



Bladder Preserving Therapy for Muscle-Invasive Urothelial Cancer

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Prejudices against Organ-Preserving Therapy for Bladder Cancer

Critics of organ-preserving therapy for bladder cancer (trimodality therapy, TMT) repeatedly argue that this approach worsens the prognosis for patients compared to radical cystectomy (RC), which is considered the standard therapy. A systematic review of this question in the literature [1] analyzed 29 and 30 studies involving 3,131 patients with TMT and 10,265 patients with RC. There is no advantage over TMT for T2 tumors or more advanced tumors, nor is there any advantage over RC with adjuvant chemotherapy. More recent analyses also show no differences in survival data [2,3] between TMT and RC.

Components and Considerations for An Optimal Organ-Preserving Therapy

Optimal TMT consists of complete transurethral tumor resection (TUR) followed by chemoradiation (CRT). Approximately 6 weeks after completion of CRT, a bladder mapping is performed again.

If complete remission is observed, the patient enters structured follow-up care. Achieving complete remission is therefore the key to organ preservation.

Complete remission after CRT is determined by the radicality of the TUR before CRT. An R0 resection in transurethral resection is an independent prognostic factor for organ preservation [4,5]. If R0 resection is not achieved, the probability to achieving complete remission is reduced by at least 10% [6].

Radiation should be administered using IMRT technology with an empty bladder up to a dose of 60 Gy [7]. The target volume should include not only the bladder but also the associated pelvic lymph nodes, because this increased target volume leads to a significant improvement in overall survival (HR 0.68; p = 0.002) [8].

Chemotherapy administered simultaneously with radiation should ideally be a doublet with cisplatin. This allows complete remission rates of up to 90% to be achieved in the TUR 6 weeks

after CRT, whereas with carboplatin or 5-Fu and mitomycin C, these rates are only about 60% and so not much better than with radiotherapy alone [6,9].

The addition of deep hyperthermia to simultaneous CRT can further improve organ preservation. A monocentric, retrospective comparison [5] of 215 patients receiving CRT and 79 patients receiving CRT and additional deep hyperthermia showed significantly higher organ preservation after 5 years (82.2% vs. 96.5%; $p = 0.006$).

Chemotherapy containing cisplatin and the addition of deep hyperthermia not only improve organ preservation, but also improve overall survival (5-year OS: CRT vs. CRT with hyperthermia: 65% vs. 85%; $p = 0.0001$) [5], while neoadjuvant chemotherapy prior to CRT does not improve bladder preservation or overall survival [10-13].

Is Neoadjuvant Chemotherapy an Option in Context of Organ-Preserving Therapy?

Although numerous analyses show that neoadjuvant chemotherapy does not have a positive effect on the prognosis of patients in context of TMT, the response to neoadjuvant chemotherapy could nevertheless be seen as a helpful marker to make a recommendation for TMT or RC. If there is a complete remission after neoadjuvant chemotherapy or a partial remission of up to 50%, an organ-preserving approach should be recommended, whereas if there is a low response to neoadjuvant chemotherapy, RC should be discussed. This treatment strategy was consistently implemented in a phase II study with 40 patients [14]. Thus, 35/40 patients showed a response of at least 50% remission to neoadjuvant chemotherapy. These patients then underwent radiation or CRT, and all showed complete remission in the TUR after CRT. A meta-analysis of 74 and 116 patients [13] also shows an improvement in overall survival (HR 0.26; $p = 0.03$) and disease-free survival (HR 0.42; $p < 0.001$) in patients who have good response to neoadjuvant chemotherapy in context of TMT.

Summary

A recommended treatment strategy for patients with non-metastatic, muscle-invasive bladder cancer could begin with a neoadjuvant chemotherapy (in combination with an PD-L-inhibitor). If there is a good response, the patient is a candidate for organ-preserving therapy with CRT and ideally deep hyperthermia.

Conflict of Interest

All authors declare no financial interests and no other interests that could influence evidence and content of this article.

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