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SUMMARY WITH CRITICAL APPRAISAL

Blue Light Cystoscopy in Patients with Suspected Non-Muscle Invasive Bladder Carcinoma: A Review of Clinical Utility

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Context and Policy Issues

According to Canadian Cancer Statistics, bladder cancer is the fifth most common cancer, accounting for more than 4% of all cancers or 7,800 cases per year.[1] Of all incidents of bladder cancer cases at first diagnosis, about 80% were non-muscle invasive bladder cancer (NMIBC) and 20% were muscle invasive and advanced bladder cancer.[2] Smoking is the main risk factor of bladder cancer.[2,3] Other risk factors include exposure to chemicals such as aromatic compounds, radiation and chemotherapy.[2,3] The most common symptom of bladder cancer is the presence of blood in the urine.[2] Bladder cancer is diagnosed by means of cystoscopy and transurethral resection of the bladder tumor (TURBT) in combination with urine analysis and cytology.[2,4] The tumors are classified based on the degree of invasion into layers of tissues; CIS (flat on surface or carcinoma in situ), Ta (raspberry growth on surface), and T1 (moves into submucosa layer) are those not yet invading into the muscle or NMIBC, while T2a, T2b, T3b and T4a are those invade deeper into the muscle layer and perivesical fat tissue.[2] About 60% of NMIBC are Ta type, while CIS and T1 account for 10% and 30%, respectively.[3] After the initial removal of NMIBC by TURBT, tumors can come back (recurrence) or come back and invade into the muscle layer (progression).[2] Tumors are graded based on the risk of progression and metastasis.[3] For instance, Ta tumors are usually low grade (non-aggressive) but have high risk of recurrence and just require repeated scraping, while CIS and T1 tumors are high grade (aggressive), have a high risk of progression to muscle layer and require more aggressive treatment.[2]

Visibility of tumors is very important during TURBT, in particular flat lesions such as CIS or low-graded tumors are often missed under standard white light cystoscopy.[5] A new technique termed “blue light” cystoscopy have been introduced to improve the visibility of tumors by using a photosensitizing agent and fluorescent light in the photodynamic diagnosis of NMIBC.[4] In fluorescent cystoscopy, the photosensitizing agent such as 5-aminolevulenic acid (5-ALA) or hexaminolevulinate (HAL), a derivative of 5-ALA, are first instilled into the bladder.[4] The drug then incorporates into the urothelial cytoplasm where abnormal cells appear red and normal cells appear blue green upon illumination with fluorescent light.[4] Thus, “blue light” or fluorescent cystoscopy may help the detection of tumors more accurately and may reduce the risk of recurrence and progression compared to white light cystoscopy. HAL needs a much shorter instillation time than 5-ALA and has been approved only for detection of bladder cancer in Europe and USA since 2010.[4] HAL, branded as Cysview, has been approved by Health Canada since November 2015 as an adjunct to cystoscopy for the detection of NMIBC in patients with known or suspicion of bladder cancer.[6,7]

The aim of this report is to review the clinical utility of “blue light” cystoscopy in patients with suspected NMIBC undergoing TURBT.

Research Question

What is the clinical utility of blue light cystoscopy in patients with suspected NMIBC undergoing TURBT?

Key Findings

Hexaminolevulinate-guided transurethral resection of bladder tumors was associated with a decreased risk of bladder cancer recurrence and a decreased risk of progression to muscle invasive bladder cancer compared to white light cystoscopy. Evidence on mortality and harms was inconclusive due to sparse data.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2012 and Jan 13, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, and if they were published prior to 2012. Conference abstracts, duplicates of publication of the same study, or SRs in which their included studies were reviewed in an more recent or more comprehensive SR were excluded.

Table 1: Selection Criteria

Population	Patients suspected of non-muscle invasive bladder carcinoma undergoing transurethral resection of bladder tumor (TURBT)
Intervention	Hexaminolevulinate (HAL)- or 5-aminolevulinic acid (5-ALA)-guided blue light cystoscopy (also referred to as fluorescent cystoscopy)
Comparator	White-light cystoscopy
Outcomes	Clinical utility outcomes (e.g., removal, resection quality, rate of recurrence [short and long term], mortality, disease progression)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), or meta-analyses (MAs)

Critical Appraisal of Individual Studies

The SIGN checklist for systematic reviews and meta-analyses were used to assess the quality of SRs and MAs.[8]

Summary of Evidence

Quantity of Research Available

A total of 223 citations were identified in the literature search. Following screening of titles and abstracts, 211 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 10 publications were excluded for various reasons, while 2 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

The characteristics of the SRs and MAs[9,10] are briefly described below and detailed in Appendix 2.

Country of Origin

The studies were conducted by authors from the USA[9] and Germany and Malaysia.[10] They were all published in 2016.

Search Methods and Results of Study Selection

Searches were conducted in multiple databases (January 1990 to October 2014)[9] or from a single database (between 2000 and 2016)[10] with restriction to English language only.[9,10] One SR[9] selected only RCTs, while the other SR[10] included RCTs and observational studies.

Patient Population

Most of the included studies in both SRs[9,10] had mixed populations including those with new diagnoses of bladder cancer, those with high risk bladder cancer, and those of mixed conditions who had initial or recurrent bladder cancer. The mean age of patients was reported in one SR and ranged from 60 to 74 years. Patients were predominantly male.[9]

Interventions and Comparators

Both SRs included studies comparing fluorescent light cystoscopy with white light cystoscopy.[9,10] One SR[9] included studies that used 5-ALA or HAL, while the other SR[10] included studies that used only HAL as the photosensitizing agent.

Outcomes

The clinical outcomes included recurrence,[9] progression,[9,10] mortality,[9] and harms.[9]

Follow-up Period

Follow-up period of the included studies ranged from four weeks to 60 months in one SR[9] and from one to 55 months in the other SR.[10] Follow-up was reserved for NMIBC patients of stage Ta, T1 or CIS on initial cystoscopy.[9]

Data Analysis and Synthesis

Data were analyzed was a meta-analysis approach and the statistical heterogeneity was described using the *p* value for the Q test and the I^2 test.[9,10] In one SR,[9] the recurrence was stratified according to the duration of follow-up as short-term (<3 months), intermediate-term (3 months to <1 year) or long-term (≥1 year). Publication bias was investigated using funnel plots.[9,10]

Study Appraisal

The Cochrane risk of bias tool was used by two SRs[9,10] to assess the methodological quality of included studies, and the strength of evidence for each body of evidence in one SR[9] was assessed based on study quality, precision, consistency and directness.

Summary of Critical Appraisal

The summary of the quality assessment for the SRs are presented below and in Appendix 3.

One SR[9] was of high quality as most of the criteria were fulfilled, including an explicit research question, a comprehensive literature search, at least two people involved in the study selection and data extraction, a description of the relevant characteristics of the included studies, a quality assessment of included studies, appropriate methods of meta-analysis, appropriate assessment of the likelihood of publication bias, and a declaration of potential conflicts of interest. Potential publication bias was detected in both systematic reviews.[9,10] The other SR[10] was of moderate quality as some of the criteria were not fulfilled or not clearly described such as a comprehensive literature search, multiple people involved in study selection, relevant characteristics of the included studies and appropriate methods of combining the individual study findings. The SR[10] was, however, explicit in terms of clearly defined research question, two people involving in data extraction, quality assessment of included studies, assessment of publication bias and declaration of conflict of interest. Neither SR provided a list of excluded studies.[9,10]

Summary of Findings

What is the clinical utility of blue light cystoscopy in patients with suspected NMIBC undergoing TURBT?

Meta-analysis was conducted for clinical outcomes including recurrence,[9] progression,[9,10] and mortality.[9] Harms were assessed by detection of local adverse events.[9] Appendix 4 presents main findings of the included SRs.

Recurrence

For the detection and resection of NMIBC with TURBT, fluorescent cystoscopy was associated with a statistically significantly reduced risk of bladder cancer recurrence compared with white light cystoscopy at short-term (evidence from 10 RCTs) and long-term follow-up (evidence from 12 RCTs).[9] Stratifying analysis by photosensitizer showed that the effects were statistically significant in trials using HAL, but not in trials using 5-ALA. However, the point estimates were similar and there were no statistically significant interactions based on photosensitizer (*p* for interaction = 0.97 for short-term or 0.41 for long-term).[9] Statistical heterogeneity remained in both subgroups.[9] The strength of evidence was low due to risk of performance or publication bias.[9]

Progression

A pooled analysis of all trials using 5-ALA or HAL showed no difference between fluorescent cystoscopy compared with white light cystoscopy in the risk of progression to muscle invasive bladder cancer.[9] Subgroup analysis showed that the risk of progression was statistically significantly lower in trials using HAL,[9] but not in trials using 5-ALA.[9] However, subgroup effect was not statistically significant (*p* for interaction = 0.18).[9] The strength of the evidence was moderate.[9] The other SR also found that HAL-guided TURBT was associated with statistically significant reduction in the risk of progression compared to white light guided TURBT.[10]

Mortality

There was no difference in mortality between fluorescent cystoscopy and white light cystoscopy in trials using 5-ALA or HAL.[9] The strength of the evidence was low due to imprecision and sparse data.

Harms

There was no difference between fluorescent cystoscopy and white light cystoscopy for local adverse events such as hematuria, dysuria, urinary frequency or urgency and bladder spasms occurred after cystoscopy.[9] Data on harms were sparse.

Limitations

One SR[9] reported that there were substantial statistical heterogeneities in some pooled analyses of recurrence, despite the stratification of the effects by follow-up intervals. The effects at short-term and long-term recurrence were inconsistent across trials. The same SR also found that, in three trials, when methods were used to reduce performance bias, fluorescent cystoscopy using HAL was not associated with decreasing long-term recurrence.[9] Funnel plots for trials investigating short-term recurrence[9] or progression[10] suggested that there was potential publication bias. The strength of the evidence was therefore low as there was a risk of performance or publication bias. In addition, there was insufficient evidence to understand the benefit of fluorescent cystoscopy in patients with different risks of NMIBC or with different tumor characteristics (i.e. grade, multiplicity, or primary versus recurrent). Follow-up periods were not long enough to better understand the effects of fluorescent cystoscopy on progression and mortality. No survival data could be identified.

Conclusions and Implications for Decision or Policy Making

Low to moderate quality evidence from recent SRs has suggested that TURBT guided by fluorescent or “blue light” cystoscopy using HAL as photosensitizing agent in the detection and resection of NMIBC was associated with a decreased risk of bladder cancer recurrence and a decreased risk of progression to muscle invasive bladder cancer compared to white light cystoscopy. The effects on recurrence and progression were not statistically significant in trials that used 5-ALA. The effects of fluorescent cystoscopy on mortality were inconclusive due to sparse data. More studies are needed with better study designs and longer term follow-up to understand the impact of HAL-based TURBT on recurrence, progression and survival in patients with different NMIBC risks, different tumor grading systems and different treatment strategies.

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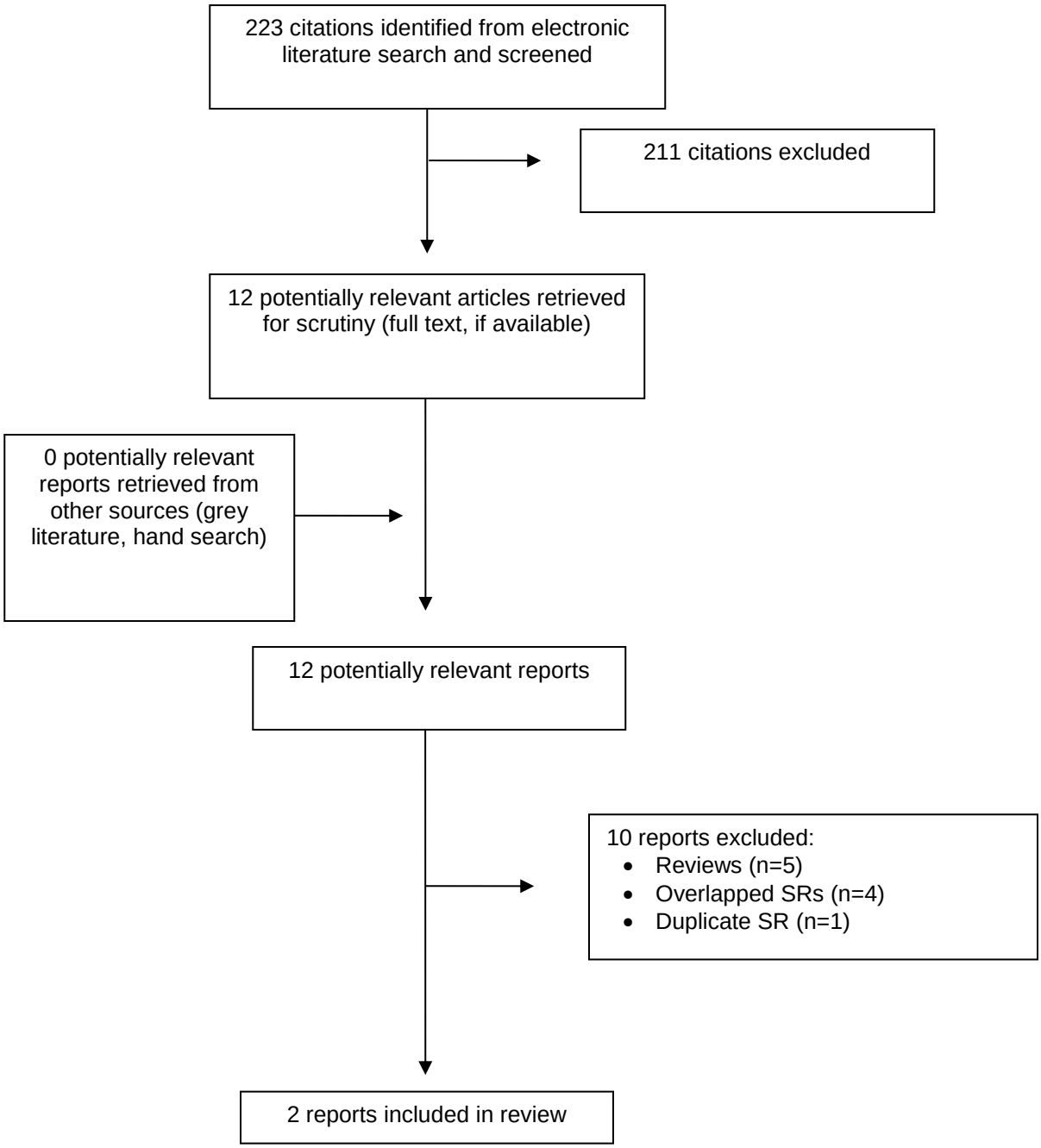
9. Chou R, Selph S, Buckley DI, Fu R, Griffin JC, Grusing S, et al. Comparative effectiveness of fluorescent versus white light cystoscopy for initial diagnosis or surveillance of bladder cancer on clinical outcomes: systematic review and meta-analysis. J Urol. 2016 Oct 22. Epub ahead of print.
10. Gakis 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 [Internet]. 2016 Jul 27 [cited 2017 Jan 18];2(3):293-300. Available from: **http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969683**

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Systematic Reviews and Meta-analyses

Study, Year, Country, Design, and Quality Assessment Tool, Funding	Electronic searches, and Search Range	Included Studies: Types, Numbers, Publication Year, Follow-up	Population: Number, conditions	Intervention and Control Groups (No. of study)	Subgroup or Meta-regression Analysis	Outcomes (No. of study)
Chou et al., 2016[9] **USA** **SR and MA** **Risk of Bias developed by the US Preventive Services Task Force** **Agency for Healthcare Research and Quality (AHRQ)** **Strength of evidence graded using AHRQ methods**	MEDLINE (Jan 1990 to Oct 2014), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through Sep 2014), ClinicalTrials.gov; restricted to English language Updated in Sep 2015	14 RCTs 2001 to 2014 Follow-up: 4 weeks to 60 months using fluorescent cystoscopy (3 RCTs) or using white light cystoscopy (11 RCTs) Follow-up was for patients with NMIBC (Ta, Ti and in some cases CIS) on initial cystoscopy: range from 4 weeks to 60 months	2,906 patients (range 44 to 551 patients) Mean age: 60 to 74 years Gender: predominantly male (ratio not reported) New bladder cancer (2 RCTs), high risk bladder cancer (2 RCTs), mixed conditions (10 RCTs)	Intervention: ALA fluorescent light cystoscopy with TURBT (6 RCTs) HAL fluorescent light cystoscopy with TURBT (9 RCTs) Control: White light cystoscopy with TURBT	By photosensitizing agent	• Recurrence[a] (10 RCTs) • Progression[b] (9 RCTs) • Mortality (3 RCTs) • Harms (3 RCTs)
Gakis and Fahmy, 2016[10] **Germany and Malaysia** **Cochrane risk of bias for RCTs and Newcastle-Ottawa scale for retrospective studies** **Funding: NR**	Pubmed and hand search; restricted to English language 2000 to 2016	4 RCTs and 1 retrospective study 2009 to 2016 Follow-up: 1 to 55 months	1,301 patients (range 44 to 516) Mean age: NR Patients with NMIBC	HAL fluorescent light cystoscopy with TURBT (5 studies) Control: White light cystoscopy with TURBT	No	• Progression[b] (5 studies)

ALA = 5-aminolevulinic acid; CIS = carcinoma in situ; HAL = hexaminolevulinic acid; MA = meta-analysis; NMIBC = non-muscle invasive bladder cancer; NR = not reported; RCT = randomized controlled trial; SR = systematic review; TURBT = transurethral bladder tumor resection; vs = versus

[a]Recurrence: short-term (less than 3 months), intermediate-term (3 months to less than 1 year), long-term (1 year or more) after initial cystoscopy

[b]Progression to muscle invasive bladder cancer

Appendix 3: Quality Assessment of Systematic Reviews and Meta-analyses

SIGN checklist: Internal Validity	Chou et al., 2016[9]	Gakis and Fahmy, 2016[10]
1. The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper	Yes	Yes
2. A comprehensive literature search is carried out	Yes	No
3. At least two people should have selected studies	Yes	Can't tell
4. At least two people should have extracted data	Yes	Yes
5. The status of publication was not used as an inclusion criteria	Yes	Yes
6. The excluded studies are listed	No	No
7. The relevant characteristics of the included studies are provided	Yes	Not clear
8. The scientific quality of the included studies was assessed and reported	Yes	Yes
9. Was the scientific quality of the included studies used appropriately?	Yes	Yes
10. Appropriate methods are used to combine the individual study findings	Yes	No
11. The likelihood of publication bias was assessed appropriately	Yes	Yes
12. Conflicts of interest are declared	Yes	Yes
Overall Assessment of the Study		
High, Moderate, Low	High	Moderate

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

Appendix 4: Main Study Findings and Author's Conclusions

Study, Year, Country, Design	Main Findings
Chou et al., 2016[9] **USA** **SR and MA**	Risk of bias: High (4 RCTs) Medium (11 RCTs) Recurrence – Short term (<3 months) Intervention | No. studies | RR (95% CI) | I^2 | Strength of evidence Overall | 10 | 0.60 (0.37 to 0.88) | 67% | Low ALA | 4 | 0.57 (0.28 to 1.16) | 84% | HAL | 6 | 0.62 (0.38 to 1.00) | 51% | Recurrence – Intermediate term (3 months to <12 months) Intervention | No. studies | RR (95% CI) | I^2 | Strength of evidence Overall | 6 | 0.70 (0.56 to 0.88) | 19% | Low ALA | 1 | 0.56 (0.34 to 0.91) | NA | HAL | 5 | 0.76 (0.62 to 0.93) | 7% | Recurrence – Long term (≥12 months) Intervention | No. studies | RR (95% CI) | I^2 | Strength of evidence Overall | 12 | 0.81 (0.70 to 0.93) | 46% | Low ALA | 5 | 0.86 (0.68 to 1.08) | 66% | HAL | 7 | 0.75 (0.62 to 0.92) | 41% | 3 (where performance bias was reduced) | 0.96 (0.79 to 1.18) | 36% Progression to muscle invasive bladder cancer Intervention | No. studies | RR (95% CI) | I^2 | Strength of evidence Overall | 9 | 0.74 (0.52 to 1.03) | 0% | Moderate ALA | 5 | 0.86 (0.57 to 1.28) | 0% | HAL | 4 | 0.51 (0.28 to 0.96) | 0% | Mortality Intervention | No. studies | RR (95% CI) | I^2 | Strength of evidence Overall | 3 | 1.28 (0.55 to 2.95) | 43% | Low ALA | 1 | 1.22 (0.34 to 4.46) | NA | HAL | 2 | 1.87 (0.29 to 12.22) | 71% | Harms: No difference between fluorescent cystoscopy and white light cystoscopy for local adverse events such as hematuria, dysuria, urinary frequency or urgency and bladder spasms occurred after cystoscopy (the frequency of events was not reported).
Authors' conclusions: "*Fluorescent cystoscopy was associated with a reduced risk of recurrence vs white light cystoscopy, although there were inconsistencies and our findings may have been affected by performance bias or publication bias. Fluorescent cystoscopy with HAL may be associated with a decreased risk of progression but more studies with long-term follow-up are needed to better understand the effects of photosensitizer used on progression. Evidence on the effects of fluorescent cystoscopy on mortality is too sparse to reach strong conclusions.*"[9] p.9	

<table>
<tr><th>Study, Year, Country, Design</th><th>Main Findings</th></tr>
<tr><td>Gakis and Fahmy, 2016[10]

Germany and Malaysia

SR and MA</td><td>Risk of bias: low to moderate

Progression to muscle invasive bladder cancer
<table>
<tr><th>Intervention</th><th>No. studies</th><th>%WL-TURBT vs % HAL-TURBT</th><th>OR (95% CI)</th><th>I^2</th></tr>
<tr><td>HAL</td><td>5</td><td>10.7 vs 6.8</td><td>1.64 (0.28 to 0.96)</td><td>0%</td></tr>
</table></td></tr>
<tr><td colspan="2">Authors' conclusions: "This meta-analysis supported the assumption that the detection and resection of NMIBC with HAL-guided TURBT reduces the risk of progression. Therefore, patients should receive hexaminolevulinate- rather than white-light-guided TURBT at their first resection as this might allow more patients at risk of progression to be treated timely and adequately."[10] p.299</td></tr>
</table>

ALA = 5-aminolevulinic acid; CI = confidence interval; HAL = hexaminolevulinic acid; MA = meta-analysis; NA = not applicable; NMIBC = non-muscle invasive bladder cancer; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; TURBT = transurethral bladder tumor resection; vs = versus; WL = white light

Appendix 5: Additional References of Potential Interest

The following SRs overlapped with the included SR by Chou et al, 2016.[9]

Chou R, Buckley D, Fu R, Gore JL, Gustafson K, Griffin J, et al. Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Oct. [cited 2017 Jan 18]. (AHRQ Comparative Effectiveness Reviews). Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0080825/pdf/PubMedHealth_PMH0080825.pdf

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