus Calmette-Guérin (U.S. Food and Drug Administration, 2010b).

Although repetitive use of hexaminolevulinate has not been evaluated in prospective clinical trials, one retrospective study with 180 patients and another study that summarized data from six controlled trials (4,324 total patients) and a European registry found no statistically significant differences in the frequency or grade of adverse events between single- and repeat-use of blue light cystoscopy with hexaminolevulinate (Lane, 2017; Witjes, 2014). A registry study that will address the safety and efficacy of repetitive use of hexaminolevulinate in urologists' practices in the United States is underway (Clinicaltrials.gov identifier: NCT02660645).

There is consistent evidence that a single application of photodynamic diagnosis added to white light cystoscopy improves the detection and resection of non-muscle invasive bladder cancer. Photodynamic diagnosis detects significantly more Ta, T1, and carcinoma *in situ* tumors than white light cystoscopy alone. This benefit extends to most subgroups, including more aggressive, higher risk primary and recurrent bladder cancer. However, the benefits must be weighed against the higher false positive rate (corresponding to lower specificity) of photodynamic diagnosis plus white light cystoscopy, which may result in an increase in unnecessary biopsies.

The added value of enhanced detection with respect to the risk of recurrence, recurrence-free survival, mortality, progression to muscle-invasive bladder cancer, or cost-effectiveness has not been established. Limited evidence with a high potential for bias suggests photodynamic diagnosis with white light cystoscopy may reduce recurrence rates up to one year, and possibly longer, but the findings were conflicting across studies (Burger, 2013; Chou, 2015; Di Stasi, 2015; Gakis, 2016; Lee, 2015).

Photodynamic diagnosis can miss some high grade lesions found on white light cystoscopy. Use of single-dose adjuvant chemotherapy following transurethral resection of bladder tumor , which alone can reduce recurrence rates, was inconsistently reported or accounted for across studies. Most studies reported a relatively short follow-up period (up to 12 months), which is insufficient to detect changes to invasive cancer, and used various definitions for disease progression. More comparative prospective studies are needed to define the optimum use of photodynamic diagnosis relative to white light cystoscopy.

Evidence-based guidelines by the American Urological Association/ Society of Urologic Oncology (Chang, 2016), National Institute for Health and Care Excellence (2015), and the European Association of Urology (2015) recommend photodynamic diagnosis-guided transurethral resection for persons with suspected bladder cancer, when available, based on the ability of photodynamic diagnosis to enhance detection and lower recurrence. There is general agreement, based on expert opinion, that photodynamic diagnosis is one of several diagnostic options for patients with a history of non-muscle invasive bladder cancer with normal white light cystoscopy and positive cytology.

Other diagnostic options include prostatic urethral biopsies, upper tract imaging, ureteroscopy, and random bladder biopsies. The European Association of Urology (2015) recommends photodynamic diagnosis-guided biopsy instead of random biopsies when carcinoma *in situ* or high-grade tumor is suspected (e.g., positive cytology or recurrent tumor with previous history of a high-grade lesion) based on moderate quality evidence, and either random biopsies or photodynamic diagnosis-guided biopsies after intravesical treatment (at three or six months) in patients with carcinoma *in situ* based on expert opinion.

In 2018, we added two guideline updates on management of bladder cancer: one by the National Comprehensive Cancer Network (2018) and the other by the European Association of Urology (2017). Their recommendations for blue light cystoscopy are consistent with the previous findings, and no policy changes are warranted.

In 2019, we identified no newly published, relevant literature to add to the policy. The policy ID was changed from CP# 13.01.04 to CCP.1295.

In 2020, we added two systematic reviews and meta-analyses (Chen, 2019; Konecki, 2019) and one randomized controlled trial (n = 699 participants; Drejer, 2019), and updated three evidence-based guidelines (European Association of Urology, 2019; National Comprehensive Cancer Network, 2019; National Institute for Health and Care Excellence, 2019). The new information confirms previous findings, and no policy changes are warranted.

In 2021, we updated guidelines by the European Association of Urology (2020) and the National Comprehensive Cancer Network (2020) with no policy changes warranted.

In 2022, we added a systematic review and meta-analysis that presented new outcome data on residual disease rates in patients with suspected or proven non-muscle-invasive bladder cancer. Sun (2021) included 18 trials (reported in 22 articles) involving 1,869 patients who underwent fluorescent light cystoscopy (with 5-aminolevulinic acid or hexaminolevulinate) and 1,749 patients who underwent white light cystoscopy only. Fluorescent light cystoscopy was associated with a lower residual tumor rate than that of white light cystoscopy (relative risk 0.44, 95% confidence interval 0.28 to 0.69, P = .0004), along with a lower residual T1 rate (P = .01) and carcinoma in situ rate (P = .01), and higher recurrence free survival at the 12-month follow-up (P = .0002) and 24-month follow-up (P < .00001). No statistically significant differences were found in progression free survival at either the 12-month follow-up (P = .17) or 24-month follow-up (P = .95). These results confirm previous findings of medical necessity, and no policy changes are warranted.

References

On January 7, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “urinary bladder neoplasms” (MeSH), “cystoscopy” (MeSH), “hexaminolevulinate,” “blue light cystoscopy,” and “enhanced cystoscopy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American Cancer Society. Bladder cancer. https://www.cancer.org/cancer/bladder-cancer.html. Undated.

Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: A meta-analysis of detection and recurrence based on raw data. *Eur Urol.* 2013;64(5):846-854. Doi: 10.1016/j.eururo.2013.03.059.

Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol.* 2016;196(4):1021-1029. Doi: 10.1016/j.juro.2016.06.049.

Chen C, Huang H, Zhao Y, et al. Diagnostic performance of image technique based transurethral resection for non-muscle invasive bladder cancer: Systematic review and diagnostic meta-analysis. *BMJ Open.* 2019;9(10):e028173. Doi: 10.1136/bmjopen-2018-028173.

Chou R, Buckley D, Fu R, et al. Emerging approaches to diagnosis and treatment of non–muscle-invasive bladder cancer. Comparative Effectiveness Review No. 153. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 15(16)-EHC017-EF. Rockville, MD: Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/products/bladder-cancer-non-muscle-invasive/research. Published October 27, 2015.

Clinicaltrials.gov. Blue light cystoscopy with Cysview® registry (BLCCR). Clinicaltrials.gov identifier: NCT02660645. https://www.clinicaltrials.gov/ct2/show/NCT02660645?term=NCT02660645&draw=2&rank=1.

Di Stasi SM, De Carlo F, Pagliarulo V, et al. Hexaminolevulinate hydrochloride in the detection of nonmuscle invasive cancer of the bladder. *Ther Adv Urol.* 2015;7(6):339-350. Doi: 10.1177/1756287215603274.

Drejer D, Moltke AL, Nielsen AM, Lam GW, Jensen JB. Dablaca-11: Photodynamic diagnosis in flexible cystoscopy - a randomised study with focus on recurrence. *Urology.* 2020 Mar;137:91-96. Doi: 10.1016/j.urology.2019.12.002.

European Association of Urology. Non-muscle-invasive bladder cancer. https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/. Published 2017. Updated 2020.

Gakis G, Fahmy O. Systematic review and meta-analysis on the impact of hexaminolevulinate- versus white-light guided transurethral bladder tumor resection on progression in non-muscle invasive bladder cancer. *Bladder Cancer.* 2016;2(3):293-300. Doi: 10.3233/blc-160060.

Konecki T, Kutwin P, Lowicki R, Juszczak AB, Jablonowski Z. Hexaminolevulinate in the management of nonmuscle invasive bladder cancer: A meta-analysis. *Photobiomodul Photomed Laser Surg.* 2019;37(9):551-558. Doi: 10.1089/photob.2019.4634.

Lane GI, Downs TM, Soubra A, et al. Tolerability of repeat use of blue light cystoscopy with hexaminolevulinate for patients with urothelial cell carcinoma. *J Urol.* 2017;197(3 Pt 1):596-601. Doi: 10.1016/j.juro.2016.09.076.

Lee JY, Cho KS, Kang DH, et al. A network meta-analysis of therapeutic outcomes after new image technology-assisted transurethral resection for non-muscle invasive bladder cancer: 5-aminolaevulinic acid fluorescence vs hexylaminolevulinate fluorescence vs narrow band imaging. *BMC Cancer.* 2015;15:566. Doi: 10.1186/s12885-015-1571-8.

Lopez A, Liao JC. Emerging endoscopic imaging technologies for bladder cancer detection. *Curr Urol Rep.* 2014;15(5):406. Doi: 10.1007/s11934-014-0406-5.

National Comprehensive Cancer Network. NCCN Guidelines Bladder Cancer. Version 6.2020. www.nccn.org. Last updated July 16, 2020.

National Institute for Health and Care Excellence. Bladder cancer: Diagnosis and management. NICE Guideline 2. https://www.nice.org.uk/guidance/ng2. Published February 2015. Updated 2019.

Sun J, Ma X, Shen H, Liu B. Effects of fluorescent light cystoscopy in non-muscle-invasive bladder cancer: A systematic review and meta-analysis. *Photodiagnosis Photodyn Ther*. 2021;34:102248. Doi: 10.1016/j.pdpdt.2021.102248.

U.S. Food and Drug Administration. Approval letter for NDA 20-965. Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1999/20965ltr.pdf. Published 1999.

U.S. Food and Drug Administration. Karl Storz Endoskope. Photodynamic Diagnostic D-Light C System. Instruction manual. http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050027c.pdf. Published 2010.(a)

U.S. Food and Drug Administration. Summary review for regulatory action. 022555Orig1s000. Cysview hexaminolevulinate hydrochloride for intravesical solution. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022555Orig1s000SumR.pdf. Published 2010.(b)

Witjes JA, Gomella LG, Stenzl A, et al. Safety of hexaminolevulinate for blue light cystoscopy in bladder cancer. A combined analysis of the trials used for registration and postmarketing data. *Urology.* 2014;84(1):122-126. Doi: 10.1016/j.urology.2014.03.006.

Zlatev DV, Altobelli E, Liao JC. Advances in imaging technologies in the evaluation of high-grade bladder cancer. *Urol Clin North Am.* 2015;42(2):147-157, vii. Doi: 10.1016/j.ucl.2015.01.001.

Policy updates

2/2017: initial review date and clinical policy effective date: 4/2017

3/2018: Policy references updated. Policy ID changed.

3/2019: Policy references updated.

3/2020: Policy references updated.

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