

Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer*

Draft review available for public comment from November 20, 2014 to December 10, 2014.

Research Review Citation: Chou R, Selph S, Buckley D, Gustafson K, Griffin J, Grusing S, Gore J. Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer. Comparative Effectiveness Review No. 152. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-1.) AHRQ Publication No. 15-EHC015-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2015. Available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	This report to the best of its ability addresses the key questions. I don't know that it is clinically meaningful since so few things were able to be answered definitively. Certainly, nothing in this report changed my view on current practice.	Thank you for the comment.
Peer Reviewer #1	Methods	The inclusion and exclusion criteria were valid and the search strategies were adequately defined. The statistical methods were appropriate.	Thank you for the comment.
Peer Reviewer #1	Results	On page 46 line 16 there is a typographical error. It should say...One study found no difference between combination cystectomy (and what? something was left out here).	The typo has been corrected.
Peer Reviewer #1	Results	The amount of detail was appropriate and mostly are explicit. No studies were overlooked.	Thank you for the comment.
Peer Reviewer #1	Discussion/ Conclusion	The implications were clearly stated and future research and the need for future research is very clear.	Thank you for the comment.
Peer Reviewer #1	Clarity and Usability	The report is generally well structured. The table 8 is the best table as it summarizes the points and strength of evidence.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The target population is explicitly defined and the audience clear. The key questions are appropriate, explicitly stated, and represent critical questions that those caring for MIBC deal with on a regular basis. The report does a superior job analyzing the data that is available. The biggest limitation of the report is not its analysis but the generally poor quality of the data from the available studies. This limits the report's ability to offer more definitive statements due to poor quality of the evidence. This is not a fault of the report or its methodology but instead a call for better quality studies and data in this disease.	Thank you for the comment.
Peer Reviewer #2	Introduction	In general factual and gives a clear overview of the topic and purpose of the report. There are some specific comments though I would take some issue with. They are: 1. page 10, lines 36-37: while I agree that locoregional N+ disease is a poor prognostic sign, several cohort studies have shown long term recurrence free survival rates of 20-30% in these patients who undergo radical cystectomy and an extended lymph node dissection. Therefore, to say that they are not amenable to curative therapy is misleading.	We revised to note that node-positive caancers and T4b cancers are considered nonlocalized and are outside the scope of the review (p 1) and we removed the statement that node-positive disease is not amenable to curative therapy.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Introduction	2. Page 10, Line 52-53: The community standard is indeed GC for neoadjuvant chemotherapy but it is important to realize that in fact GC has never been formally tested in this setting. MVAC has been tested, and there are those who feel strongly that because of this it should remain the gold standard. I am therefore not comfortable with the idea that GC be put forward as the gold standard. Better to say cisplatin based multi-drug regimens such as GC and MVAC.	We revised to state: “For non-metastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin).”
Peer Reviewer #2	Methods	The inclusion and exclusion criteria are justifiable, though I would have preferred inclusion of locoregional N+ disease as I already alluded to in section b. Search strategies are explicitly state and logical, outcomes measures are reasonable and appropriate as are the statistical methods. The one thing that was repeatedly included was carboplatin/gemcitabine as chemotherapy. while this is commonly used for those with renal impairment, there is very limited data on its effectiveness in this clinical setting and its important that it be avoided in the setting of neoadjuvant chemotherapy since it has never been tested in that context.	The decision to restrict to localized MIBC was made in conjunction with the TEP. Carboplatin/gemcitabine was included because it is used as an alternative regimen; one of the purposes of the review was to determine the comparative effectiveness of carboplatin/gemcitabine versus cisplatin-based regimen.

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Peer Reviewer #2	Results	Results: The detail is appropriate, the studies well described, and key messages explicit and applicable. Figures/Tables are adequate given the state of the literature/data available. One study has not been included that addresses Key Question 1d, for example on page 18 line 13-16 (though the same idea appears multiple times such as page 24 lines 16-19). It is James ND1, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, Crundwell M, Sizer B, Sreenivasan T, Hendron C, Lewis R, Waters R, Huddart RA; BC2001 Investigators: "Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer." N Engl J Med. 2012 Apr 19;366(16):1477-88. doi: 10.1056/NEJMoa1106106. This high quality study shows that if bladder preservation therapy with radiation is to be pursued then this should be done with concurrent radiosensitizing chemotherapy.	We added this trial to KQ 1d, since it compares two types of bladder-preserving treatment (radiation + chemotherapy vs. radiation alone).
Peer Reviewer #2	Results	Some small points/typos page 19, line11: "AC", did you mean NAC?	Typo corrected.
Peer Reviewer #2	Results	page 20, line 19: "...found no that neither..." There must be a typographical error here.	Typo corrected
Peer Reviewer #2	Results	page 26, line 39-42 middle column is blank, did you mean to have "Insufficient" in this space?	It should say "insufficient" (no studies) and has been added.

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Peer Reviewer #2	Discussion/ Conclusion	This section is clear and meets the goals as outlined above. In particular, this clearly outlines the need for better studies and what areas need such new research.	Thank you for the comment.
Peer Reviewer #2	Clarity and Usability	the report is well structured and organized and its points clearly presented. For the few things that can be stated with moderate certainty there are clear policy and practice implications. Lapses in this regard are a reflection of the literature, not the report.	Thank you for the comment.
Peer Reviewer #3	General Comments	Well done. No changes needed	Thank you for the comment.
Peer Reviewer #3	Introduction	well done.	Thank you for the comment
Peer Reviewer #3	Methods	no changes needed.	Thank you for the comment
Peer Reviewer #3	Results	The authors seem to minimize the importance of the SWOG trial with neoadjuvant MVAC, perhaps because it failed to achieve a p value of .05 on a two tailed test. It is viewed in the US as a strongly positive trial and it at least deserves comment under key question 3.	We don't believe that the results of this study are downplayed, though we do report the HR and associated CI and note that the result was not statistically significant. The overall conclusion was that NAC is associated with decreased risk (or trend towards decreased risk) of mortality versus no NAC.

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Peer Reviewer #3	Results	also, the likelihood of pathologic down staging to P0 is considered a valid endpoint as it is strongly associated with improved survivals. This should be one of the factors discussed under key question 3 for neoadjuvant approaches.	The review focuses on clinical outcomes such as mortality and progression, as well as recurrence.
Peer Reviewer #3	Introduction	In their discussion (page 34) they suggest that neoadjuvant chemotherapy with Gem-Cis followed by cystectomy is standard of care. I think they are overstating the case as it is not at all clear that Gem-Cis is the best neoadjuvant regimen. It has also been shown that it is frequently not utilized in the US. If they want to state the standard of care, I would say that the best evidence suggests that neoadjuvant chemotherapy followed by cystectomy is best practice and that Gem-Cis is the most common regimen currently utilized.	We revised to state: “For non-metastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin).”

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Peer Reviewer #3	Discussion/ Conclusion	page 16- they describe a study that reported that at least four nodes should be resected to decrease mortality. I would refer to the Herr study that analyzed this and found that at least 12 nodes should be resected for improved survival based on the SWOG MVAC trial. This article was excluded in their analysis perhaps because it was not part of the initial trial design. It was compelling data nevertheless.	We added 2 studies by Herr (2002 and 2004) on effects of more versus less extensive lymph node dissection on clinical outcomes.
Peer Reviewer #3	Clarity and Usability	yes	Noted.
Peer Reviewer #4	General Comments	Extremely well written and incredibly thorough collation, synthesis and analysis of the literature. A few minor comments are noted in each of the sections below.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	Well written. Most reviews and guidelines suggest that a combination of neoadjuvant gemcitabine and cisplatin is standard, but there is limited high quality evidence to support this statement. The high quality studies that established this standard utilized MVAC and the use of gemcitabine/cisplatin is based on convenience, perceived toxicity, and lower quality data suggesting similar rates of p0 status in the surgical specimen, which is considered a marker of efficacy.	We revised to state: “For non-metastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin).”
Peer Reviewer #4	Methods	Superb	Thank you for the comment.
Peer Reviewer #4	Results	Key Question 3a: comparative effectiveness of various combinations. While it is true that various chemotherapy regimens have not been adequately compared in the perioperative setting, they have been compared in the metastatic setting and it would be useful to include some of the data and information here. This is especially relevant for last paragraph ES-18 and the general conclusion that cisplatin based therapies are standard.	Management of metastatic disease was outside the scope of our report; in addition, our understanding is that direct comparisons of carboplatin- versus cisplatin-based chemotherapy in metastatic disease are also limited. Therefore, we did not make any changes.

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Peer Reviewer #4	Results	Key Question 3d: neoadjuvant versus adjuvant. The one cited trial was actually a trial of 2 cycle neoadjuvant chemo followed by 3 cycles of adjuvant versus 5 cycles of adjuvant chemotherapy. This is less clear in the executive summary. In this small study there was no difference in overall survival as stated, but 54 (77%) of 70 received at least two cycles of chemotherapy after surgery in the latter group, whereas 68 (97%) of 70 received at least two cycles among patients assigned initial chemotherapy. This speaks at least to the tolerability of giving pre- versus post-surgical chemotherapy.	We revised to make the regimens compared clearer (p 24, lines 24-26).
Peer Reviewer #4	Discussion/ Conclusion	Well done with the caveats noted above regarding the general preference and recommendation for gemcitabine/cisplatin in the peri-operative setting	Thank you for the comment.
Peer Reviewer #4	Clarity and Usability	Excellent.	Thank you for the comment.

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Peer Reviewer #5	General	1) Suggest revising title to state that this is a review of clinically non-metastatic muscle invasive cancer since approximately 25 percent have occult node metastases at time of diagnosis and up to 50% occult node and/or visceral metastases	We did not change the title because some studies in which radical cystectomy was performed may have excluded patients with node-positive disease as determined by pathological staging. However, we revised the “Populations and Conditions of Interest” section to note that patients staged clinically could have occult metastasis (p 7 line 30).
Peer Reviewer #5	General	2) key question 1(a) – should add primary vs. recurrent	We did add these patient characteristics; we are not aware of any studies that have evaluated how the comparative effectiveness of bladder sparing treatments varied according to whether the cancer was recurrent or primary, and studies did not report the proportion that were recurrent vs. primary.
Peer Reviewer #5	General	3) question 2(b) – many feel that the anatomic extent rather than the number of nodes identified by the pathologist is the more relevant variable affecting outcome	We revised KQ 2b: “...(e.g., as measured by the number of lymph nodes removed or the anatomic extent of dissection.)”

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Peer Reviewer #5	General	4) Question 3(d) – missed opportunity to evaluate dose intensity as there have been studies looking at dose dense MVAC and this is currently in use in several centers and is the protocol defined method for MVAC in SWOG 1314 (opened June 2014)	We identified no studies that compared dose-dense MVAC versus standard MVAC. The only studies of dose-dense MVAC had no comparison treatment arm and did not meet inclusion criteria. We did revise the Research Gaps section to note that trials are needed to compare dose-dense versus standard dosing regimens, and cited the clinicaltrials.gov entry for the (open) SWOG 1314 study.
Peer Reviewer #5	General	Very good overview of the data on treatment of patients with non-metastatic invasive bladder cancer. The report is timely, clinically relevant and serves as a good review of the evidence.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Introduction	<p>ES</p> <p>Suggest using 2014 statistics Page 10 line 48 – would add pRB Page 10 starting line 51 – suggest revision. GC has never been tested in a phase III trial of NAC so it is not the gold standard. MVAC has been tested and therefore the gold standard. While the individual chemotherapy agents have approval the combination regimens do not have specific FDA indications for bladder cancer. The language in the ES is odd as this is never mentioned in the text Page 11 line 13 – regional PLND is also associated with improved loco-regional control compared to no or limited PLND Q3b – SWOG 8710 did report a significant benefit when risk stratified by stage though this was not part of the pre-planned analysis – this should be included in the ES and main text</p>	<p>We revised with the updated 2014 statistics on bladder cancer incidence and mortality.</p> <p>Added pRB as one of the biomarkers (ES-1, line 48). We revised to note that recommended chemotherapy regimens are cisplatin-based (e.g., MVAC, CMV, and GC) and that the individual combinations are FDA-approved, but that the combinations do not have a bladder cancer specific indication.</p> <p>As noted in the second bullet of KQ2b, there was insufficient evidence to determine effects of extent of lymph node dissection on risk of bladder cancer recurrence or progression. SWOG 8710 (Grossman et al) found no interaction between tumor stage and effects of treatment, as noted on p 23 (lines 26-28).</p>

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Peer Reviewer #5	Discussion/ Conclusion	ePLND “might be” more effective than standard - pretty vague page 29 line 27 – please clarify that SWOG 1011 compares extended to standard PLND. Secondary endpoints include comparison of AEs between the two arms. Also suggest adding the German trial of similar design that has completed accrual.	<p>The sentence in the Conclusion states, “extended lymph node dissection might be more effective than standard lymph node dissection for improving survival”; the word “might be” is used b/c the SOE was rated as low, indicating uncertainty about the estimates.</p> <p>We revised the description of SWOG 2011 to note that it compared extended to standard lymph node dissection (p 58 ln 38). We could not find a direct reference or protocol for the recently completely German trial, but added a reference to a review article that mentions it and note that trials of extended vs. standard lymph node dissection are in progress or have been completed.</p>
Peer Reviewer #5	Methods	all excellent	Thank you for the comment.

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Peer Reviewer #5	Results	1) a significant factor limiting analysis of Q 2 is the lack of outcome measure of loco-regional control	We focused on mortality, recurrence, progression, and quality of life, based on input from the TEP. Results based on loco-regional control were generally consistent with the included outcomes, so we do not think it is necessary to add them.
Peer Reviewer #5	Clarity and Usability	excellent	Thank you for the comment.
Peer Reviewer #6	General	Very good overview of the data on treatment of patients with non-metastatic invasive bladder cancer. The report is timely, clinically relevant and serves as a good review of the evidence.	Thank you for the comment.
Peer Reviewer #6	Introduction	Well stated	Thank you for the comment.
Peer Reviewer #6	Methods	Strategy is clearly stated and logical. Methods appropriate.	Thank you for the comment.
Peer Reviewer #6	Results	Tables are appropriate.	Thank you for the comment.
Peer Reviewer #6	Discussion/ Conclusion	Limitations are clearly stated. Might want to discuss the potential role of personalized / precision-based strategy to predict response to chemotherapy.	Thank you for the comment.
Peer Reviewer #6	Clarity and Usability	The report is well structured and organized. The report accurately reviews the relevant RCTs with respect to NAC and AC in muscle invasive bladder cancer.	Thank you for the comment.

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Peer Reviewer #7	General	The target population and audience are explicitly defined, and the key questions are appropriately stated, however the timing of this report is unfortunate. Between 1/2014 and the end of 2015 there has been and will be more new data now with respect to biomarkers predictive of chemotherapy response, and accelerated modern chemotherapy regimens that are more and more commonly used in this space. I think this report would be much more meaningful if issued in a few years. Right now the sources are all decades old, and don't contribute much that is applicable to current practice.	Thank you for the comment. The report is based on the currently available evidence, but might warrant updating in a few years when more evidence becomes available.
Peer Reviewer #7	Introduction	P v, lines 50-51, typo “currently regimens”	Typo corrected.
Peer Reviewer #7	Introduction	P ES-2: line 20. Brachytherapy is not ever used to my knowledge, and is not in the NCCN guidelines. Not sure if it should be included here.	Based on TEP input brachytherapy was included, though there was little evidence on it.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	Too much emphasis on very old literature that is not reflective of current practice. For instance, the NCCN guideline papers are not cited. The NCCN guidelines currently excludes standard MVAC as an option due to toxicity, in favor of gem cis or accelerated/dose dense MVAC. While the data was admittedly lacking at the time of data cutoff, progress has been made and some key publications have emerged since then. It is a flaw in this report that due to the cutoff of 1/2014 used, and the swell of emergent data so far in 2014 and expected to further emerge in 2015, that the information contained is already outdated.	Thank you for the comment. The report is based on the currently available evidence, but might warrant updating in a few years when more evidence becomes available.
Peer Reviewer #7	Methods	Here are some examples of the literature emergent in 2014 1. Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, Roth B, Cheng T, Tran M, Lee IL, Melquist J, Bondaruk J, Majewski T, Zhang S, Pretzsch S, Baggerly K, Siefker-Radtke A, Czerniak B, Dinney CP, McConkey DJ. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014;25(2):152-65. doi: 10.1016/j.ccr.2014.01.009. PubMed PMID: 24525232; PMCID: 4011497.	This study does not meet inclusion criteria as it does not compare different chemotherapeutic regimens and is an observational study.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	2.Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Treter C, Bubley GJ, Stack EC, Signoretti S, Walsh M, Steele G, Hirsch M, Sweeney CJ, Taplin ME, Kibel AS, Krajewski KM, Kantoff PW, Ross RW, Rosenberg JE. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. J Clin Oncol. 2014;32(18):1889-94. doi: 10.1200/JCO.2013.52.4785. PubMed PMID: 24821883.	This study does not meet inclusion criteria because it does not have a comparison treatment arm.
Peer Reviewer #7	Methods	3.Culp SH, Dickstein RJ, Grossman HB, Pretzsch SM, Porten S, Daneshmand S, Cai J, Groshen S, Siefker-Radtke A, Millikan RE, Czerniak B, Navai N, Wszolek MF, Kamat AM, Dinney CPN. Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy. The Journal of Urology. 2014;191(1):40-7. doi: http://dx.doi.org/10.1016/j.juro.2013.07.061 .	This study does not meet inclusion criteria because it does not compare different treatments.
Peer Reviewer #7	Methods	4.Damrauer JS, Hoadley KA, Chism DD, Fan C, Tiganelli CJ, Wobker SE, Yeh JJ, Milowsky MI, Iyer G, Parker JS, Kim WY. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. Proc Natl Acad Sci U S A. 2014;111(8):3110-5. doi: 10.1073/pnas.1318376111. PubMed PMID: 24520177; PMCID: 3939870.	This study does not meet inclusion criteria because it does not compare different treatments.

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Peer Reviewer #7	Methods	5.Kim PH, Cha EK, Sfakianos JP, Iyer G, Zabor EC, Scott SN, Ostrovnaya I, Ramirez R, Sun A, Shah R, Yee AM, Reuter VE, Bajorin DF, Rosenberg JE, Schultz N, Berger MF, Al-Ahmadie HA, Solit DB, Bochner BH. Genomic Predictors of Survival in Patients with High-grade Urothelial Carcinoma of the Bladder. Eur Urol. 2014. doi: 10.1016/j.eururo.2014.06.050. PubMed PMID: 25092538.	This study does not meet inclusion criteria because it does not compared different treatments.
Peer Reviewer #7	Methods	6.Kitamura H, Tsukamoto T, Shibata T, Masumori N, Fujimoto H, Hirao Y, Fujimoto K, Kitamura Y, Tomita Y, Tobisu K, Niwakawa M, Naito S, Eto M, Kakehi Y, Urologic Oncology Study Group of the Japan Clinical Oncology G. Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209. Ann Oncol. 2014;25(6):1192-8. doi: 10.1093/annonc/mdu126. PubMed PMID: 24669010.	We added this trial, which was e-published in 2014 and compared NAC + cystectomy versus cystectomy alone.

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Peer Reviewer #7	Methods	7.Plimack ER, Dunbrack R, Brennan T, Wei Q, Yelensky R, Serebriiskii I, Hoffman-Censits JH, Kutikov A, Alpaugh RK, Dulaimi E, Viterbo R, Greenberg RE, Chen DYT, Lallas CD, Wong Y-N, Trabulsi EJ, Palma NA, Miller VA, Golemis E, Ross EA. Next-generation sequencing to identify molecular alterations in DNA repair and chromatin maintenance genes associated with pathologic complete response (pT0) to neoadjuvant accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) in muscle-invasive bladder cancer (MIBC). ASCO Meeting Abstracts. 2014;32(15_suppl):4538.	This study does not meet inclusion criteria because it does not address any of the key questions; in addition it is a non-comparative study and is only published as an abstract.
Peer Reviewer #7	Methods	8.Plimack ER, Hoffman-Censits JH, Viterbo R, Trabulsi EJ, Ross EA, Greenberg RE, Chen DY, Lallas CD, Wong YN, Lin J, Kutikov A, Dotan E, Brennan TA, Palma N, Dulaimi E, Mehrazin R, Boorjian SA, Kelly WK, Uzzo RG, Hudes GR. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol. 2014;32(18):1895-901. doi: 10.1200/JCO.2013.53.2465. PubMed PMID: 24821881; PMCID: 4050203.	This study does not meet inclusion criteria because it does not have a comparison treatment arm.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	9.Sternberg CN, Apolo AB. Everything old is new again! Neoadjuvant chemotherapy in the treatment of muscle-invasive bladder cancer. J Clin Oncol. 2014;32(18):1868-70. doi: 10.1200/JCO.2014.55.4055. PubMed PMID: 24821880.	This citation does not meet inclusion criteria because it does not report original data.
Peer Reviewer #7	Methods	10.Van Allen EM, Mouw KW, Kim P, Iyer G, Wagle N, Al-Ahmadie H, Zhu C, Ostrovnaya I, Kryukov GV, O'Connor KW, Sfakianos J, Garcia-Grossman I, Kim J, Guancial EA, Bambury R, Bahl S, Gupta N, Farlow D, Qu A, Signoretti S, Barletta JA, Reuter V, Boehm J, Lawrence M, Getz G, Kantoff P, Bochner BH, Choueiri TK, Bajorin DF, Solit DB, Gabriel S, D'Andrea A, Garraway LA, Rosenberg JE. Somatic ERCC2 Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma. Cancer Discov. 2014;4(10):1140-53. doi: 10.1158/2159-8290.CD-14-0623. PubMed PMID: 25096233.	This study does not meet inclusion criteria because it does not compare different treatments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	While I understand that there are strict criteria for inclusion of studies in this report, due to the paucity of data (as the authors discuss) those of us who treat bladder cancer rely on extrapolations and this is outlined in the NCCN guideline papers. Review of these papers may have provided some guidance as to which papers to include. I personally think a wider net, reviewing the studies from which we extrapolate and those retrospective data we rely on should have been considered even though clearly not considered high level evidence.	To clarify, we did include observational studies that compared different treatments as described in the PICOTS. We reviewed the citations suggested by the reviewer; 1 of the trials met inclusion criteria (Kitamura) and has been added.
Peer Reviewer #7	Results	The amount of detail is appropriate. The characteristics of the studies are clearly described and the results speak to the key questions. figures and tables are thorough.	Thank you for the comment.
Peer Reviewer #7	Discussion/ Conclusion	The applicability of these findings is appropriately caveated in the discussion section - findings not applicable due to emphasis on old, outdated, and no longer used regimens, as well as the unfortunately timed data cutoff of this report.	Thank you for the comment.
Peer Reviewer #7	Clarity and Usability	It is long, perhaps could be tightened, but the format and content is overall good.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Clarity and Usability	Again, I don't think these conclusions can inform practice given the lack of updated data sources in this report.	Thank you for the comment. The report is based on the currently available evidence, but might warrant updating in a few years when more evidence becomes available.
TEP #1	General	Are there data re: types of surgical intervention (e.g. robotic versus open approach). This data should be analyzed included in a key question: Does surgical technique impact outcomes/complications?	Thank you for the comment. The comparative effectiveness and harms of different radical cystectomy techniques was not one of the KQ's and is outside the scope of the review. However, we revised the "Limitations of the Review Process" section to note that some potentially important areas such as this were not addressed.
TEP #1	General	Some evidence exists re: timing of therapy; delay of cystectomy is associated with worse outcomes. Can this data be examined and statements made re: timeliness issues	Thank you for the comment. The impact of timing of radical cystectomy on outcomes was not one of the KQ's and was outside the scope of the review. However, we revised the "Limitations of the Review Process" section to note that some potentially important areas such as this were not addressed.

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Commentator & Affiliation	Section	Comment	Response
TEP #1	General	Is there any data re: followup strategies and protocols	Thank you for the comment. This was not one of the KQ's. We revised the "Limitations of the Review Process" section to note that some potentially important areas such as this were not addressed.
TEP #1	General	Any information on impact on best treatment strategies for patients who have been upstaged or still have poor-risk disease after chemotherapy? e.g. patients with positive surgical margins-what is best treatment and/or f/up; best way to monitor urethra or upper tract; best treatment for patients who have had NAC but who have persistent or residual LN+ disease at time of cystectomy	Thank you for the comment. This was not one of the KQ's. We revised the "Limitations of the Review Process" section to note that some potentially important areas such as this were not addressed.

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Commentator & Affiliation	Section	Comment	Response
TEP #1	Introduction	On page 10, I am unsure one can categorically say that gold standard is gem/cis and cystectomy, esp since randomized trials that showed improvement were w mvac and cmv.	We revised (p 2, line 53-57) to state: "For non-metastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin)."
TEP #1	Results	When examining the bladder sparing techniques, one would want to know how many ultimately went ahead with cystectomy and thus required BOTH treatment modalities.	As noted on p 14 (line 47-49), one study found that 72% of patients who underwent bladder sparing therapy subsequently required salvage radical cystectomy; none of the other studies reported the number of patients who underwent cystectomy.
TEP #1	Results	P 19--is there a typo in line 11 (shouldn't AC be in fact NAC)?	Typo corrected.
TEP #1	Clarity and Usability	helpful	Thank you for the comment.

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TEP #2	General	<p>The report lacks much clinical utility but this is a reflection of the poor state of the scientific literature in the field of non-metastatic, muscle-invasive bladder cancer. While there are a number of randomized trials addressing the neoadjuvant chemotherapy issue, there is a paucity of useful data that examines the other key questions. Please note that one of the major issues re: key question 1 and the non-randomized comparisons is that radical cystectomy patients have pathologic staging and bladder preservation patients only have clinical staging. This is a major problem when one compares these two approaches. For example, if a patient with cT2cN0 bladder cancer was scheduled to undergo cystectomy and during the operation, lymphatic metastases were detected (pN+) and the surgery was abandoned, this unfortunate patient would likely not appear in the cystectomy database used for the comparison with bladder preservation (this patient would remain a cT2cN0 patient and would likely have a poor prognosis).</p>	<p>Regarding the issue of whether patients undergoing radical cystectomy may have been more likely to be upstaged and how that could have impacted outcomes of studies of bladder-preserving therapy vs. radical cystectomy, we reviewed the studies and found that none reported the proportion of patients undergoing radical cystectomy who were upstaged (found to have lymph node metastasis) or whether such patients were excluded from the analysis. We revised the Results for KQ 1 to note this.</p>

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results	Regarding the single randomized trial of radiotherapy vs. radical cystectomy, I don't think you note explicitly that the radiation is given without the use of concurrent chemotherapy. This is important because randomized trials have shown that chemotherapy plus radiotherapy is superior to radiotherapy alone in this setting (James ND, et al. NEJM 366:1477, 2012) and radiotherapy plus chemotherapy is widely considered standard in this situation.	We revised the Discussion to more explicitly note that radiation therapy was not used in combination with chemotherapy and added the James et al trial citation.
TEP #2	Discussion/ Conclusion	See my Results comment.	We revised the Discussion to more explicitly note that radiation therapy was not used in combination with chemotherapy and added the James et al trial citation.
TEP #2	Clarity and Usability	No comments. Clear and well structured.	Thank you for the comment.
TEP #3	General	The report is clinically meaningful with the target population and key questions well stated.	Thank you for the comment.
TEP #3	General	line 50 in abstract: current instead of currently	Typo corrected.
TEP #3	Introduction	The scope of the problem is well articulated in the abstract.	Thank you for the comment.

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Commentator & Affiliation	Section	Comment	Response
TEP #3	Introduction	P34 line 55: Cannot consider Gem Cis to be standard of care versus MVAC for NAC. Trials were done with MVAC, and dose dense or accelerated MVAC is gaining wider use.	We revised to state: “For non-metastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin).”
TEP #3	Methods	The methodology is well documented and the inclusion and exclusion of articles well justified. I like the inclusion of the excluded articles as an appendix with the justification for exclusion included.	Thank you for the comment.
TEP #3	Results	The results are well established. The tables explain the data well. There were a few issues in the summary and the main results sections that would benefit from minor edits.	Thank you for the comment.
TEP #3	Results	Page 19, line 11; needs to say NAC, not AC Page 20, line 19; remove no Page 65: Result for Solsana study progression does not appear correct 74% (74/75)	We corrected the typos.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Discussion/ Conclusion	The future research section is clear, but I am not sure how easily it would be to translate the CER questions raised by the article into new research.	Thank you for the comment.
TEP #3	Clarity and Usability	The report is very well structured. The results can inform practice decisions, but more importantly reveal the poor quality of current CER research in muscle invasive bladder cancer.	Thank you for the comment.
TEP #4	General	I do not understand KQ3D. I don't think dosing frequency is an important question. Consider eliminating studies with high risk of bias as the report is already very long.	The key questions were developed through a standardized process with input from the TEP, Key Informants, and the public. There were no studies that addressed effects of dosing frequency, however. We did not exclude high risk of bias studies a priori as the evidence was quite limited for most key questions already, and there is variability in how studies are assessed and the effects of risk of bias assessments on estimates of effects. However, results emphasize results from lower risk of bias studies.

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Commentator & Affiliation	Section	Comment	Response
TEP #4	Introduction	intro page 2 line 55--GC is not the standard of care--no Phase 3 evidence supporting its use. I would just say cisplatin based.	We revised to state: “For non-metastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin).”

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Commentator & Affiliation	Section	Comment	Response
TEP #4	Methods	<p>This review may be strengthened by the addition of phase 2 studies for neoadjuvant therapy and the provide the most contemporary data (Plimack JCO and Choueri JCO both 2013).</p> <p>This is important for assessment of harms. Did studies need to complete planned accrual to be included. The small size of many of these make me wonder if many of these are underpowered. Sample sizes of all studies should be included.</p>	<p>The two cited studies are uncontrolled studies that do not meet inclusion criteria. However, we revised the Research Gaps section to note that trials that compare newer “dose-dense” treatment regimens vs. standard regimens are needed.</p> <p>The sample sizes of the chemotherapy trials are described on p 20 (line 30) and are presented in the tables. Although some trials may be underpowered, conclusions were based on the totality of evidence.</p>
TEP #4	Results	<p>See above re: newer studies. Harms of NAC are cited from older studies. That do not reflect modern antiemetics and growth factors. These high rates of AEs are no longer seen. This should be addressed . I do think report harms of regimens that are not use (cis/mtx) is of help to the reader</p>	<p>We revised the “Limitations of the Evidence Base” section to note that estimates of harms were primarily based on older trials that didn’t use the antiemetics and growth factors often utilized in current practice.</p>

Commentator & Affiliation	Section	Comment	Response
TEP #4	Results	If found this comment on page 52 confusing (talk about decreased risk but later note no statistically sig effect. why say 4 studies reported decreased risk if not statistically significant. “Four trials found adjuvant chemotherapy (AC) associated with decreased risk of mortality versus no AC, but no trial reported a statistically significant effect and there was some inconsistency in findings (SOE: low).”	Some studies may have been underpowered to detect differences. Therefore, it is appropriate to note that the point estimates all favored NAC, while also noting that no study reported a statistically significant effect. We did not attempt to pool due to the small number of trials and clinical heterogeneity.
TEP #4	Discussion/ Conclusion	this report clearly points out the research gaps	Thank you for the comment.
TEP #4	Clarity and Usability	this is very dense. Many of the studies are older and harms do not reflect the availability of modern supportive care regimens. It would be helpful to know what endpoint the smaller studies were powered for (endpoint wise) I am not sure what the differences is between table 2 and 3, 3 and 4 etc.	We revised the “Limitations of the Evidence Base” section to note that estimates of harms were primarily based on older trials that didn’t use the antiemetics and growth factors often utilized in current practice. The samples sizes of the studies are summarized in the Results for each KQ and presented in the Tables and Evidence Tables. The tables are labeled (e.g., Table 2 shows study characteristics for studies included in KQ 1, Table 3 shows results).

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