ROLE OF LOCAL RADIATION THERAPY IN THE METASTATIC SETTING

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• No disclosures
• Traditional Practice:
  – No role for local therapy with M1 disease
  – Cancer has already spread
  – Local control has no impact on disease progression

• Is removal or irradiation of the primary site dangerous?
  – Mechanisms

• Can eradication of local disease improve overall survival?
  – Radical prostatectomy
  – Radiation therapy
“Hit the primary”: A paradigm shift in the treatment of metastatic prostate cancer?

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Radiation Therapy to a Primary Tumor Accelerates Metastatic Growth in Mice

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Joint Center for Radiation Therapy [K. C., M. S. O.], and the Departments of Surgery [M. A. M., J. F.] and Cell Biology [J. F.], Harvard Medical School, Boston, Massachusetts 02115; Laboratory for Surgical Research and the Department of Surgery, Children’s Hospital, Boston, Massachusetts 02115 [K. C., M. A. M., W-D. B., J. F., M. S. O.]; and the Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan 48109 [M. K. K.]

The surgical removal of a primary tumor can result in the rapid growth of metastases. The production of angiogenesis inhibitors by the primary tumor is one mechanism for the inhibition of metastatic tumor growth.

Fig. 2. Increased metastatic burden after local radiotherapy to a LLC-LM tumor. Twenty-four mice whose tumors were 750 mm³ were separated into two groups, one of which received radiation to the primary tumor. Within 18–21 days, the number of surface metastases (A) and the lung weights (B) had increased significantly in the irradiated mice compared with the nonirradiated mice.
Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy

Edward M Messing, Judith Manola, Jorge Yao, Maureen Kiernan, David Crawford, George Wilding, P Anthony di’SantAgnese, Donald Trump, on behalf of the Eastern Cooperative Oncology Group study EST 3886

_Lancet Oncol_ 2006; 7: 472–79

**Interpretation** Early ADT benefits patients with nodal metastases who have undergone prostatectomy and lymphadenectomy, compared with those who receive deferred treatment. The beneficial effects of early ADT, rather than an imbalance in risk factors, are likely to explain the differences in outcomes between treatments.

![Graph showing progression-free survival](image-url)

- **Log-rank p=0.0001**
- **Hazard ratio (95% CI)=3.42 (1.96–5.98)**

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Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy

Edward M Messing, Judith Manola, Jorge Yao, Maureen Kiernan, David Crawford, George Wilding, P Anthony di’SantAgnese, Donald Trump, on behalf of the Eastern Cooperative Oncology Group study EST 3886

**A** Overall survival

**B** Prostate-cancer-specific survival

Number at risk

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Log-rank p=0.0004
Hazard ratio (95% CI)=4.09 (1.76-9.49)

Log-rank p=0.04
Hazard ratio (95% CI)=1.84 (1.01-3.35)
Systemic effects of local radiotherapy

Silvia C Formenti, Sandra Demaria

Abscopal effects

By contrast with the systemic, tumour-enhancing effects discussed above, experimental and clinical evidence have also reported an inhibitory role for local radiation on distant tumour growth. Although the term abscopal effect is sometimes used to mean systemic effects of other types of local therapy, we refer only to the original definition,

Lancet Oncology 2009

Figure 4: Clinical response outside the treatment field in a patient with thymic carcinoma. CT image of the patient in figure 3, showing the original apical lesion that was not included in the radiation field (A). The same lesion two months after treatment of a different, caudal metastasis with radiation and GM-CSF (B).
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. The abscopal effect may be mediated by activation of the immune system. Ipilimumab is a monoclonal antibody that inhibits an immunologic checkpoint on T cells, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). We report a case of the abscopal effect
Figure 1. Results of Diagnostic and Radiotherapy Simulation Imaging throughout the Disease Course.
Axial CT images are shown, corresponding to the timeline showing therapy and disease status. White arrows indicate the paraspinal mass, red circles indicate the right hilar lymphadenopathy and spleen, and black arrows indicate an incidental hepatic hemangioma. Panel A (top) represents the status before treatment with ipilimumab. Panel B shows enlargement of the paraspinal mass (top), stable right hilar lymphadenopathy (middle), and new splenic lesions (bottom). Panel C shows images 1 month after radiotherapy, when the response to radiotherapy had not yet occurred, with apparent continued worsening disease at all three sites. Several months after radiotherapy, the targeted paraspinal mass showed a response (Panel D, top). Furthermore, disease response outside of the radiation field was seen with decreased right hilar lymphadenopathy (middle) and resolution of splenic lesions (bottom). The response was durable, as shown in Panel E. Panel F shows the CT simulation image for radiotherapy planning, with the target volume (indicated in purple) encompassing the right paraspinal metastatic mass. The isodose lines represent total doses of 2850 cGy (pink), 2000 cGy (orange), 1000 cGy (green), and 200 cGy (blue). Disease regression was confirmed by means of three-dimensional volumetric assessment (Table 2 in the Supplementary Appendix).
Survival Benefit of Radical Prostatectomy in Lymph Node–Positive Patients with Prostate Cancer

Jutta Engel\textsuperscript{a,1,*}, Patrick J. Bastian\textsuperscript{b,1}, Helmut Baur\textsuperscript{c}, Volker Beer\textsuperscript{d}, Christian Chaussy\textsuperscript{e}, Juergen E. Gschwend\textsuperscript{f}, Ralph Oberneder\textsuperscript{g}, Karl H. Rothenberger\textsuperscript{h}, Christian G. Stief\textsuperscript{b}, Dieter Hölzel\textsuperscript{a}

\textsuperscript{a}Munich Cancer Registry of the Munich Cancer Center, Department of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Survival_plot.png}
\caption{Survival}
\end{figure}

\begin{tabular}{|c|c|c|}
\hline
\hline
n & 27,956 & 27,956 \\
\% & 100.0 & 100.0 \\
\hline
\end{tabular}
Fig. 2 – (a) Overall survival (OS) and (b) relative survival (RS) according to positive lymph nodes (LNs) after radical prostatectomy for all patients of the Munich Cancer Registry with detailed information of the exact number of positive LNs. RS is computed by the ratio of the observed survival rate to the expected survival rate of the general German population. Values of >100% describe a better prognosis relative to the general population.
Fig. 3 – (a) Overall survival (OS) and (b) relative survival (RS) for patients with positive lymph node status according to radical prostatectomy and for five random samples of the cohort with prostatectomy.
Might Men Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor? A SEER-Based Study

*Stephen H. Culp* a,*, Paul F. Schellhammer b, Michael B. Williams b

a Department of Urology, University of Virginia, Charlottesville, VA, USA; b Department of Urology, Eastern Virginia Medical School, Norfolk, VA, USA

SEER database analysis
Identifying Optimal Candidates for Local Treatment of the Primary Tumor Among Patients Diagnosed with Metastatic Prostate Cancer: A SEER-based Study

Nicola Fossati\textsuperscript{a,b}, Quoc-Dien Trinh\textsuperscript{c}, Jesse Sammon\textsuperscript{d}, Akshay Sood\textsuperscript{d}, Alessandro Larcher\textsuperscript{b,e}, Maxine Sun\textsuperscript{e}, Pierre Karakiewicz\textsuperscript{e}, Giorgio Guazzoni\textsuperscript{b}, Francesco Montorsi\textsuperscript{b}, Alberto Briganti\textsuperscript{b}, Mani Menon\textsuperscript{d}, Firas Abdollah\textsuperscript{d,*}

At multivariable analysis, all predictors were significantly associated with CSM, and the interaction test was statistically significant ($p < 0.0001$). Local treatment of the primary tumor, compared with NLT, conferred a higher CSM-free survival rate in patients with a predicted CSM risk $<40\%$. The number needed to treat according to the predicted CSM risk was 3.9.

Fig. 1 – Cancer-specific mortality (CSM)-free survival rate plotted against predicted probability of CSM at 3 yr after diagnosis. Dashed green line indicates local treatment of the primary tumor. Solid orange line indicates no local treatment of the primary tumor. CSM = cancer-specific mortality.
Role of Radical Prostatectomy in Metastatic Prostate Cancer: Data from the Munich Cancer Registry

Christian Gratzke\textsuperscript{a,*}
Jutta Engel\textsuperscript{b}
Christian G. Stief\textsuperscript{a}

Eur urol 2004

Fig. 1 – Survival of patients in the Munich Cancer Registry who did and did not undergo radical prostatectomy: (a) patient cohort, 1998–2010; (b) overall survival in M1 prostate cancer patients.
ADT = androgen deprivation therapy; RP = radical prostatectomy; RPE = extraperitoneal radical prostatectomy; XRT = external-beam radiation therapy.
A cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: Results of a feasibility and case-control study.

Axel Heidenreich,* David Pfister and Daniel Porres

From the Department of Urology, Uniklinik RWTH Aachen, Aachen, Germany

THE JOURNAL OF UROLOGY®

Vol. 193, 832-838, March 2015

A, time to castration resistance in patients with vs without CRP. B, median CSS. bNED, no biochemical evidence of disease.
Favorable outcome of intraoperative radiotherapy to the primary site in patients with metastatic prostate cancer

Toshihiro Kanda\textsuperscript{1} · Syohei Fukuda\textsuperscript{1} · Naotaka Fukui\textsuperscript{1} · Yu Ohkubo\textsuperscript{2} · Tomoko Kazumoto\textsuperscript{2} · Yoshihiro Saito\textsuperscript{2} · Ayataka Ishikawa\textsuperscript{3} · Masafumi Kurosumi\textsuperscript{3} · Yukio Kageyama\textsuperscript{1} · Yasuhisa Fujii\textsuperscript{4} · Kazunori Kihara\textsuperscript{4}

Published online: 11 January 2016

A single dose of 30 or 25 Gy

30 Gy in 2 Gy daily fractions was delivered to the prostatic region through four oblique fields using 10 or 14 MV X-rays.

Fig. 1 Schema of IORT. After PLND, a sterile cone was inserted through the lower abdominal incision and attached to the tumor. A spacer was inserted into the rectum to minimize the dose of radiation to the posterior rectal wall.
Fig. 2  a OS of the IORT group. The 5- and 10-year overall survival rates were 61.0, and 31.7 %, respectively, with a median survival of 72 months. b CSS of the IORT group. The 5- and 10-year CSS rates were 75.9, and 52.7 %, respectively, with a median of 200 months.
LOCAL THERAPY IMPROVES OVERALL SURVIVAL IN PATIENTS WITH NEWLY DIAGNOSED METASTATIC PROSTATE CANCER

• NCDB (National Cancer Database)
• 6,051 patients
  – 5224 – no local therapy
  – 622 (RP), 52 (IMRT), 153 (3D RT)
• Five-Year Overall Survival:
  – Local therapy: 45.7%
  – No local therapy: 17% (p<0.01)
• MVA: RP and IMRT were independently associated with superior survival