

Is Surgery Needed for Muscle-Invasive Bladder Cancer?

Pam Harrison | May 16, 2016

Should urologists rethink radical cystectomy (RC) as the best choice for most patients with muscle-invasive bladder cancer (MIBC)?

Yes, says radiation oncologist Timur Mitin, MD, PhD, Oregon Health and Science University, in Portland, who is a staunch proponent of bladder-preserving trimodality therapy (TMT) as an alternative to the gold-standard RC.

No, say Peter Black, MD, and Edmund Chedgy, MBBS, Vancouver Prostate Center, University of British Columbia, Canada, who argue in favor of the gold-standard RC. Both viewpoints were published online May 5 in *JAMA Oncology*.

"Based on new published evidence in 2015, bladder preservation trimodality therapy should be considered first for patients with MIBC, with cystectomy reserved for patients unable or unwilling to undergo bladder preservation or as a salvage option for local recurrences," Dr Mitin writes.

A recent, large meta-analysis comparing the two approaches showed that the median 5-year overall survival rate was 57% for patients who had undergone TMT compared with between 51% and 53% for patients who had undergone RC. Variation in overall survival rates depended on whether patients received RC alone or RC plus chemotherapy.

The analysis also showed that there was an absolute benefit of 5% in favor of TMT in terms of mortality gains regardless of whether RC patients received RC alone or RC plus chemotherapy.

"Radical surgery is very radical, and it has real measurable postoperative complications and mortality risk," Dr Mitin told *Medscape Medical News*.

Radical surgery is very radical. Dr Tim Mitin

"What's happening now in the US is that aggressive surgeons operate on 90-year-old patients, which I think is wrong in most cases," he added.

According to a SEER database analysis, postoperative mortality at 90 days post RC is only 1% for those younger than 60 years, but it is as high as 14% for patients older than 89 years, Dr Mitin pointed out.

Limited to younger patients, outcomes following RC may well be superior to those following TMT, Dr Mitin suggests in his written viewpoint.

For now, though, with the data that are available, "I'm saying for most patients, TMT gives the same outcomes as radical cystectomy – perhaps even better, based on this meta-analysis – so I think patients should hear about all options and then weigh in with what makes more sense to them."

What's to Like About TMT?

Some have suggested that the radiation required as part of the TMT protocol causes late adverse events (AEs) and leads to a poor quality of life (QoL).

But in an RTOG study, researchers found that only 7% of a group of 157 patients who underwent TMT for MIBC experienced late grade 3 genitourinary or gastrointestinal AEs, and there were no late grade 4 AEs.

At the 2015 meeting of the American Society for Radiation Oncology (ASTRO), researchers reported that patients who received TMT had a significantly better general quality of life by an average of 6 to 7 points than RC patients and that TMT was associated with significantly better bowel function (average 4.5 points) post procedure, although urinary quality of life was equivalent between the two groups (ASTRO 2015, abstract 50).

In this study, patients had undergone TMT for a median of 9 years prior to the quality of life analysis, whereas patients had undergone RC for a median of 6 years before the analysis.

"I would think that for most patients, the choice of keeping their bladder is a no-brainer," Dr Mitin affirmed.

In his former position at the Massachusetts General Hospital in Boston, patients diagnosed with MIBC would meet with a surgeon, a medical oncologist, and a radiation oncologist at the same time to discuss which course of action appealed to them the most.

"We all talked about different options," Dr Mitin recalls. "And there were very few patients who said, 'I want my bladder out'," he added.

"But if that was their choice, I had no problem with that because RC is the gold standard."

Other arguments against the TMT approach is that patients would not be able to undergo salvage RC for local recurrence because the bowel had been previously irradiated.

In his experience, Dr Mitin has found that perioperative morbidity and mortality rates in patients who underwent salvage cystectomy at the Massachusetts General Hospital were "remarkably similar" to rates seen following RC given without radiation.

However, his biggest argument in favor of offering TMT first is that, although there is a 30% chance of recurrence following bladder preservation treatment modality, "there's a 70% chance that there will be no recurrence," he said.

In fact, the risk for recurrence following bladder preservation trimodality therapy is not as high as recurrence rates following chemoradiation therapy for anal cancer, for example, which can range between 10% and 50%.

"Yet we still treat all patients with anal cancer with chemoradiation and reserve salvage abdominoperineal resection and colostomy creation for patients who have a recurrence, because there is still a 50% to 90% chance patients won't need surgery, they won't need a colostomy bag for the rest of their life," Dr Mitin said.

Chances are overwhelming that it'll work for most patients. Dr Tim Mitin

"It is still worth a shot for most patients to keep their bladder, because chances are good this approach will work for them and they won't need a salvage operation."

Cystectomy as Front-line Therapy

"The fact that all the major guidelines recommend cystectomy as front-line therapy is a reflection of the data and the general consensus of the genitourinary community," Dr Black told *Medscape Medical News*. That said, most North American and European guidelines now accept TMT as an alternative to RC.

Dr Black noted that as a urologist, he supports the alternative TMT procedure and feels TMT is a viable option in well-selected patients.

But as he pointed out, "There simply aren't that many patients in the literature who've been treated with TMT, and of those who have been, a lot of the data are from major centers, such as the Massachusetts General Hospital, or from clinical trials, and we know that patients do a lot better in clinical trials than they do in real life," Dr Black said.

Furthermore, depending on the series, disease-specific survival rates do appear to be better with RC than with TMT. One contemporary international series, for example, demonstrated a 75% 5-year cancer-specific survival for all stages of muscle-invasive bladder cancer in 742 patients who underwent robot-assisted RC, as Dr Black and Dr Chedgy point out in their commentary.

By comparison, in most experienced centers, the 5-year disease-specific survival rate for muscle-invasive bladder cancer is 64%, although 5-year disease-specific survival rates approach those for robot-assisted RC for clinical T2 disease.

Dr Black and Dr Chedgy argue that patients need to understand that, should TMT fail, "cystectomy following TMT failure is technically challenging and is associated with a higher complication rate."

Moreover, they are not convinced that quality of life is necessarily better following bladder preservation surgery, as the authors of at least one study found. In that study, the data were not robust enough *to* allow evaluation of QoL outcomes following TMT relative to RC.

"Despite a higher rate of morbidity with RC, there appears to be no significant evidence to suggest that patients undergoing TMT have a better QoL than those undergoing RC," Dr. Black and Dr Chedgy observe.

However, Dr. Black and Dr Chedgy do not feel that the discussion of RC and TMT should "pit one against the other" but rather should focus on the treatment gap between what is currently being done for patients with MIBC in the United States and what should be done.

"Approximately half of patients with MIBC in the United States are receiving any treatment with curative intent," as they point out.

Although perhaps 10% to 15% of those not receiving treatment with curative intent may be *too* old or *too* sick *to* withstand all but palliative radiation, "what about the other 35% of patients who aren't getting treatment with curative intent?" Dr Black asked.

"So especially for patients who are borderline cystectomy candidates, we need *to* make sure they get something, and since TMT is given with curative intent, it is going to have an impact," Dr Black added.

Asked whether some patients refuse RC because they do not want to lose their bladder, Dr Black acknowledged that there is a small subset of patients who cannot accept the idea of having their bladder removed.

"These patients should be offered TMT," he insisted.

"We need to open the door and get as many patients with MIBC treated as possible."

At the same time, the Vancouver urologist emphasized that if physicians are convinced that RC is so much better than TMT, "we need to do it right," he said.

"We need to do it at high-volume centers; we need to give neoadjuvant chemotherapy; and we need to perform thorough lymph node dissection," he added.

"Optimal delivery of RC includes more than just removing the bladder safely."

Dr Mitin has disclosed no relevant financial relationships. Dr Black has served or serves on the advisory boards of Novartis, AbbVie, Astellas, Janssen, Amgen, Biocancell, Cubist, Sitka, Bayer, and Merck. He has also served or serves on the speaker's bureau for Novartis, AbbVie, Janssen, Ferring, and RedLeaf Medical and has received grant funding from New B Innovation, iProgen, and GenomeDx and has received consulting fees or honorarium from Pendopharm as well.

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