ASTRO
TARGETING CANCER CARE

September 10, 2015

Peter E. Clark, MD
Chair, NCCN Bladder Cancer Guidelines (Version 2.2015)
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Dear Dr. Clark,

The American Society for Radiation Oncology is pleased to provide the results of an exhaustive review of the NCCN bladder cancer guidelines. Our bladder cancer experts reviewed the guidelines for gaps relative to radiation therapy (appropriate modality, dose, timing, etc.) and offer these recommendations supported by evidence-based rationale for your consideration when the NCCN Bladder Cancer Guideline Panel convenes in October.

We are excited about the prospect of contributing to the quality of cancer care for patients undergoing treatment for bladder cancer. The attached document provides a summary of the findings, recommendations and rationale from the evaluators. In the meantime, if you have any questions or concerns, please contact Nadine Eads, Director of Quality Improvement, at nadinee@astro.org.

Sincerely,

Laura Thevenot

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CEO

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Overall Treatment Algorithm Section

Finding One: In the treatment algorithms for cT2 (page BL-4) and cT3-T4a (page BL-5), bladder preservation is appropriately offered as an alternative treatment modality to cystectomy. However, the current format of this algorithm may inadvertently create an impression that formal bladder preservation is only for patients with no extensive comorbidities and with good performance status, in other words, for cystectomy candidates. For patients with poor performance and comorbid diseases, i.e. poor cystectomy candidates, the bladder preservation is not listed as the best treatment modality, and comes second to TURBT alone.

Recommendation: Re-write algorithms on pages BL4 and BL5 to accentuate that bladder preservation is an alternative to cystectomy not only for good cystectomy candidates, but is also the best treatment modality for poor surgical candidates (Category 2A).

Rationale: TURBT with chemo-RT offers the best chance of local control and overall survival. TURBT alone offers a poor local control in most patients and is only appropriate for patients with very limited life expectancy (Grob and Macchia, J EndoUrol 2001; 15:419-423; Herr. J Urol 1987; 138:1162-1163; Leibovici et al., Urology 2007;70;473-476). TURBT followed by RT alone has been shown in a randomized trial to have a higher locoregional recurrence rate compared to TURBT followed by chemo-RT (James et al., NEJM 2012:366:1477-1488). Therefore patients unfit for cystectomy should be first considered for the most effective treatment modality (bladder preservation with maximum TURBT followed by chemo-RT). Only if they are unable to tolerate chemo-RT after TURBT, should they be considered for TURBT with RT alone, and only if they are unable to tolerate pelvic RT, should they be considered for TURBT alone.

Finding Two: In the treatment algorithms for cT2 (pg. BL-4) and cT3-T4a (pg. BL-5), the bladder preservation approach allows RT dose to either 40-45 Gy with subsequent re-evaluation or after full dose 60-65 Gy with subsequent re-evaluation. In the absence of tumor, the algorithm offers a choice between observation and completion of RT to 66 Gy. One may inappropriately conclude that with no tumor after 40-45 Gy it is appropriate to choose observation and not to continue to the full dose of 66 Gy.

Recommendation: Modify treatment algorithms on pages BL-4 and BL-5 to make it clear that dose of 40-45 Gy is NOT sufficient for proper tumor control and the target dose should be 60-66 Gy. Observation is not appropriate if patients did not receive a full dose of RT.

Rationale: The biological principles dictate that a dose of 40-45 Gy is not sufficient for macroscopic tumor eradication, which is usually the case after TURBT for cT2 and especially cT3 or cT4a disease. This dose may be sufficient for elective lymph node coverage to eradicate potential microscopic disease. Stopping at 40-45 Gy with bladder preservation is likely to undertreat tumor in the bladder and lead to suboptimal treatment outcomes.

Finding Three: For patients with denovo high-grade T1 (page BL-2), residual T1 (page BL-2) or recurrent non-muscle invasive bladder cancer after BCG or MMC (cT1)(pg. BL-3) cystectomy is an accepted standard of treatment. However, bladder preservation is not listed as an alternative therapy for patients who are not cystectomy candidates or refuse cystectomy on these treatment algorithms, although that is stated in the "Principles of Radiation Management of Invasive Disease" section (pg. BL-H, pages 1-2 of 2).

Recommendations: Add trimodality bladder preservation treatment into the treatment algorithms on pages BL-2 and BL-3 as an alternative treatment option to cystectomy for patients with de-novo high-grade T1, residual T1 or recurrent NMIBC after BCG or MMC (Category 3).

Rationale: For patients who develop recurrence of superficial bladder cancer after TURBT and intravesical therapy (or are not candidates for intravesical therapy), with cT1 disease, the current standard curative treatment is cystectomy. However, some patients may not be candidates for cystectomy or may not elect cystectomy. Retrospective data suggest that these patients could be treated with bladder conserving concurrent chemoradiotherapy using an approach similar to muscle-invasive disease (Wo, et al., British Journal of Urology International, Volume 104: 179-183,2009; and Gray et al., Curr Opin Urol. 2013 Sep;23(5):429-34.). This should be a clear option for this group of patients. RTOG 0926 is currently evaluating this approach in patients who are candidates for cystectomy.

Principles of Radiation Management Invasive Disease Section

Finding Four: On page BL-H, 1 of 2, there is a description of the treatment volume and dose to use as follows: "Treat the whole bladder with or without pelvic lymph nodes with 40 to 45 Gy and then boost the bladder tumor to a total dose up to 66 Gy excluding, if possible, normal areas of the bladder from the high-dose volume". This statement would benefit from having more detailed discussion regarding the volume to treat and the doses to use.

Recommendations:

1.) Specify a range for the total dose when doing conventional fractionation (in 1.8 -2 Gy/fraction). The current guideline just states a dose up to 66 Gy, instead it should indicate a dose range of 60-66 Gy
2.) Indicate an alternative hypofractionated course of radiotherapy (for example 50-55 in 20 fractions) for select patients. These regimens usually target the bladder only.
3.) Discuss that the treatment of the whole pelvis in addition to the bladder is controversial, and anticipated patient tolerance to whole pelvic radiotherapy based on age and comorbidity should be considered in making this clinical decision. When treating the whole pelvis treat to 40-45 Gy followed by a boost to the bladder and the tumor to 60-66 Gy.

Rationale:

1.) The range of conventionally fractionated RT in most trials/series of RT alone or chemoRT is 60-66 Gy
2.) Multiple older randomized trials have shown no difference in outcomes with conventional fractionation vs. hypofractionation (Quilty PM, Duncan W, Kerr GR. Results of a randomized study to evaluate influence of dose on morbidity in radiotherapy for bladder cancer. *Clin Radiol* 1985, 36:615-618; Whillis D, Howard GC, Kerr GR, et al. Radical radiotherapy with salvage surgery for invasive bladder cancer: results following a reduction in radiation dose. *J R Coll Surg Edinb* 1992, 37:42-45). More recently, BC2001 randomized patients with bladder cancer to RT alone or concurrent 5-FU and Mitomycin C with RT (James ND, Hussain SA, Hall E, et al. Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer. *N Engl J Med* 2012; 366:1477-88). The two standard dose/fractionation regimens were 64 Gy in 2 Gy/fraction or 55 Gy in 2.75 Gy/fraction.
3.) The classic RTOG treatment paradigm has utilized an initial "small pelvis" treatment volume in order to treat micrometastatic disease in the draining lymph node regions, and the bulk of the prospective multi-institutional long-term outcomes data in the U.S. are based on this approach. The rationale is that surgical series suggest there is a significant risk of nodal involvement for muscle-invasive bladder cancer (Goldsmith B, Baumann BC, He J, et al. Occult pelvic lymph node involvement in bladder cancer: implications for definitive radiation. *Int J Radiaton Oncol Biol Phys* 2014; Vol 88,

No. 3, 603-610.). However, in the Europe, bladder only treatment is a commonly utilized approach, as exemplified by the BC2001 study in which all patients were treated to the bladder only. In this study, the risk of pelvic nodal failure was only 4.9-6.7%, challenging the benefit of treatment of the nodal regions. It is possible that a usual margin of 1.5 to 2.5 cm margin around the bladder that is usually added in treatment planning covers proximal pelvic lymph nodes and therefore leads to low risk of pelvic nodal failure. The only randomized data evaluating bladder only compared to whole pelvis with bladder boost are from a single institution RCT from Pakistan, which revealed no benefit to whole pelvic treatment, although in this study there was a high rate of pelvic failure in both arms (~15-16%) and it may have been underpowered to detect small differences (Tunio MA, Hashmi AQ, Mohsin R, et al. Whole-Pelvis or Bladder-Only Chemoradiation for Lymph Node-negative Invasive Bladder Cancer: Single-Institution Experience. *Int J Radiation Oncol Biol Phys* 2012; Vol 82, No. 3, e457-e462)

Principles of Chemotherapy Management Section

Finding Five:

1.) On page BL-G, 3 of 4, it is appropriately stated that carboplatin should not be used instead of cisplatin with RT. However, this note is at the bottom of the page and may be inadvertently missed.
2.) Reference citations are incorrect on page BL-G, 4 of 4.
3.) Chemotherapy doses are not clearly spelled out.

Recommendations:

1.) Add the note of carboplatin inadequacy as a chemo-sensitization with RT immediately next to the cisplatin recommendation.
2.) On page BL-G, 4 of 4, Citation 12 (James ND, Hussain SA, Hall E, et al; BC 2001 Investigators. Radiotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477-1488.) should be used for MMC-5FU combination, whereas citation 13 (Mitin T, Hunt D, Shipley W, et al. Transurethral surgery and twice daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomized multicenter phase 2 trial. Lancet Oncol 2013;14:863-872.) should be used for both cis-5FU and cis-paclitaxel chemotherapy options. Low-dose gemcitabine should be referenced as De Santis, M, Bachner, M, Cerveny, M et al., Ann Oncol. 2014 Sep;25(9):1789-94, and Oh KS, Soto DE, Smith DC et al., Int J Radiat Oncol Biol Phys. 2009 Jun 1;74(2):511-7.
3.) Specify doses and schedules for radiosensitizing chemotherapy for bladder-preserving chemoradiation:Cisplatin 100 mg/m2 q3 weeks during RT
    - Cisplatin (15 mg/m2 days 1-3 every week) and 5-FU (400 mg/m2 days 1-3 every other week) with twice a day radiation therapy
    - Cisplatin (15 mg/m2 days 1-3) and Paclitaxel (50 mg/m2 days 1, 8, 15) with twice a day radiation therapy
    - MMC (12 mg/m2 day 1) and 5-FU (500 mg/m2 with fractions 1-5 and 16-20) with once a day RT
    - Gemcitabine 27 mg/m2 days twice a week with daily RT.

Rationale:

1.) Many community medical oncologists routinely consider carboplatin as a gentler form of cisplatin. Whenever they see a cisplatin option and an elderly patient with poor performance status or with medical comorbidities, they automatically substitute carboplatin for cisplatin. Although the guidelines include a small note at the bottom of the page, this may be missed and patients may be inappropriately treated with carboplatin in the setting of definitive RT.

2.) Appropriate citations will help physicians pick the right article and see the appropriate doses, administration schedules. This is especially critical for low-dose gemcitabine, as physicians need to be prompted to the correct dose of gemcitabine in this clinical setting.
3.) Other NCCN guidelines are very specific in chemotherapy dosing. This allows for fewer mistakes done in the community practices that do not treat bladder cancer routinely.