Should the primary tumor be treated in patients with metastatic bladder cancer?

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### Potential harm in treating the primary tumor

<table>
<thead>
<tr>
<th>Detrimental oncological sequelae</th>
<th>Negative palliative sequelae</th>
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</thead>
<tbody>
<tr>
<td>‘Awakening’ of metastatic dormancy</td>
<td>Loss/compromise of the bladder!</td>
</tr>
<tr>
<td>Dissemination of disease during surgery</td>
<td>LUTS/Irritative symptoms/treatment-induced cystitis treatment pain</td>
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<tr>
<td>Complications of treatment</td>
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<td>Delays in systemic therapy</td>
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LUTS/Irritative symptoms/treatment-induced cystitis treatment pain
Surgery for Cancer: A Trigger for Metastases
Samer Tohme, Richard L Simmons, and Allan Tsung

Abstract

Surgery is a crucial intervention and provides a chance of cure for patients with cancer. The perioperative period is characterized by an increased risk for accelerated growth of micrometastatic disease and increased formation of new metastatic foci. The true impact for cancer patients remains unclear. This review summarizes the often fragmentary clinical and experimental evidence supporting the role of surgery and inflammation as potential triggers for disease recurrence. Surgery induces increased shedding of cancer cells into the circulation, suppresses antitumor immunity allowing circulating cells to survive, upregulates adhesion molecules in target organs, recruits immune cells capable of entrapping tumor cells, and induces changes in the target tissue and in the cancer cells themselves to enhance migration and invasion to establish at the target site. Surgical trauma induces local and systemic inflammatory responses that can also contribute to the accelerated growth of residual and micrometastatic disease. Furthermore, we address the role of perioperative factors, including anesthesia, transfusions, hypothermia, and postoperative complications, as probable deleterious factors contributing to early recurrence. Through the admittedly limited understanding of these processes, we will attempt to provide suggestions for potential new therapeutic approaches to target the protumorigenic perioperative window and ultimately improve long-term oncological outcomes. Cancer Res; 77(7): 1548–52. ©2017 AACR.
Figure 1.

Surgery: primary or metastatic lesion

↑ Tumor cell dissemination

COX inhibitors, Beta blockers

↑ Pro-inflammatory cytokines, prostaglandins and catecholamines

Immune modulation

↑ Survival in circulation
↑ Immune escape

↑ Adhesion
↑ ECM exposure

NETs
↑ Entrapment
↑ Invasion and migration

DNAase

New metastatic foci or micrometastatic disease

↑ Immunosuppression
↓ Cytotoxicity
↑ Pro-inflammatory factors
↑ Tumor proliferation

Immune modulation
Early chemotherapy
COX inhibitors/Beta blockers
Potential negative palliative outcome of over-treatment

• Radiation cystitis
• Pain
• Lower urinary tract symptoms

• Treat per symptoms and not prophylactically
Potential benefit of treating the primary tumor

<table>
<thead>
<tr>
<th>Oncological benefit</th>
<th>Palliative benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent further dissemination of metastases → Improve outcome</td>
<td>To palliate symptoms derived from the primary tumor in-situ – Pain Irritative symptoms impaired bladder emptying/ tenesmus resulting from a reduction in bladder capacity Obstruction Hemorrhage</td>
</tr>
</tbody>
</table>
Survival advantage?

In this commentary, we propose that recent findings in bladder cancer are subject to such fundamental methodologic shortcomings that the purported findings of benefit to aggressive therapy are likely false and potentially dangerous to patients.
Significant limitations

• Staging issues – patients not deemed metastatic at presentation

Very low/unequivocal tumor burden

Misclassifications.

• ‘Immortal time’ bias – Patients could not be included in the high-intensity LT group unless they survived long enough to undergo RC or RT; patients in this group had a zero risk of dying during the period between diagnosis and treatment. Conversely, patients who did not undergo RC or RT were automatically included in the conservative LT group and were exposed to the risk of death from date of diagnosis.

• No correction for performance status or visceral metastases.

We therefore believe that the difference in survival between the high intensity LT and conservative LT groups in their study is almost certainly the result of residual confounding. *Booth et al.*
Surgery in metastatic bladder cancer- meta-analysis results

• The beneficial role of consolidation surgery in metastatic bladder cancer is still unproven.

• In patients with clinically evident lymph node metastasis, data suggest a survival advantage for patients undergoing postchemotherapy radical cystectomy with lymphadenectomy, especially in those with measurable response to chemotherapy.

• Anecdotal reports of resection of pulmonary metastasis as part of multimodal approach suggest possible improved survival in well-selected patients.

• Conclusion - Consolidative extirpative surgery may be considered in patients with clinically evident pelvic or retroperitoneal lymph nodal metastases but only if they have had a response to chemotherapy.
Potential palliative local treatments of bladder tumor

- Cystectomy
- TURBT
- Radiotherapy – palliative (‘hypo-fractionated’) or ‘definitive’
- Bladder irrigation
Radiotherapy of the primary tumor in macro-metastatic disease - general

• Almost half of the cases with muscle-invasive tumors are already systemically spread.

• To date, no standard regimen exists for the delivery of palliative pelvic radiotherapy.

• Various radiotherapy schedules manage successful and long-term palliation of pelvic symptoms in most patients and result in acceptable toxicity.

• For bladder cancer, the most common dose and fractionation ranges from 20 Gy in 5 fractions to 40 Gy in 20 fractions.

• Some retrospective studies reviewed 6 weekly fractions of 6 Gy to a total dose of 36 Gy.
Radiotherapy for prevention of bleeding

• The haemostatic effect of radiotherapy is proven for many tumor entities and usually begins after only a few fractions.

• This early effect can be explained by increased adherence of platelets to vascular endothelial cells.

• In the long term, finally, the reduction of the risk of bleeding is due to a fibrosis of the blood vessels, possibly in conjunction with a tumor regression.

• Hypofractionated irradiation schemes are recommended in these setups.

• At Sheba medical center, we often administer 1-2 fractions of 8 Gy.

A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09

Treatment of the primary bladder tumor in a patient with metastatic disease - summary

<table>
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<tr>
<th>Oncological benefit</th>
<th>Palliative benefit</th>
<th>Oncological harm</th>
<th>Palliative harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No good evidence</td>
<td>In symptomatic patients</td>
<td>Evidence from mice models; no good clinical data</td>
<td>Rare if performed properly</td>
</tr>
</tbody>
</table>

- There is little evidence to support surgery as a primary palliative modality or as means to improve outcome.
- Surgery may be considered in LN-only disease and after achievement of response to systemic chemotherapy.
- Radiation therapy has an important role in preventing bladder symptomatology; hypo-fractionation is the mainstay of treatment.
Thank you