Reply to K. Lu

We thank Lu1 for his thoughtful comments on our study.2 He appropriately raises some of the limitations of meta-analyses in general that we thoroughly address in the discussion, including their retrospective nature, and the possibility of heterogeneity in results, data availability bias, and publication bias. We concur that compared with the gold standard of randomized controlled trials, the results of meta-analysis need to be weighed critically. This is why we performed careful scrutiny of articles with multiple sensitivity analyses to minimize the risk of these various biases influencing our results; while the inherent limitations of meta-analysis remain, we believe that the robustness of our findings to multiple sensitivity analyses supports our overall conclusions. Unless large controlled trials are conducted to address these difficult questions, careful pooling of the available data will need to provide the best available answers. Our report is presently the most thorough existing data analysis on high grade T1 tumors, and also identifies lower rates of both recurrence and progression in this condition than were previously recognized, which update the classical values mentioned in his letter.

Lu1 also questions the utility and reliability of using depth of invasion into the muscularis mucosae to identify patients at higher risk of progression, as “muscularis mucosae are often absent or difficult to identify.” In addition to the need for having properly performed transurethral bladder resections, the classical substaging approach (T1a/T1b) has faced similar criticism for decades and its usefulness and effectiveness have been debated; historically the muscularis mucosae had been considered to be identifiable in only approximately 70% of specimens, and misorientation, cautery artifacts and necrosis have been considered challenges to pathologic evaluation. However, the wider applicability of this evaluation has been improved by an evolution in technique that includes assignment to T1a or T1b based on extent of invasion into the lamina propria in vessels of the associated vascular plexus in tumor-free areas of the same or other transurethral bladder resection chips. Reports from the last several years on these refinements to the substaging technique show that up to 100% of patients can now be assigned to T1a or T1b substage, with significant impact on long-term outcomes.3,4 To clarify, the series by Orsola et al4 (reference 4 of Dr Lu’s correspondence1) did not rely on a cutoff of “greater than 1.5-mm depth of invasion” as Dr. Lu’s letter suggests, but on the expanded definition of the T1a/T1b approach. In terms of the reliability of substaging, Cottrell et al5 tested the consistency of microstaging by general pathologists and elegantly showed a high concordance rate.

Finally, we agree that there remain many unanswered questions about optimal patient selection for early cystectomy in high-grade T1 bladder cancer. It was precisely this fact that spurred us to meta-analyze the available data.

While many important questions remain, we feel that our findings enhance the ability of physicians to share prognostic information with their patients, and will help shared decision making in this challenging setting.

William Martin-Doyle and Anna Orsola
Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA
Joaquim Bellmunt
Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA; University Hospital del Mar-IMIM, Barcelona, Spain

REFERENCES

DOI: 10.1200/JCO.2015.62.5301; published online ahead of print at www.jco.org on July 20, 2015
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reply to K. Lu

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

William Martin-Doyle
No relationship to disclose

Anna Orsola
No relationship to disclose

Joaquim Bellmunt
Consulting or Advisory Role: Pierre Fabre, Astellas Pharma, Pfizer
Research Funding: Takeda/Millennium (Inst), Sanofi (Inst)
Travel, Accommodations, Expenses: Pfizer, MSD Oncology