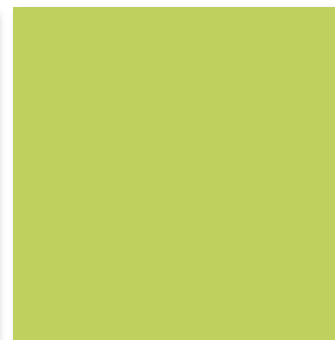


# Muskelinvasives Blasenkarzinom Strahlentherapie

Claus Belka



# Grundsätzliche Themenkomplexe

## 1.) Daten zur Strahlentherapie / Radiochemotherapie

- Daten zur Rolle der Radiochemo vs. Radiotherapie
- Daten zur Rolle einzelner Substanzen
- Daten zur Fraktionierung

## 2.) Nebenwirkungen und Lebensqualität

## 3.) Vergleich mit chirurgischen Therapieoptionen

## 4.) Ausblicke



# Definitive Radiatio vs Radiochemo

Platinum Priority – Bladder Cancer

Editorial by Abhishek A. Solanki, Max R. Kates, Phuoc T. Tran on pp. 280–282 of this issue

## Chemoradiotherapy in Muscle-invasive Bladder Cancer: 10-yr Follow-up of the Phase 3 Randomised Controlled BC2001 Trial

Emma Hall<sup>a,1,\*</sup>, Syed A. Hussain<sup>b,1</sup>, Nuria Porta<sup>a</sup>, Rebecca Lewis<sup>a</sup>, Malcolm Crundwell<sup>c</sup>, Peter Jenkins<sup>d</sup>, Christine Rawlings<sup>e</sup>, Jean Tremlett<sup>f</sup>, Thiagarajan Sreenivasan<sup>g</sup>, Jan Wallace<sup>h</sup>, Isabel Syndikus<sup>i</sup>, Denise Sheehan<sup>c</sup>, Anna Lydon<sup>c</sup>, Robert Huddart<sup>a,j,‡</sup>, Nicholas James<sup>a,i,‡</sup>, on behalf of the BC2001 Investigators

ORIGINAL ARTICLE

### Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

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EUROPEAN UROLOGY 82 (2022) 273–279

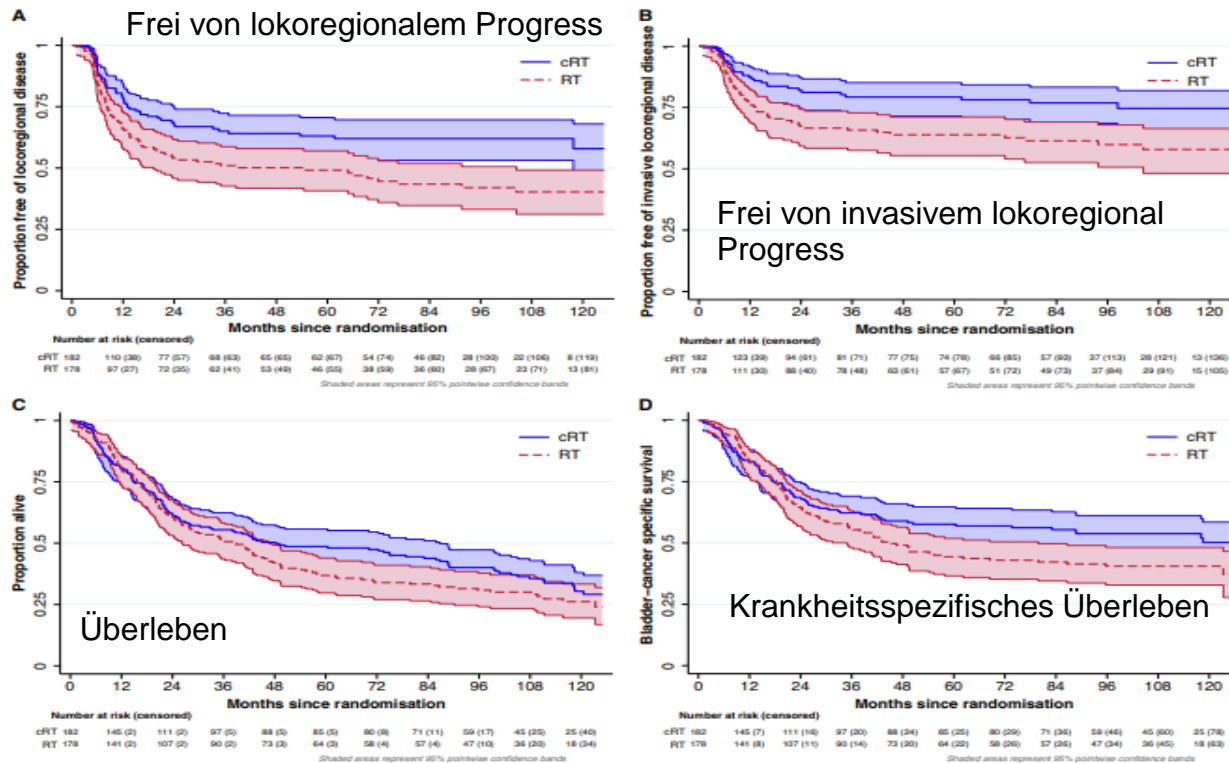


Fig. 1 – Disease outcomes for the chemotherapy comparison: (A) locoregional control; (B) invasive locoregional control; (C) overall survival; and (D) bladder cancer-specific survival. cRT = chemoradiotherapy; RT = radiotherapy.

Factoriale 2:2 Studie  
45 UK NHS Krankenhäuser  
(1) RT allein vs RT mit 5FU/MMC  
(2) Standard Bestrahlung der ganzen Blase (sRT) vs. RHDVRT Bestrahlung mit lokaler Dosisaufsättigung

HR signifikant verbessert für lokoregionäre Kontrolle und Zystektomiefreiheit – Rest grenzwertig signifikant/n.s.

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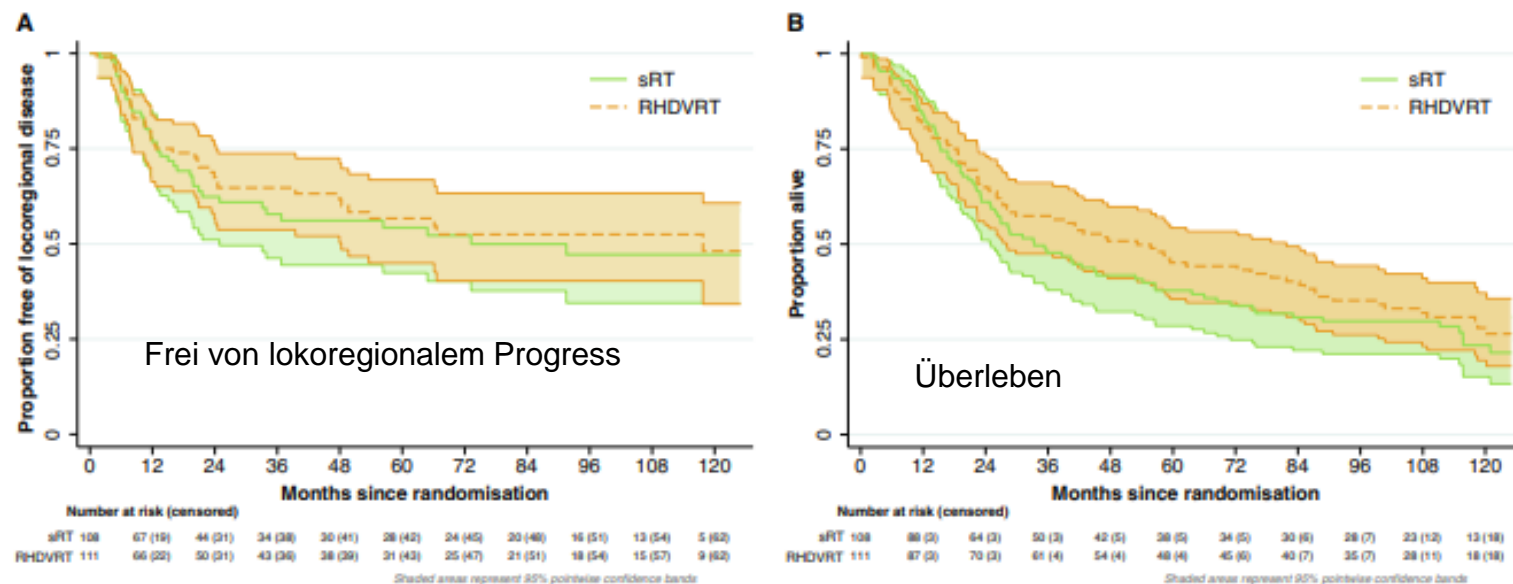


Fig. 2 – Disease outcomes for the radiotherapy comparison: (A) locoregional control and (B) overall survival. RHDVRT = reduced high-dose-volume RT; RT = radiotherapy; sRT = standard whole-bladder RT.

Keine Bedeutung des lokalen Boosts



# Definitive Radiatio vs Radiochemo

## Platinum Priority – Bladder Cancer

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Table 1 – Late toxicity: RTOG and LENT/SOM grades at 1, 2, and 5 yr and over the entire follow-up period<sup>a,b</sup>

|          | Worst grade $\geq 3$            | Chemotherapy comparison |              |         | Radiotherapy comparison |                 |         |      |       |      |      |
|----------|---------------------------------|-------------------------|--------------|---------|-------------------------|-----------------|---------|------|-------|------|------|
|          |                                 | cRT (N = 178)           | RT (N = 182) | p value | sRT (N = 120)           | RHDVRT (N = 95) | p value |      |       |      |      |
| RTOG     | At 1 yr                         | 3/94                    | 3.2%         | 2/80    | 2.5%                    | 0.7             | 3/56    | 5.4% | 2/53  | 3.8% | 0.5  |
|          | At 2 yr                         | 3/69                    | 4.3%         | 3/60    | 5.0%                    | 0.9             | 1/43    | 2.3% | 3/37  | 8.1% | 0.3  |
|          | At 5 yr                         | 2/53                    | 3.8%         | 1/38    | 2.6%                    | 0.9             | 0/24    | 0    | 1/17  | 5.9% | 0.2  |
|          | After 5 yr                      | 2/44                    | 4.6%         | 1/34    | 2.9%                    | 0.8             | 1/25    | 4%   | 1/15  | 6.7% | 0.8  |
|          | Over all follow-up <sup>c</sup> | 11/120                  | 9.2%         | 19/110  | 17%                     | 0.06            | 12/86   | 14%  | 13/67 | 19%  | 0.5  |
| RTOG GU  | At 1 yr                         | 3/94                    | 3.2%         | 1/80    | 1.3%                    | 0.3             | 2/56    | 3.6% | 1/53  | 1.9% | 0.5  |
|          | At 2 yr                         | 3/69                    | 4.3%         | 3/60    | 5.0%                    | 0.9             | 1/43    | 2.3% | 2/37  | 5.4% | 0.5  |
|          | At 5 yr                         | 2/52                    | 3.9%         | 1/37    | 2.7%                    | 0.9             | 0/24    | 0    | 1/17  | 5.9% | 0.2  |
|          | After 5 yr                      | 2/44                    | 4.6%         | 1/33    | 3.0%                    | 0.8             | 1/25    | 4%   | 1/15  | 6.7% | 0.8  |
|          | Over all follow-up <sup>c</sup> | 10/120                  | 8.3%         | 14/110  | 13%                     | 0.3             | 9/86    | 11%  | 11/67 | 16%  | 0.4  |
| LENT/SOM | At 1 yr                         | 29/79                   | 37%          | 24/77   | 31%                     | 0.5             | 17/53   | 32%  | 18/42 | 43%  | 0.3  |
|          | At 2 yr                         | 21/64                   | 33%          | 21/55   | 38%                     | 0.5             | 11/36   | 31%  | 14/33 | 42%  | 0.2  |
|          | At 5 yr                         | 13/47                   | 28%          | 7/33    | 21%                     | 0.5             | 5/23    | 22%  | 4/16  | 25%  | 1    |
|          | Over 5 yr                       | 65/117                  | 56%          | 55/101  | 55%                     | 0.9             | 39/78   | 50%  | 38/61 | 62%  | 0.18 |

cRT = chemotherapy; LENT/SOM = Late Effects of Normal Tissue (Subjective, Objective, and Management elements); RHDVRT = reduced high-dose-volume RT;

RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; sRT = standard whole-bladder RT.

<sup>a</sup> Analysis performed by treatment received (safety population) rather than by treatment allocated.

<sup>b</sup> The p values were calculated by means of the stratified Mantel-Haenszel chi-square test.

<sup>c</sup> For LENT/SOM, follow-up includes all visits from 6 mo to 5 yr after randomisation, and for RTOG, it includes long-term follow-up (>5 yr).

Toxizitäten nicht stark/deutlich unterschiedlich

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# Definitive Radiotherapy vs Radiochemo

## Patient-reported Quality of Life Outcomes in Patients Treated for Muscle-invasive Bladder Cancer with Radiotherapy ± Chemotherapy in the BC2001 Phase III Randomised Controlled Trial

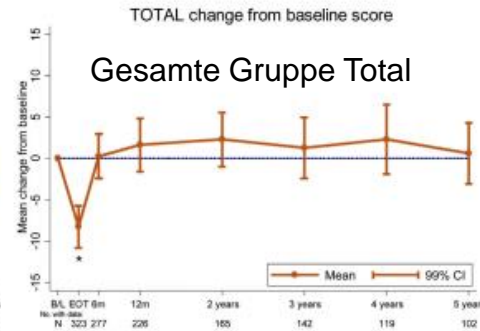
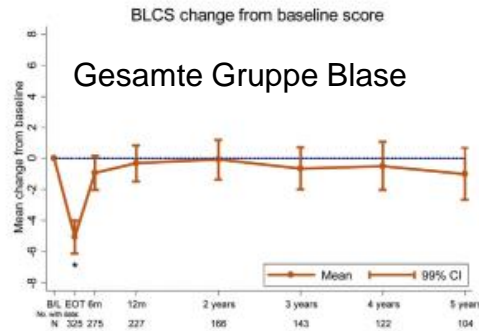
Robert A. Huddart<sup>a,i,j,k</sup>, Emma Hall<sup>a,j</sup>, Rebecca Lewis<sup>a</sup>, Nuria Porta<sup>a</sup>, Malcolm Crundwell<sup>b</sup>, Peter J. Jenkins<sup>c</sup>, Christine Rawlings<sup>d</sup>, Jean Tremlett<sup>e</sup>, Leila Campani<sup>f</sup>, Carey Hendron<sup>f</sup>, Syed A. Hussain<sup>g,i</sup>, Nicholas D. James<sup>f,h,i</sup>, on behalf of the BC2001 Investigators

## Platinum Priority – Bladder Cancer

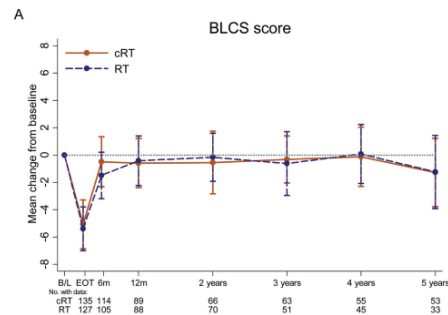
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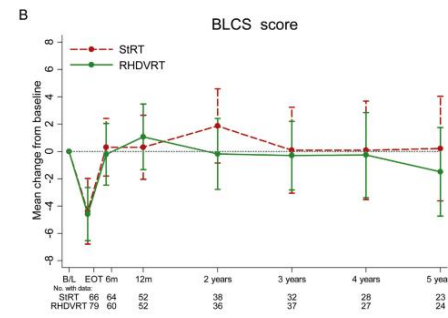
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## Blase XRT vs CHX CHXRT



## Blase XRT vs XRT Boost



# Definitive Radiotherapy vs Radiochemo

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### Gesamte Gruppe Blase Einzelitems

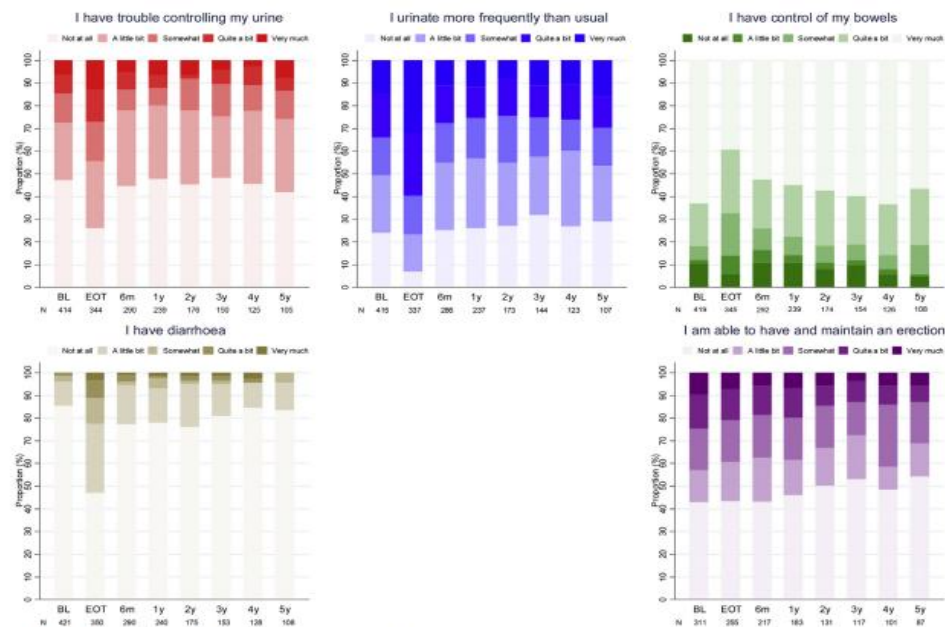
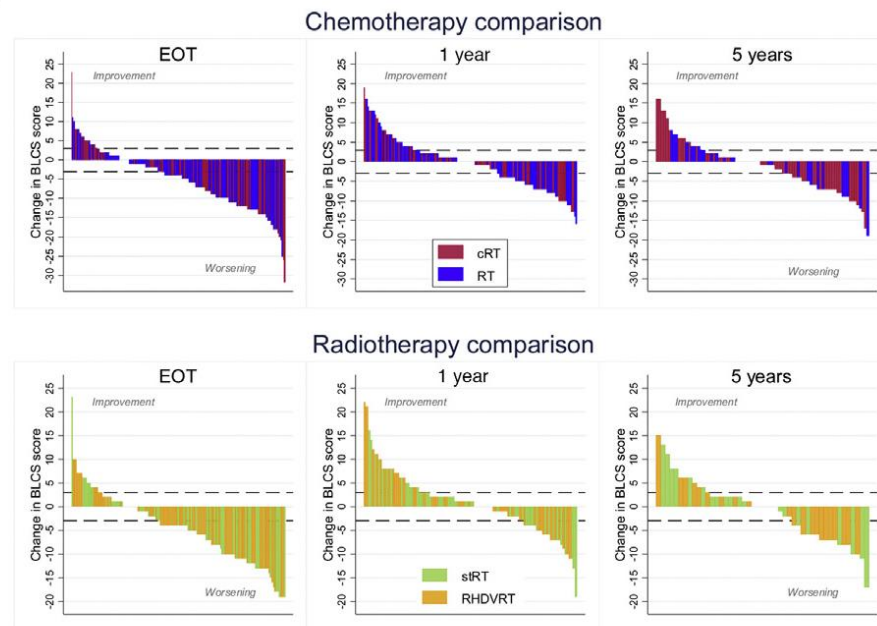


Fig. 3 – Individual items in the bladder cancer subscale of FACT-BL. BL = baseline; EoT = end of treatment; FACT-BL = Functional Assessment of Cancer Therapy—Bladder.

### Auflösung nach Behandlung

B



Lebensqualität nach initialem DROP weitgehend wie Baseline  
Nicht stark/deutlich unterschiedlich zwischen XRT vs CHX XRT

| Studie     | Studienziel   | Ergebnis  | Tox  | Bemerkungen                                   |
|------------|---|---|--|---|
| RTOG 85-12 | 40 Gy in 4 weeks and cisplatin 100 mg/m <sup>2</sup> CR plus 24 Gy bladder boost residual → radical cystectomy.   | 67 % CR, OS 64% 3 Jahre   | Moderately well  | Initiator Trial                               |
| RTOG 97-06 | TURBT → hyperfract RT, mit Cis-Plat. residual → <u>Cystectomie</u> → adjuv 3 MCV  | <50% Protokolltreue<br>3 Jahre locoregional failure 27%, distant metastasis, 29%, overall survival 61% bladder-intact survival 48%,   | Relevante Tox  | Zeigt Machbarkeit jedoch Tox limits           |
| RTOG 99-06 | HFX XRT & paclitaxel and cisplatin (TCI) repeat biopsy <T1 → TCI was given. >T1 disease → cystectomy adjuvant gem & cisplatin to all patients   | complete response rate was 81% (65/80), 36 of the 80 patients died (22 of bladder cancer). At a median follow-up of 49.4 months, the actuarial 5-year overall and disease-specific survival rate was 56% and 71%,   | 26% & 8% grade 3-4. Adj CHX in 70% grade 3 in 46% and grade 4 in 26%. bladder XRT tox 3 of 53 late grade 3 | Zeigt Machbarkeit jedoch Tox. limits          |
| Erlangen   | 415 patients with bladder cancer radiotherapy n = 126) or radiochemotherapy (RCT; n = 289) after transurethral resection (TUR). CR patients were observed. persistent or recurrent invasive tumor, salvage-cystectomy was recommended | CR in 72% of patients. LRC after CR in 64% of patients at 10 years. Distant metastases 35% at 10 years. Total Ten-year DSF 42%, 80% of survivors preserved bladder. RCT more effective than RT alone for CR and survival. Nach salvage cystectomy 45% DSF 10 years. | Cystectomy because of a contracted bladder was restricted to 2% of patients.                               | <b>Sehr grosser</b> monozentrischer Datensatz |
| MGH Pooled | 475 Pt in RTOG Trials, gepooled   | 70 % Blasenerhalt Mit TURB dtl besser DSS bei 85% moderne Ansätze, dtl Verbesserung über die Zeit   | Moderate Tox je nach indiv. RTOG Studie auch mehr  | Sehr grosser gepoolter Datensatz              |



# Definitive Radiochemo

original report

## Bladder Preservation With Twice-a-Day Radiation Plus Fluorouracil/Cisplatin or Once Daily Radiation Plus Gemcitabine for Muscle-Invasive Bladder Cancer: NRG/RTOG 0712—A Randomized Phase II Trial

John J. Coen, MD<sup>1</sup>; Peixin Zhang, PhD<sup>2</sup>; Philip J. Saylor, MD<sup>3</sup>; Cheryl T. Lee, MD<sup>4</sup>; Chin-Lee Wu, MD, PhD<sup>5</sup>; William Parker, MSc<sup>6</sup>; Timothy Lautenschlaeger, MD<sup>6</sup>; Anthony L. Zietman, MD<sup>3</sup>; Jason A. Efstathiou, MD, DPhil<sup>3</sup>; Ashesh B. Jani, MD<sup>7</sup>; Omer Kucuk, MD<sup>7</sup>; Luis Souhami, MD<sup>8</sup>; Joseph P. Rodgers, MS<sup>2</sup>; Howard M. Sandler, MD<sup>7</sup>; and William U. Shipley, MD<sup>3</sup>

### Vergleich XRT einmal täglich mit GEM vs HFX XRT mit Cis-5-FU

**TABLE 4.** Bladder-Intact Metastatic Disease-Free Survival at 3 Years

| Variable   | FCT Arm (n = 30) | GD Arm (n = 29) |
|--|------------------|-----------------|
| No. (%) of patients                                    | 20 (66.7)        | 21 (72.4)       |
| 95% CI, %  | 52.4 to 80.8     | 58.8 to 86.1    |
| Type of failure (first, if multiple occurred), No. (%) | (n = 10)         | (n = 8)         |
| Distant metastasis                                     | 5 (50.0)         | 3 (37.5)        |
| Death  | 3 (30.0)         | 2 (25.0)        |
| Undergoing cystectomy                                  | 2 (20.0)         | 3 (37.5)        |

Abbreviations: FCT, fluorouracil plus cisplatin and radiation twice a day; GD, gemcitabine and once daily radiation.

**TABLE 3.** Adverse Events That Occurred During Treatment by Specific Category (GU, GI, and hematologic toxicities) Definitely, Probably, or Possibly Related to Protocol Treatment

| Category              | FCT Arm (n = 33)             |           |           |          |         | GD Arm (n = 33)              |           |           |         |         |
|-----------------------|------------------------------|-----------|-----------|----------|---------|------------------------------|-----------|-----------|---------|---------|
|                       | No. (%) of Patients by Grade |           |           |          |         | No. (%) of Patients by Grade |           |           |         |         |
|                       | 1                            | 2         | 3         | 4        | 5       | 1                            | 2         | 3         | 4       | 5       |
| Overall highest grade | 5 (15.2)                     | 9 (27.3)  | 12 (36.4) | 7 (21.2) | 0 (0.0) | 9 (27.3)                     | 7 (21.2)  | 15 (45.5) | 2 (6.1) | 0 (0.0) |
| Blood/bone marrow     | 5 (15.2)                     | 8 (24.2)  | 11 (33.3) | 7 (21.2) | 0 (0.0) | 14 (42.4)                    | 3 (9.1)   | 12 (36.4) | 2 (6.1) | 0 (0.0) |
| GI                    | 12 (36.4)                    | 15 (45.5) | 2 (6.1)   | 0 (0.0)  | 0 (0.0) | 15 (45.5)                    | 15 (45.5) | 3 (9.1)   | 0 (0.0) | 0 (0.0) |
| Renal/GU              | 14 (42.4)                    | 5 (15.2)  | 2 (6.1)   | 0 (0.0)  | 0 (0.0) | 7 (21.2)                     | 10 (30.3) | 2 (6.1)   | 0 (0.0) | 0 (0.0) |

NOTE. Adverse events were graded using Common Terminology Criteria for Adverse Events version 3.0. Overall highest grade is based on blood/bone marrow, gastrointestinal, or renal/GU adverse events.

Abbreviations: FCT, fluorouracil plus cisplatin and radiation twice a day; GD, gemcitabine and once daily radiation; GU, genitourinary.

Beide Vorgehensweisen vergleichbar ggf. Normo Fx mit GEM einfacher



## Definitive Radiochemo

### Long-term Outcomes of Chemoradiation for Muscle-invasive Bladder Cancer in Noncystectomy Candidates. Final Results of NRG Oncology RTOG 0524-A Phase 1/2 Trial of Paclitaxel + Trastuzumab with Daily Radiation or Paclitaxel Alone with Daily Irradiation

Wöchentliches PAC & Trastuzumab versus wöchentliches PAC zur Strahlentherapie 1.8 Gy bis 64.8 Gy.

- 1.) **Protokollerfüllung** Gruppe 1 60% and Gruppe 2 76%
- 2.) **CR nach 12 Wochen** bei 62% in jeder Gruppe.
- 3.) **AEs CTC  $\geq$  Grad3** bei 80% Gruppe 1 und 58% Gruppe 2.
- 4.) **OS 5 Jahre** Gruppe 1 25.0% und Gruppe 2 37.8%
- 5.) **DSF** 15.0% 1 und 31.1% Gruppe 2

#### Interpretation:

**Bei inoperablen Patienten ist eine platinfreie CHX-XRT effizient mit gutem CR und OS  
– jedoch mit relevanten Toxizitäten**



## Definitive Radiochemo

Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial

**Paclitaxel plus cisplatin (paclitaxel group) versus fluorouracil plus cisplatin (fluorouracil group) with twice-daily radiation. Bei CR XRT bis 64,3 gefolgt von adj. Cis,Gem,PAC**

Paclitaxel 98% completed induction 35% with grade 3–4 toxicity), 85% completed induction and consolidation 24% with grade 3–4 67% completed the entire protocol with adjuvant chemotherapy. 85% grade 3–4 toxicity during adjuvant chemotherapy.

Fluorouracil, 96% completed induction 19% with grade 3–4 toxicity, 83% completed induction and consolidation 26% had grade 3–4 toxicity 25 53% completed the entire protocol with adjuvant chemotherapy. 76% had 3–4 toxicity during adjuvant chemotherapy.

11% patients treated with the paclitaxel regimen and three 6% patients treated with the fluorouracil regimen developed late grade 3–4 radiotherapy toxicities.

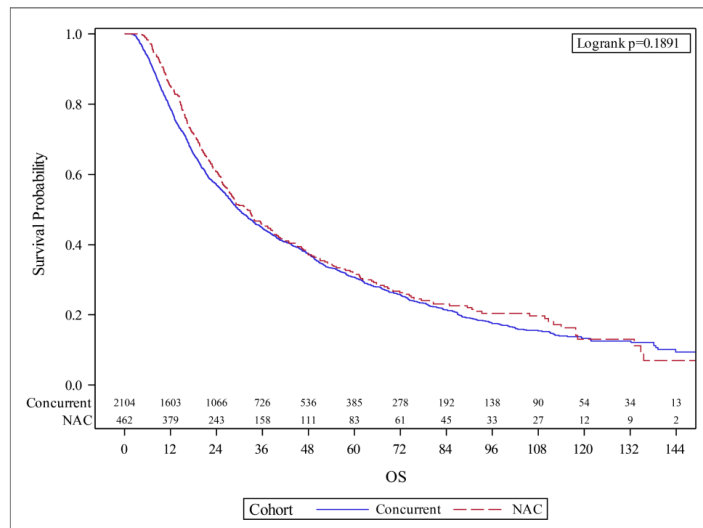
**Beide Vorgehensweisen vergleichbar aber Tox bleibt nenneswert**



# Definitive Radio(chemo)

## Trimodality therapy with or without neoadjuvant chemotherapy for muscle invasive bladder cancer

Trevor J. Royce, MD MS MPH<sup>1</sup>, Yuan Liu, PhD MS<sup>2</sup>, Matthew I. Milowsky, MD<sup>3</sup>, Jason A. Efstathiou, MD DPhil<sup>4</sup>, Ashesh B. Jani, MD<sup>5</sup>, Benjamin Fischer-Valuck, MD<sup>5</sup>, Sagar A. Patel, MD<sup>5</sup>



| Cohort     | No. of Subject | Event      | Censored  | Median Survival (95% CI) | 60 Mo Survival       | 120 Mo Survival      |
|------------|----------------|------------|-----------|--------------------------|----------------------|----------------------|
| Concurrent | 2104           | 1459 (69%) | 645 (31%) | 29.8 (28, 32.2)          | 30.6% (28.4%, 32.9%) | 13.3% (11.2%, 15.5%) |
| NAC        | 462            | 308 (67%)  | 154 (33%) | 32.2 (27.5, 37.4)        | 31.8% (27.0%, 36.8%) | 13.0% (8.4%, 18.7%)  |

Table 4.

Multivariate overall survival (OS) analysis among patients who received trimodality therapy (TMT) with or without neoadjuvant chemo (NAC) for muscle invasive bladder sensitivity analysis using overall survival defined from start date of radiation.

| Variable | Level   | N    | Hazard Ratio (95% CI) | P-value* |
|----------|---------|------|-----------------------|----------|
| Cohort   | TMT     | 2087 | -                     |          |
|          | NAC+TMT | 458  | 0.97 (0.86-1.10)      | 0.618    |

The estimated stratified treatment effect was controlled by: age, comorbidity, facility, income, education, insurance, race, region, T stage, and year.

Eine Hinzunahme von einer neoadj. CHX vor TMT hat eher keinen Benefit bei gepoolter Analyse





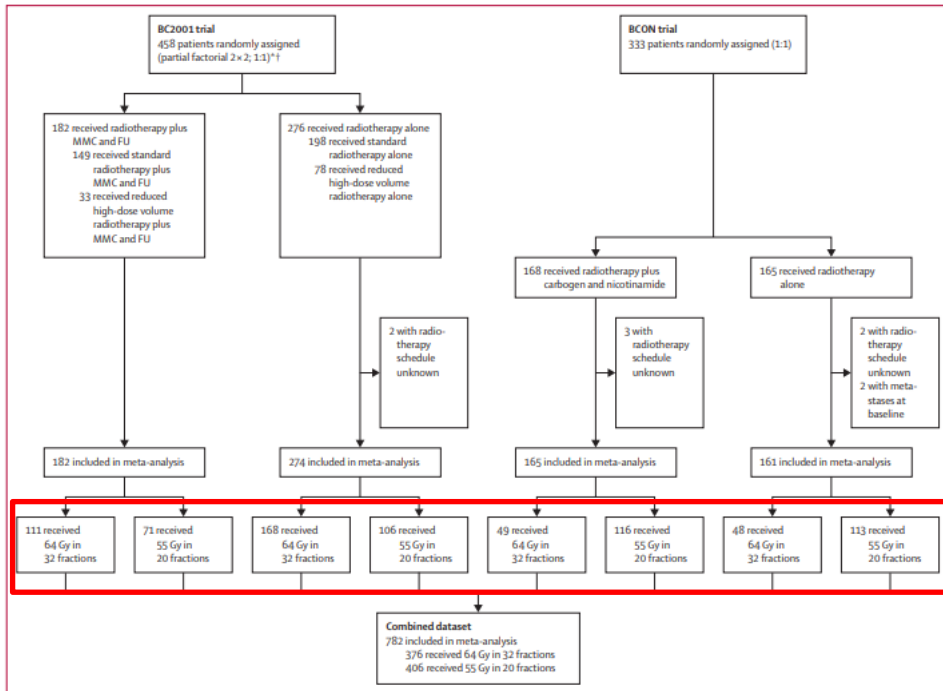
# Definitive Radio(chemo)



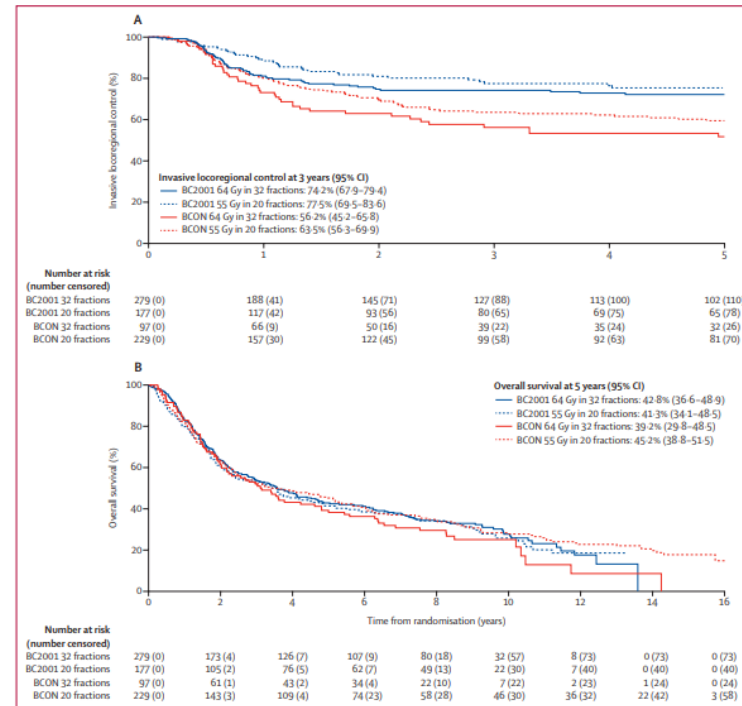
## Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials



Ananya Choudhury\*, Nuria Porta\*, Emma Hall, Yee Pei Song, Ruth Owen, Randal MacKay, Catharine M L West, Rebecca Lewis, Syed A Hussain, Nicholas D James†, Robert Huddart†, Peter Hoskin†, on behalf of the BC2001 and BCON investigators



**Figure 1: Trial profiles and final dataset**  
MMC=mytomicin C, FU=fluorouracil. \*98 excluded from chemotherapy randomisation (radiotherapy plus chemotherapy vs radiotherapy alone): 53 ineligible for chemotherapy; 34 withdrew or were withdrawn by physician; four had other reasons; and seven had unknown reasons. †239 excluded from radiotherapy randomisation (standard radiotherapy vs reduced high-dose volume radiotherapy): 84 entered the trial after radiotherapy randomisation closed; 54 at centres not participating in radiotherapy randomisation; 47 with multiple tumours; 44 withdrew or were withdrawn by physician; and ten with administrative or unknown reasons.



**Figure 2: Kaplan-Meier estimates of observed invasive locoregional control (A) and observed overall survival (B) by trial and fractionation group**

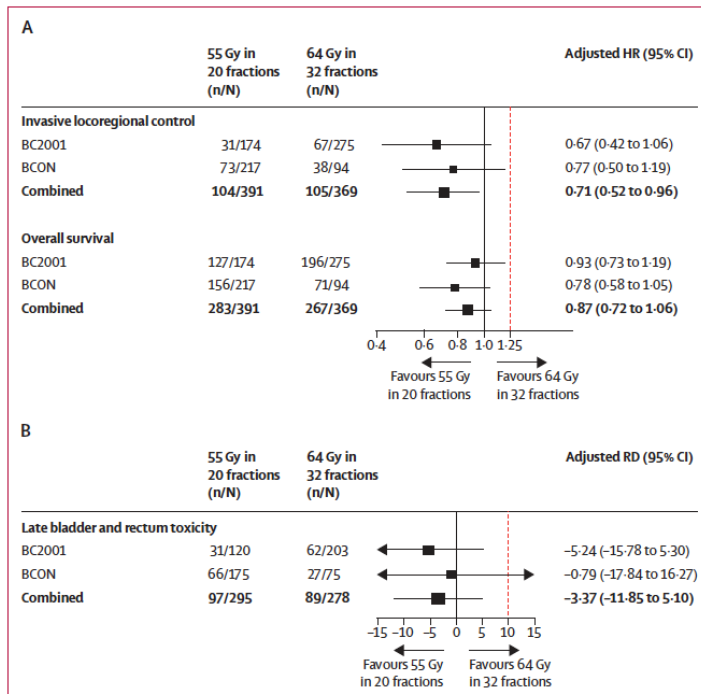
# Definitive Radio(chemo)



## Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials



Ananya Choudhury\*, Nuria Porta\*, Emma Hall, Yee Pei Song, Ruth Owen, Randal MacKay, Catharine M L West, Rebecca Lewis, Syed A Hussain, Nicholas D James†, Robert Huddart‡, Peter Hoskin†, on behalf of the BC2001 and BCON investigators

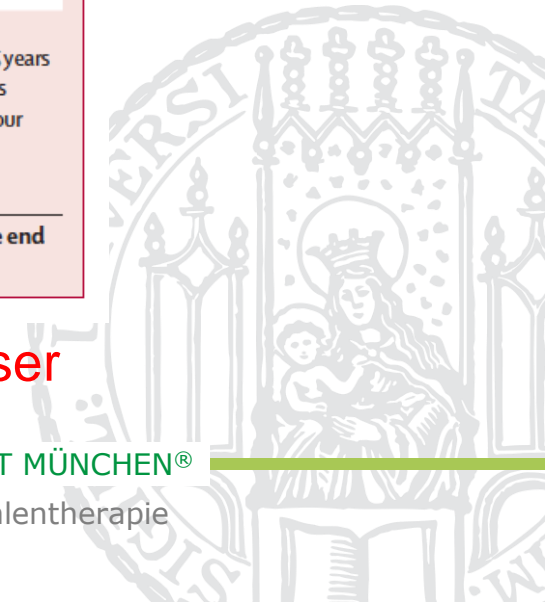


|                             | 64 Gy in 32 fractions (n=278) | 55 Gy in 20 fractions (n=295) |
|-----------------------------|-------------------------------|-------------------------------|
| <b>2-year late toxicity</b> |                               |                               |
| Rectum                      | 7 (3%)                        | 17 (6%)                       |
| Bladder                     | 66 (24%)                      | 74 (25%)                      |
| Rectum or bladder           | 69 (25%)*                     | 82 (28%)†                     |
| <b>5-year late toxicity</b> |                               |                               |
| Rectum                      | 8 (3%)                        | 21 (7%)                       |
| Bladder                     | 86 (31%)                      | 88 (30%)                      |
| Rectum or bladder           | 89 (32%)‡                     | 97 (33%)§                     |

LENT-SOMA urinary and rectal dysfunction subscales were recorded up to 5 years after radiotherapy in the BC2001 and BCON trials. LENT-SOMA=Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic. \*Four patients with both. †Nine patients with both. ‡Five patients with both. §12 patients with both.

**Table 2: LENT-SOMA grade 3-4 bladder or rectum toxicity after the end of treatment by fractionation groups**

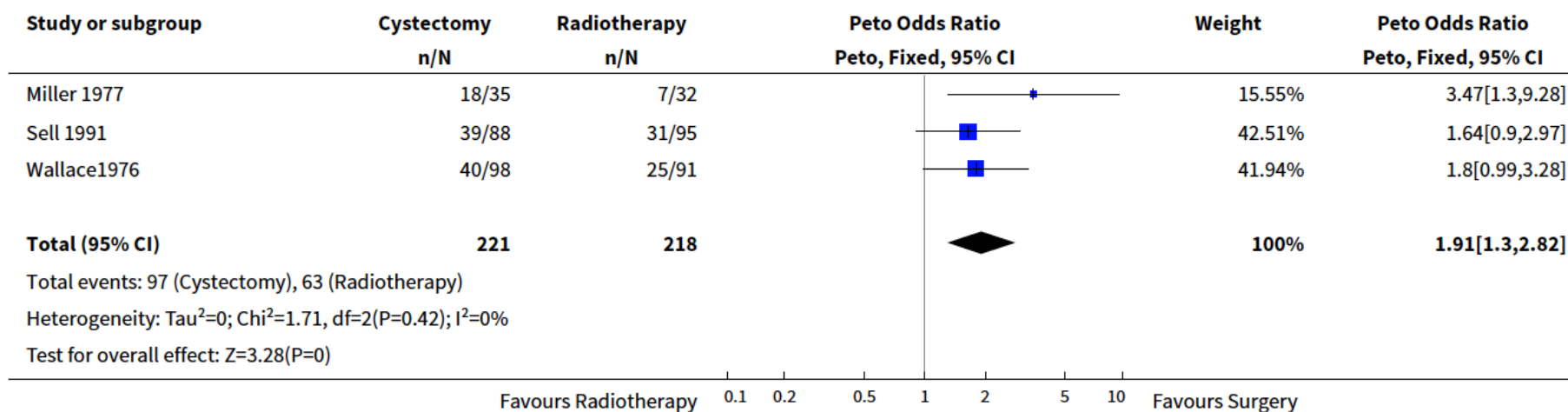
Milde Hypofraktionierung 55Gy in 20 Fx wahrscheinlich besser



# Chirurgisches Vorgehen versus Definitive Radio(chemo)

Shelley M, Barber J, Wilt TJ, Mason M.  
 Surgery versus radiotherapy for muscle invasive bladder cancer.  
*Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD002079.  
 DOI: [10.1002/14651858.CD002079](https://doi.org/10.1002/14651858.CD002079).

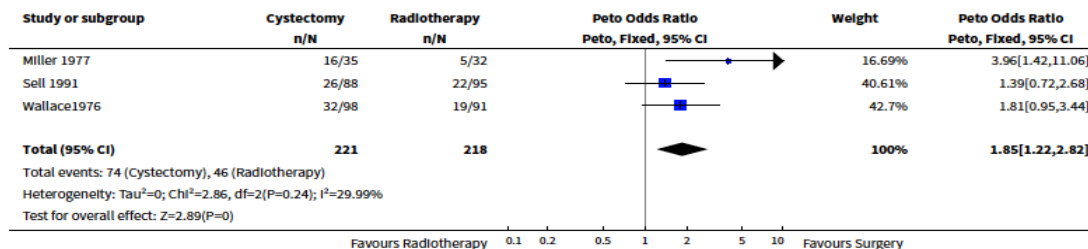
## Analysis 1.1. Comparison 1 Preoperative Radiotherapy plus Cystectomy versus Radical Radiotherapy plus Salvage Cystectomy, Outcome 1 overall survival at 3 years: intention to treat analysis.



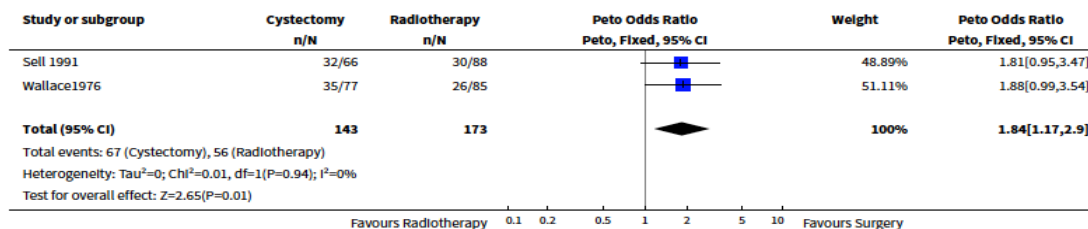
Medizinhistorisch wertvoll

# Chirurgisches Vorgehen versus Definitive Radio(chemo)

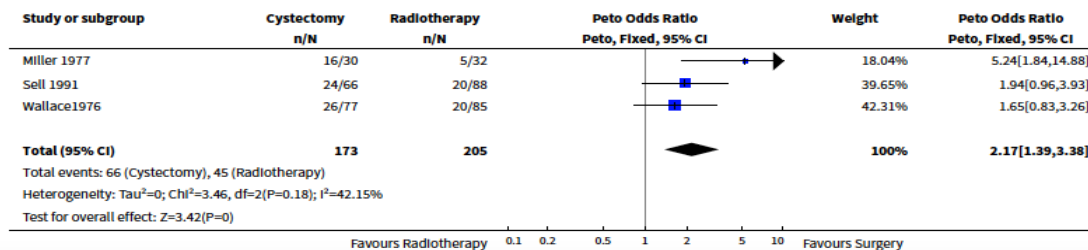
## Analysis 1.2. Comparison 1 Preoperative Radiotherapy plus Cystectomy versus Radical Radiotherapy plus Salvage Cystectomy, Outcome 2 overall survival at 5 years: intention to treat analysis.



## Analysis 1.3. Comparison 1 Preoperative Radiotherapy plus Cystectomy versus Radical Radiotherapy plus Salvage Cystectomy, Outcome 3 overall survival at 3 years: treatment received analysis.



## Analysis 1.4. Comparison 1 Preoperative Radiotherapy plus Cystectomy versus Radical Radiotherapy plus Salvage Cystectomy, Outcome 4 overall survival at 5 years: treatment received analysis.





# Chirurgisches Vorgehen versus Definitive Radio(chemo)

- Keine Phase 3 Studie verfügbar
- Nach Abbruch des UK Spare Trial mit 45 Pat. auch unwahrscheinlich
- Somit nur pooled Data vergleich, Meta Analysen, Register etc



# Chirurgisches Vorgehen versus Definitive Radio(chemo)

## Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Alexandre R Zlotta\*, Leslie K Ballas, Andrzej Niemierko†, Katherine Lajkosz†, Cynthia Kuk, Gus Miranda, Michael Drumm, Andrea Mari, Ethan Thio, Neil E Fleshner, Girish S Kulkarni, Michael A S Jewett, Robert G Bristow, Charles Catton, Alejandro Berlin, Srikala S Sridhar, Anne Schuckman, Adam S Feldman, Matthew Wszolek, Douglas M Dahl, Richard J Lee, Philip J Saylor, M Dror Michaelson, David T Miyamoto, Anthony Zietman, William Shipley, Peter Chung, Siamak Daneshmand, Jason A Efstathiou\*

|                                      | Before matching            |                              |         | After 3:1 matching          |                              |         |
|--------------------------------------|----------------------------|------------------------------|---------|-----------------------------|------------------------------|---------|
|                                      | Radical cystectomy (n=440) | Trimodality therapy (n=282)* | p value | Radical cystectomy (n=837)† | Trimodality therapy (n=282)* | p value |
| Age, years                           | 71.2 (63.7-77.2)           | 71.6 (64.0-78.9)             | 0.22    | 71.4 (66.0-77.1)            | 71.6 (64.0-78.9)             | 0.76    |
| Sex                                  |                            |                              | 0.31    |                             |                              | 0.65    |
| Female                               | 92 (21%)                   | 68 (24%)                     | ..      | 213 (25%)                   | 68 (24%)                     | ..      |
| Male                                 | 348 (79%)                  | 214 (76%)                    | ..      | 624 (75%)                   | 214 (76%)                    | ..      |
| Carcinoma in situ                    |                            |                              | 0.096   |                             |                              | 0.51    |
| No                                   | 324 (74%)                  | 223 (79%)                    | ..      | 646 (77%)                   | 223 (79%)                    | ..      |
| Yes                                  | 116 (26%)                  | 59 (21%)                     | ..      | 191 (23%)                   | 59 (21%)                     | ..      |
| Clinical T-stage                     |                            |                              | 0.0024  |                             |                              | 0.91    |
| T2                                   | 362 (82%)                  | 255 (90%)                    | ..      | 755 (90%)                   | 255 (90%)                    | ..      |
| T3-4                                 | 78 (18%)                   | 27 (10%)                     | ..      | 82 (10%)                    | 27 (10%)                     | ..      |
| BMI                                  |                            |                              | 0.014   |                             |                              | 0.40    |
| <30 kg/m <sup>2</sup>                | 340 (77%)                  | 192 (69%)                    | ..      | 600 (72%)                   | 192 (69%)                    | ..      |
| ≥30 kg/m <sup>2</sup>                | 100 (23%)                  | 86 (31%)                     | ..      | 237 (28%)                   | 86 (31%)                     | ..      |
| Missing                              | 0                          | 4                            | ..      | 0                           | 4                            | ..      |
| Hydronephrosis                       |                            |                              | <0.0001 |                             |                              | 0.35    |
| No                                   | 339 (77%)                  | 255 (90%)                    | ..      | 740 (88%)                   | 255 (90%)                    | ..      |
| Yes                                  | 101 (23%)                  | 27 (10%)                     | ..      | 97 (12%)                    | 27 (10%)                     | ..      |
| Neoadjuvant or adjuvant chemotherapy |                            |                              | <0.0001 |                             |                              | 0.42    |
| No                                   | 259 (60%)                  | 123 (44%)                    | ..      | 340 (41%)                   | 123 (44%)                    | ..      |
| Yes                                  | 176 (40%)                  | 159 (56%)                    | ..      | 492 (59%)                   | 159 (56%)                    | ..      |
| Missing                              | 5                          | 0                            | ..      | 5                           | 0                            | ..      |
| Smoking history                      |                            |                              | 0.57    |                             |                              | 0.91    |
| Never smoked                         | 115 (26%)                  | 69 (24%)                     | ..      | 201 (24%)                   | 69 (24%)                     | ..      |
| Current or former smoker             | 321 (74%)                  | 213 (76%)                    | ..      | 632 (76%)                   | 213 (76%)                    | ..      |
| Missing                              | 4                          | 0                            | ..      | 4                           | 0                            | ..      |
| ECOG status                          |                            |                              | 0.59    |                             |                              | 0.57    |
| 0                                    | 189 (75%)                  | 218 (77%)                    | ..      | 392 (76%)                   | 218 (77%)                    | ..      |
| 1 or 2                               | 62 (25%)                   | 64 (23%)                     | ..      | 127 (24%)                   | 64 (23%)                     | ..      |
| Missing                              | 189                        | 0                            | ..      | 318                         | 0                            | ..      |

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. \*All patients in the trimodality therapy cohort received concurrent radiosensitising chemotherapy. †Of the 282 trimodality therapy patients, with 3:1 matching, nine could only be matched to two radical cystectomy patients, therefore resulting in a total of 837 matched radical cystectomy patients, instead of 846.

**Table: Baseline characteristics before and after matching**



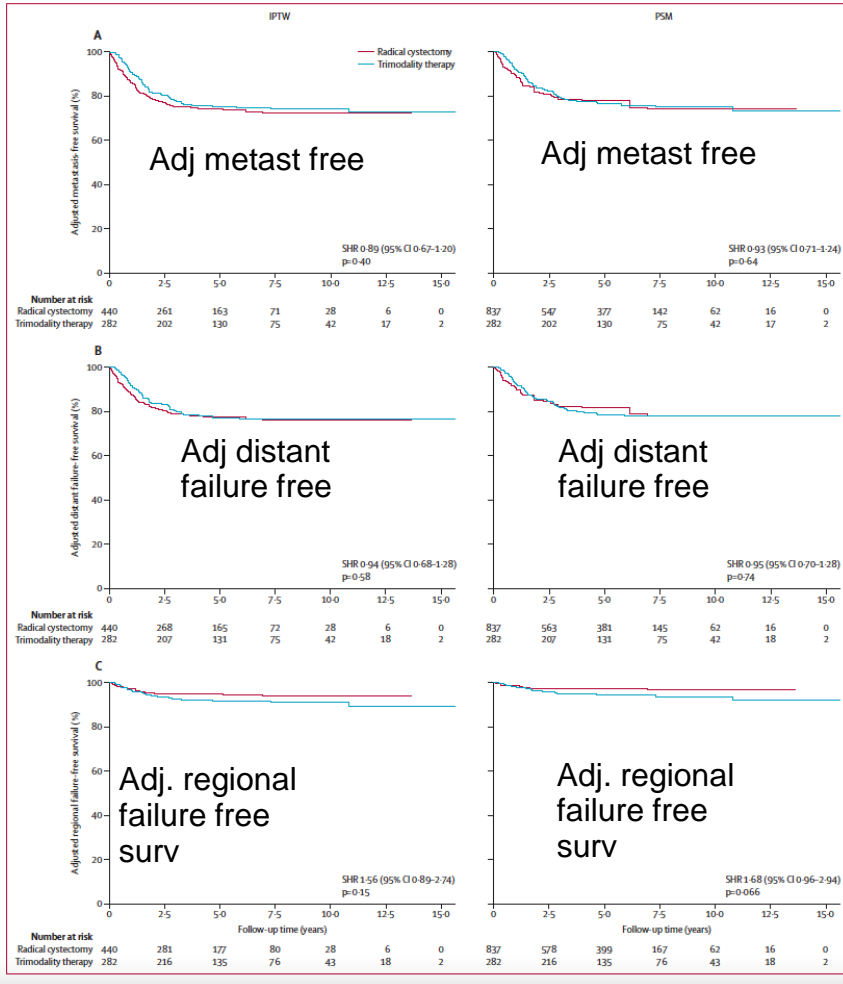
# Chirurgisches Vorgehen versus Definitive Radio(chemo)

Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Alexandre R Zietze<sup>1</sup>, Linder K Ballek, Andrzej Niemien<sup>2</sup>, Katharine Lajko<sup>3</sup>, Cynthia Kik, Gazi Miranda, Michael Drum, Andrea Mari, Elnor Thi, Neil E Flaherty, Gadi S Elkam, Michael A Szwert, Robert G Bostow, Charles Cotton, Algeniba Berlin, Srikish S Sridhar, Anne Schwinnen, Adam S Friedman, Matthew Pirovski, Douglas M Dalk, Richard Lee, Philip Sogker, Al Dine Mchalek, David Takiyama, Anthony Zietman, William Shipkey, Peter Chung, Samak Danechmand, Jason A Fitzhugh<sup>4</sup>

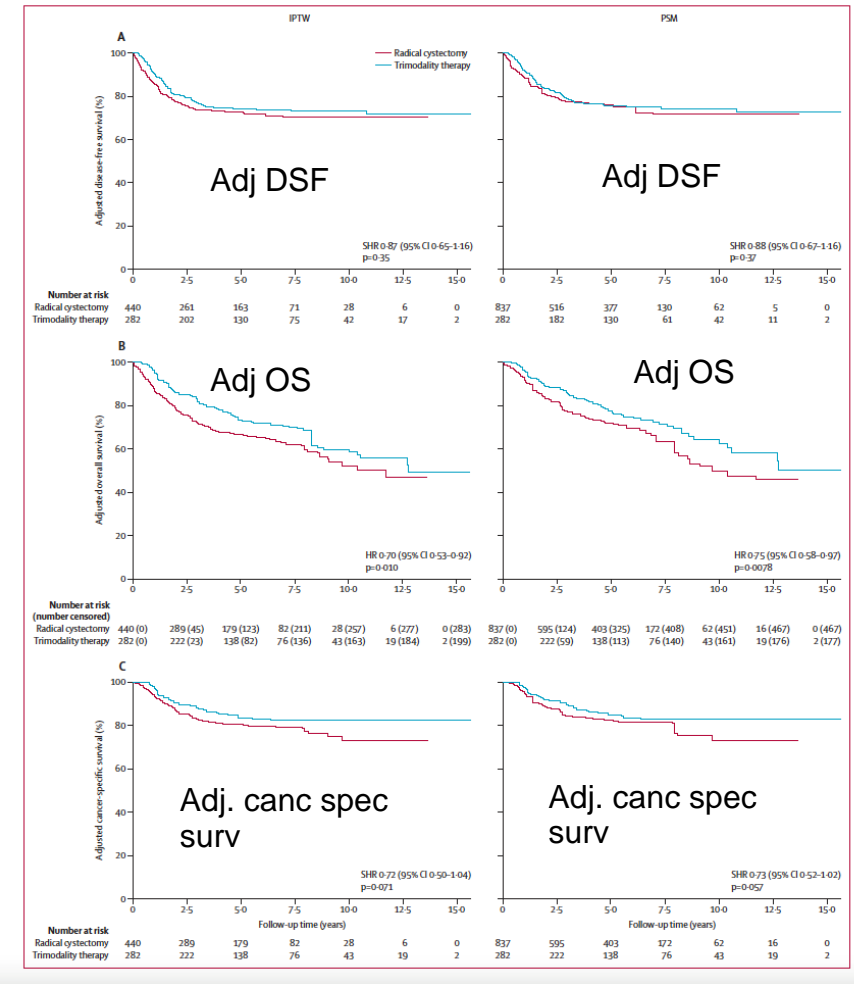
inverse probability treatment weighting (IPTW)

propensity score matching (PSM)



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# Chirurgisches Vorgehen versus Definitive Radio(chemo)

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Alexandre R Zlotoff\*, Leslie K Ballou, Andraz Nisnietkovic, Katherine L Lagoutz, Cynthia Kik, Gus Miranoff, Michael Drumis, Andrea Mori, Ednan Thio, Neil E Flehner, Girish S Kulkarni, Michael A Siewert, Robert G Brinnow, Charles Cottone, Alejandro Berlin, Srikala S Siddhu, Anne Schoenman, Adam S Feldman, Matthew Wozniak, Douglas M Dahl, Richard Lee, Philip J Saylor, M Dair Michaelson, David T Miyamoto, Anthony Zetterman, William Shipley, Peter Chung, Sumak Dameshmand, Jason A Efstathiou\*

Sensitivity analysis

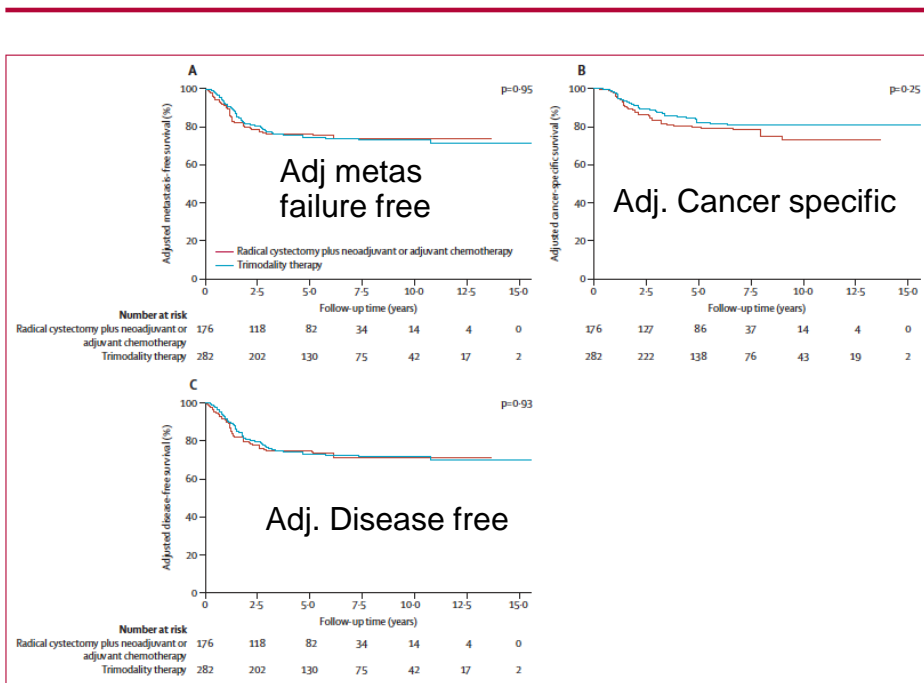


Figure 3: Sensitivity analysis—radical cystectomy plus neoadjuvant or adjuvant chemotherapy (176 patients) vs trimodality therapy (282 patients). All panels show inverse probability treatment weighting analyses. (A) Adjusted metastasis-free survival by treatment. Death without metastases was considered a competing risk. (B) Adjusted cancer-specific survival by treatment. Death due to other causes was a competing risk. (C) Adjusted disease-free survival by treatment. Death due to other causes was a competing risk.

Standortauflösung

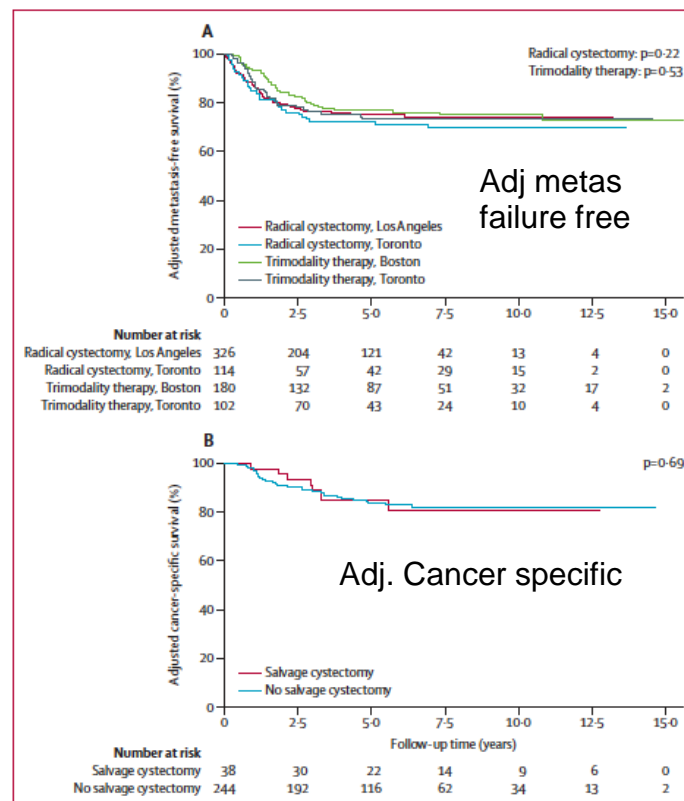


Figure 4: Adjusted metastasis-free survival by treatment group and centre, and cancer-specific survival in trimodality therapy patients by salvage cystectomy status. (A) Adjusted metastasis-free survival by treatment group and centre in the full unmatched cohort (n=722). Inverse probability treatment weighted metastasis-free survival was calculated by treatment group and centres in the full, unmatched cohort. Models used to derive the adjusted survival probabilities also incorporated centre. (B) Adjusted cancer-specific survival in patients who underwent trimodality therapy stratified by salvage cystectomy status (underwent n=38, did not undergo n=244).

Keine erkennbaren Unterschiede  
Aber Behandlung nur in Top Zentren



# Chirurgisches Vorgehen versus Definitive Radio(chemo)

Scientific Article

## Comparative Effectiveness of Radiation Versus Radical Cystectomy for Localized Muscle-Invasive Bladder Cancer



Yoshiyuki Yamamoto, MD, PhD,<sup>a,b</sup> Atsunari Kawashima, MD, PhD,<sup>a,c</sup> Toshitaka Morishima, MD, PhD,<sup>c</sup> Toshihiro Uemura, MD,<sup>a</sup> Akinaru Yamamoto, MD,<sup>a</sup> Gaku Yamamichi, MD,<sup>a</sup> Eisuke Tomiyama, MD,<sup>a</sup> Makoto Matsushita, MD, PhD,<sup>a</sup> Taigo Kato, MD, PhD,<sup>a</sup> Koji Hatano, MD, PhD,<sup>a</sup> Isao Miyashiro, MD, PhD,<sup>c</sup> and Norio Nonomura, MD, PhD<sup>a</sup>

<sup>a</sup>Department of Urology, Osaka University Graduate School of Medicine, Suita, Japan; <sup>b</sup>Department of Urology, Osaka International Cancer Institute, Osaka, Japan; and <sup>c</sup>Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan

Received 15 July 2022; accepted 19 December 2022

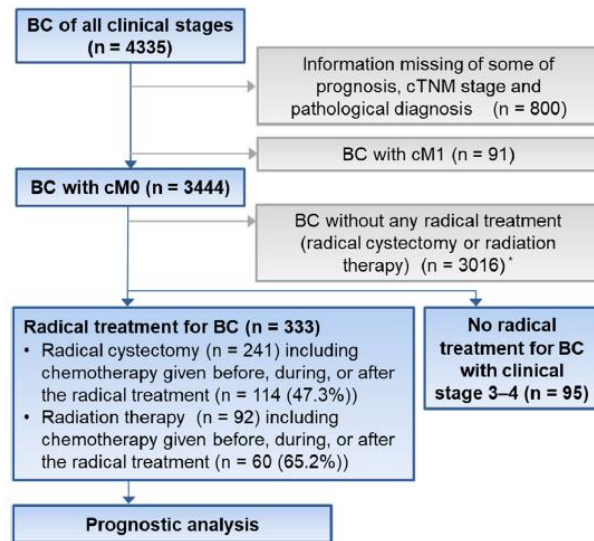


Table 1 Patient characteristics and outcomes

|   | Cystectomy (n = 241) |           | RT (n = 92) |           | P-value |
|---|----------------------|-----------|-------------|-----------|---------|
| Age, y, median, range                     | 71                   | 37-98     | 76.5        | 30-93     | <.001   |
| Sex                                       |                      |           |             |           |         |
| Male                                      | 186                  | 77.2%     | 64          | 69.6%     | .159    |
| Female                                    | 55                   | 22.8%     | 28          | 30.4%     |         |
| Charlson Comorbidity Index                |                      |           |             |           |         |
| 0   | 141                  | 58.5%     | 66          | 71.7%     | .064    |
| 1-2                                       | 77                   | 32.0%     | 18          | 19.6%     |         |
| >3  | 23                   | 9.5%      | 8           | 8.7%      |         |
| Unknown                                   | 0                    | 0.0%      | 0           | 0.0%      |         |
| Barthel index                             |                      |           |             |           |         |
| No disability                             | 209                  | 86.7%     | 70          | 76.1%     | <.001   |
| Moderate disability                       | 22                   | 9.1%      | 7           | 7.6%      |         |
| Severe disability                         | 8                    | 3.3%      | 14          | 15.2%     |         |
| Unknown                                   | 2                    | 0.8%      | 1           | 1.1%      |         |
| Pathology                                 |                      |           |             |           |         |
| UC  | 233                  | 96.7%     | 82          | 89.1%     | .012    |
| Non-UC                                    | 8                    | 3.3%      | 10          | 10.9%     |         |
| cT  |                      |           |             |           |         |
| <1  | 62                   | 25.7%     | 10          | 10.9%     | .003    |
| 2   | 95                   | 39.4%     | 34          | 37.0%     |         |
| >3  | 84                   | 34.9%     | 48          | 52.2%     |         |
| cN  |                      |           |             |           |         |
| 0   | 227                  | 94.2%     | 76          | 82.6%     | .004    |
| 1   | 9                    | 3.7%      | 11          | 12.0%     |         |
| 2-3                                       | 5                    | 2.1%      | 5           | 5.4%      |         |
| cM  |                      |           |             |           |         |
| 0   | 0                    | 0.0%      | 0           | 0.0%      |         |
| Clinical stage                            |                      |           |             |           |         |
| <1  | 62                   | 25.7%     | 10          | 10.9%     | .002    |
| 2   | 91                   | 37.8%     | 32          | 34.8%     |         |
| >3  | 88                   | 36.5%     | 50          | 54.3%     |         |
| Chemotherapy around the radical treatment |                      |           |             |           |         |
| Yes                                       | 114                  | 47.3%     | 60          | 65.2%     | .005    |
| No  | 127                  | 52.7%     | 32          | 34.8%     |         |
| Duration of observation, y, median, range | 3.29                 | 0.03-6.27 | 1.78        | 0.15-6.29 | .003    |
| Outcome                                   |                      |           |             |           |         |
| Alive                                     | 110                  | 45.6%     | 26          | 32.1%     |         |
| Dead                                      | 131                  | 54.4%     | 66          | 81.5%     |         |

Abbreviations: cM = clinical M stage; cN = clinical N stage; cT = clinical T stage; RT = radiation therapy; UC = urothelial carcinoma.



# Chirurgisches Vorgehen versus Definitive Radio(chemo)

Scientific Article

## Comparative Effectiveness of Radiation Versus Radical Cystectomy for Localized Muscle-Invasive Bladder Cancer



Yoshiyuki Yamamoto, MD, PhD,<sup>a,b</sup> Atsunari Kawashima, MD, PhD,<sup>a,\*</sup>  
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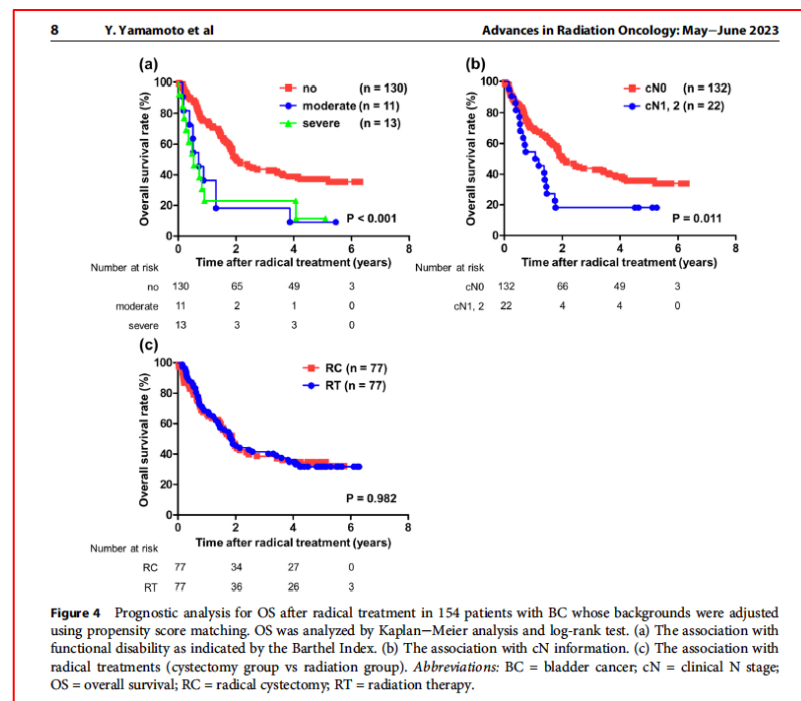
<sup>a</sup>Department of Urology, Osaka University Graduate School of Medicine, Suita, Japan; <sup>b</sup>Department of Urology, Osaka International Cancer Institute, Osaka, Japan; and <sup>c</sup>Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan

Received 15 July 2022; accepted 19 December 2022

**Table 2** Prognostic analysis of overall survival in all 333 patients with bladder cancer

| Characteristics                            | Univariate |              |         | Multivariate |              |         |
|--|------------|--------------|---------|--------------|--------------|---------|
|  | HR         | 95% CI       | P-value | HR           | 95% CI       | P-value |
| Age, range                                 | 16.239     | 5.589-48.453 | <.001   | 7.631        | 2.524-24.077 | <.001   |
| Sex, male vs female                        | 1.018      | 0.739-1.404  | .911    |              |              |         |
| Charlson Comorbidity Index, >1 vs 0        | 1.091      | 0.819-1.454  | .551    |              |              |         |
| Barthel index                              |            |              |         |              |              |         |
| Severe disability vs no                    | 3.787      | 2.364-6.066  | <.001   | 3.222        | 1.909-5.438  | <.001   |
| Moderate disability vs no                  | 2.037      | 1.313-3.162  | .002    | 1.809        | 1.141-2.868  | .012    |
| cT, >3 vs <2                               | 1.496      | 1.129-1.981  | .005    | 1.311        | 0.968-1.776  | .080    |
| cN, 1-3 vs 0                               | 2.427      | 1.590-3.704  | <.001   | 2.450        | 1.554-3.865  | <.001   |
| Pathology, UC vs non-UC                    | 1.999      | 1.180-3.387  | .010    | 2.132        | 1.213-3.748  | .009    |
| Radical treatment, radiation vs cystectomy | 1.645      | 1.223-2.214  | .001    | 1.048        | 0.748-1.469  | .784    |
| Chemotherapy around the radical treatment  | 1.081      | 0.817-1.431  | .587    |              |              |         |

Abbreviations: BC = bladder cancer; CI = confidence interval; cN = clinical N stage; cT = clinical T stage; HR = hazard ratio; UC = urothelial carcinoma.



Keine erkennbaren Unterschiede  
 Behandlung in 45 Zentren somit eher „real world“

# Chirurgisches Vorgehen versus Definitive Radio(chemo)

A systematic review and meta-analysis on outcomes after TMT and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer, Fahmy 2018)

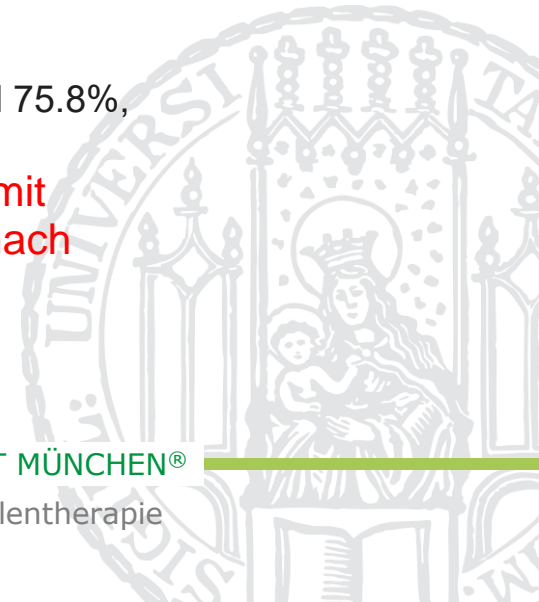
(57 Studien mit 30,293 Patienten - 10-Jahr OS DSS RFS wurden untersucht)

**Mean 10-Jahres OS 30.9% TMT und 35.1% RC ( $P = 0.32$ ).**

**Mean 10-Jahres DSS 50.9% TMT 57.8% RC ( $P = 0.26$ ).**

- NAC bei 13.3% mit TMT and 3.0% mit RC  $P < 0.001$
- CR 75.3% bei TMT. 5-Jahres OS, DSS, RFS nach CR 66.9%, 78.3%, and 52.5%
- Downstaging nach TURB oder NAC nach  $\leq pT1$  bei RC in 29.1%
- NAC erhöht pT0 Rate von 20.2% zu 34.3% ( $P = 0.007$ ) in cT2 und von 3.8% nach 23.9% ( $P < 0.001$ ) bei cT3–4.
- 5-Jahres OS, DSS, and RFS nach Downstaging ( $\leq pT1$ ) bei RC waren 75.7%, 88.3%, and 75.8%,

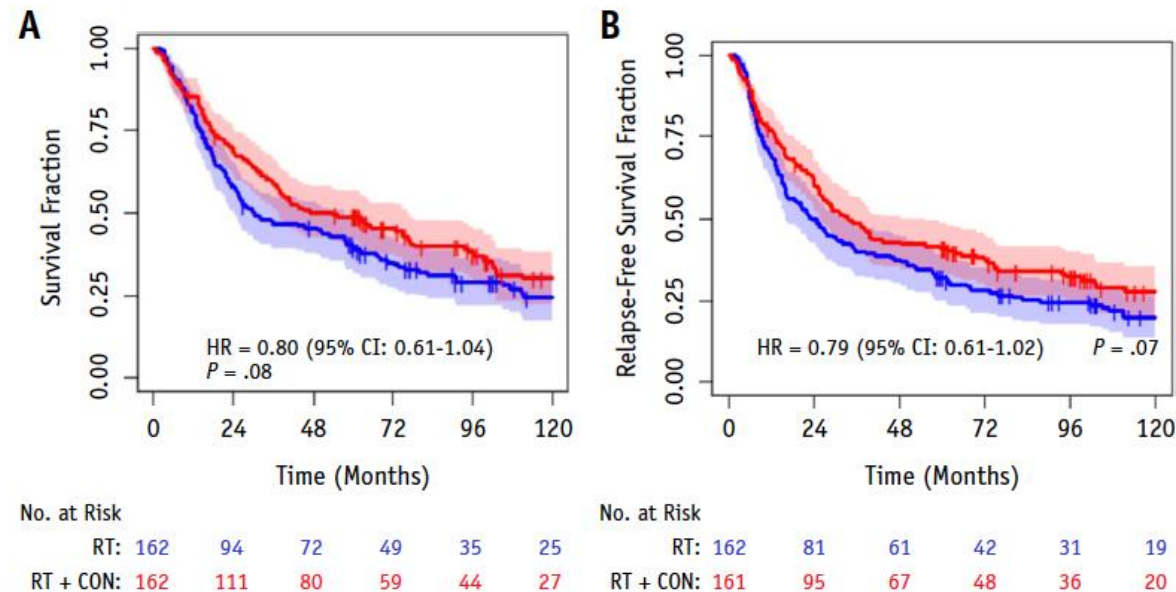
Überlebensendpunkte nach TMT oder RC für MIBC sind vergleichbar. Patienten mit Downstaging NAC und RC hatten verbessertes OS ggü. RC allein. Bestes OS nach TMT bei Patienten mit CR



# Komplexe Ansätze & Zukunft

Clinical Investigation

**Long-Term Outcomes of Radical Radiation Therapy with Hypoxia Modification with Biomarker Discovery for Stratification: 10-Year Update of the BCON (Bladder Carbogen Nicotinamide) Phase 3 Randomized Trial (ISRCTN45938399)**



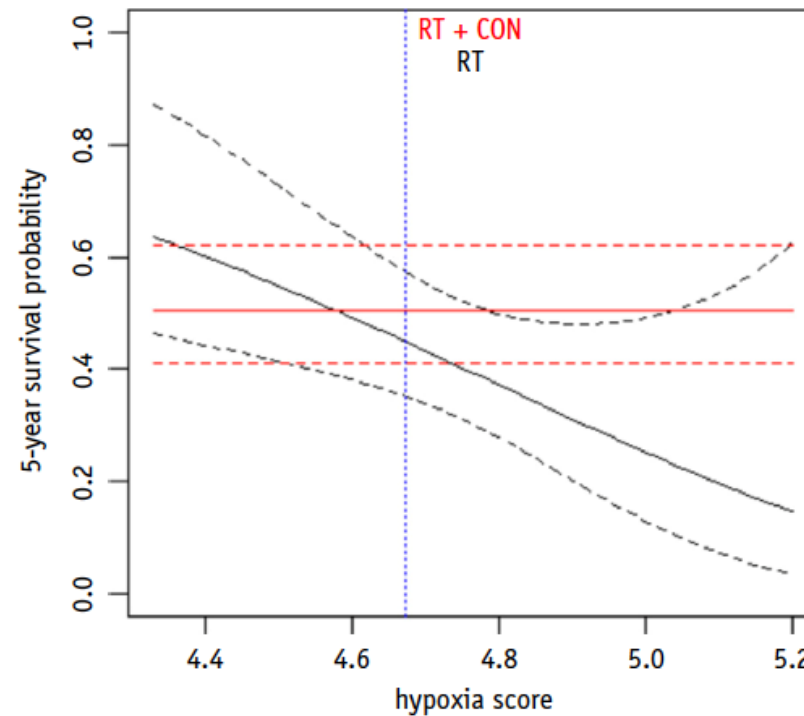
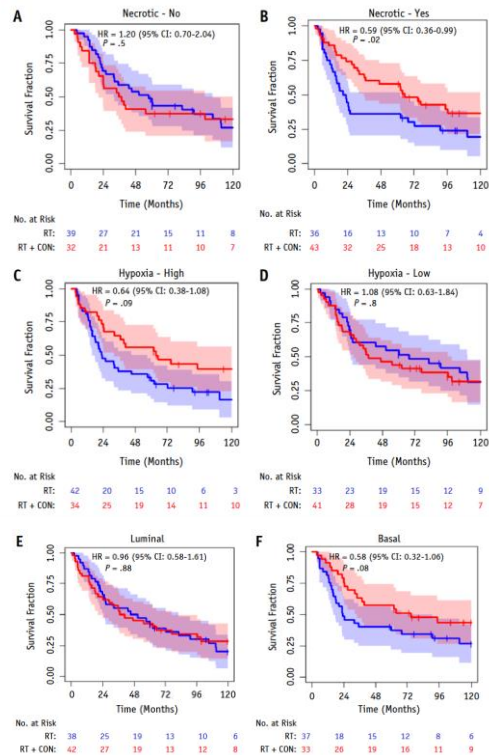
Keine sign. Unterschiede durch hypox. Sensitizer



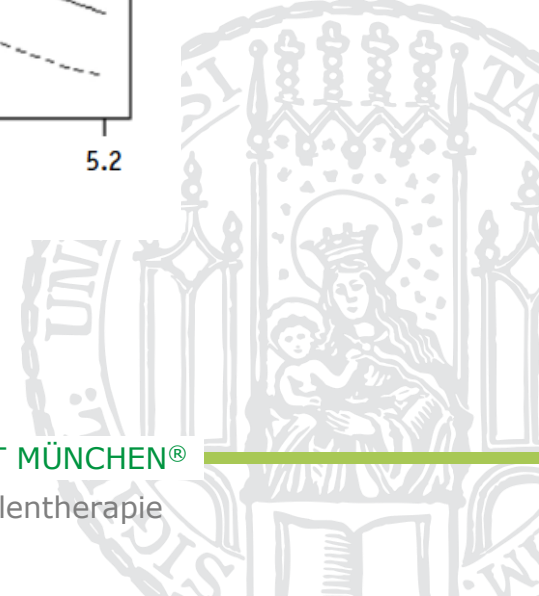
# Komplexe Ansätze & Zukunft

Clinical Investigation

## Long-Term Outcomes of Radical Radiation Therapy with Hypoxia Modification with Biomarker Discovery for Stratification: 10-Year Update of the BCON (Bladder Carbogen Nicotinamide) Phase 3 Randomized Trial (ISRCTN45938399)



Hinweise auf Unterschiede durch hypox. Sensitizer in spezifischen Gruppen





# Komplexe Ansätze & Zukunft

**Table 1**  
Some reported studies of bladder sparing treatment with immunotherapy.

| Authors   | Country       | Research type    | No. of patients | Stages          | Treatment protocol                           | Immunotherapy regimen                             | CR rate (%) | Prognostic data                                 | Adverse events (AE)                    |
|---|---------------|------------------|-----------------|-----------------|--|---|-------------|---|--|
| A.Weickhardt et al.(Weickhardt, 2020).                    | Australian    | Phase II trial   | 10              | T2-T4aNO-xM0    | TMT + pembrolizumab                          | Pembrolizumab*7 cycles                            | 90          |   | G3-4 non-urinary AE: 40%               |
| U.N.Vaishampayan et al.(Monika Joshi et al., 2021).       | United States | Phase II trial   | 17              | T2-T4aNO-1M0    | RT + nivolumab                               | Nivolumab for maximum 6 months                    | 42.86       |   | IRAE: 29.4%                            |
| Gautier Marcq et al.(Marcq, 2021).                        | Canada        | Phase Ib trial   | 8               | T2-T4aN0M0      | TMT+ atezolizumab                            | Atezolizumab *16 cycles                           | —           |   | G3 AE: 37.5%                           |
| Parminder Singh et al.(Singh, 2021).                      | United States | Phase III trial  | 37 vs. 36       | T2-T4aN0M0      | TMT + atezolizumab vs. TMT                   | Atezolizumab for 6 months                         | —           |   | G3-4 AE: 62.2% vs. 30.6%               |
| Monika Joshi et al.(Sergio Vazquez-Estevez et al., 2022). | United States | Phase II trial   | 26              | T2-4N0-2M0      | RT + durvalumab                              | Durvalumab for 1 year                             | —           | 1y-PFS: 73%,<br>1y-OS:83.8%,<br>DCR: 70%        | —                                      |
| Xavier Garcia del Muro et al.(Mariniello, 2020).          | Spain         | Phase II trial   | 32              | T2-4aN0M0       | RT+durvalumab+tremelimumab                   | Durvalumab+tremelimumab* 3 cycles                 | 81          | 6 m BIDFS: 76%,<br>6 m DFS: 80%,<br>6 m OS: 93% | G3-4 AE: 31%                           |
| Arjun Vasant Balar et al.(Balar, 2021).                   | United States | Phase II trial   | 54              | T2-T4aN0M0      | TMT+pembrolizumab                            | Pembrolizumab *3 cycles                           | 83          | 1y-BIDFS: 77%                                   | G3-4 AE: 35%                           |
| Galsky MD et al.(Shen, 2022).                             | United States | Phase II trial   | 76              | cT2-T4aN0M0     | Chemotherapy + nivolumab                     | Nivolumab *12 cycles                              | 48          | LRR: 25.8%                                      | —                                      |
| Yali Shen et al.(Niu, 2022).                              | China         | Real world study | 25 vs. 16       | cT2-4bN0-3M0-1a | Chemotherapy+PD-1 ICI vs. chemotherapy alone | Pembrolizumab, tislelizumab and toripalimab       | 50 vs. 0    | DCR: 95.5% vs. 66.7%.                           | G3-4 hematological AE: 15.9% vs. 6.4%. |
| Sumati Gupta et al.(Sumati Gupta et al., 2022).           | United States | Phase II trial   | 20              | T2-T4bN0-N + M0 | CRT + adjuvant nivolumab                     | Nivolumab within 90 days of completion of CRT     | —           | 6 m FFS: 88.2%,                                 | G3-4 AEs: 15%                          |
| Sergio Vazquez-Estevez et al.(Y. Nagumo et al., 2022).    | Spain         | Phase II trial   | 26              | T2-T4aN0M0      | RT + atezolizumab                            | Atezolizumab *6 cycles                            | 100         |   | AE: 91%,<br>SAE: 32%                   |
| Yuanjie Niu et al.(Necchi, 2018).                         | China         | Phase II trial   | 22              | T2-4aNxM0       | Nab-paclitaxel+ tislelizumab                 | Tislelizumab *3 cycles                            | 77.3        | 1y-RFS: 82%                                     | G3-4 AE: 13.6%                         |
| Ben-Maxde Ruitter et al.(de Ruitter, 2022).               | Netherlands   | Phase Ib trial   | 26              | T2-4aN0-1M0     | TMT+nivolumab± ipilimumab                    | Nivolumab *3cycles, nivolumab+ipilimumab*4 cycles | —           | 2y-MFS:90%,<br>2y-OS:90%,                       | G≥ 3 AE: 0-50%                         |
| A.Weickhardt et al.(A.J. Weickhardt et al., 2022).        | Australian    | Phase II trial   | 27              | T2 – T4aN0-xM0  | TMT + pembrolizumab                          | Pembrolizumab *7 cycles                           | 88          |   | G3-4 AE: 22.2%                         |
| Yoshiyuki Nagumo et al.(Muro, 2021).                      | Japan         | Phase II trial   | 45              | T1-3N0M0        | RT + atezolizumab                            | Atezolizumab *7 cycles                            | 84.4        |   | G3 AE: 13.3%                           |

# Komplexe Ansätze & Zukunft

## PLUMMB Trial:

The trial has been paused and the protocol will be amended to reduce radiation therapy dose per fraction. The authors advise caution to those combining radiation therapy and ICB

## Marcq Trial:

Concurrent administration of atezolizumab with concomitant hypofractionated XRT & GEM appears to be associated with unacceptable GI Tox



# Zusammenfassung

- Radiochemo ist besser als Radiatio allein
- Kein klarer Vorteil einzelner Substanzen
- Dosiskonzepte 55 in 20 Fx möglicherweise optimal
- Keine klaren Daten in mit Vorteil von Hyper-Fx Protokollen
- Rolle von Hypoxie bleibt offen
  - Einsatz von Hypoxie Sensitizern muss spezifisch erfolgen
- TMT vs. NAC plus OP wahrscheinlich vergleichbar
  - Dringendes Credo für systematisches Shared Decision Making
- Ansprechen auf TMT als „Biomarker“
- Kombination mit Checkpoint Inhib.verführerisch ABER cave Tox.
- Biomarker für „Radiosensität“ fehlen

