Adjuvant Clinical Trials

Surgical Considerations in Bladder Cancer

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Disclosures

Scientific Advisor for:

Cold Genesys
Heat Biologics
Telesta
Taris Biomedical
Photocure
Roche/Genentech
Fidia

Boston Scientific
Merk
Karl Storz
Urogen
Biocancell
Epivax Oncology
MDxHealth

Background

- Bladder cancer drug development has been stagnant for >30 yrs
- Imvigor210
  - Led to advanced approval of atezolizumab in metastatic bladder cancer
- Explosion of immunotherapy drugs
  - PD1, PDL-1, CTLA4, IDO1
- Immunotherapy moving into adjuvant space
  - Need to accrue for trials to be successful

Barriers to Adjuvant Trial Accrual

- IMvigor010
  - Objective
    - Phase 3 comparing Atezo vs. observation in high risk bladder cancer or upper-tract urothelial cancer
  - Outcome
    - Disease free survival
  - Exclusion
    - *Positive surgical margin*
  - Inclusion
    - *Node positive?*

Barriers to Adjuvant Trial Accrual

- CheckMate 274
  - Objective
    - Phase 3 comparing Nivolumab vs. placebo in high risk bladder cancer or upper-tract urothelial cancer
  - Outcome
    - Disease free survival
  - Exclusion
    - *Positive Surgical Margin*

Barriers to Adjuvant Trial Accrual

- Ambassador Trial - Alliance
  - Objective
    - Phase 3 comparing Pembro vs. observation in high risk bladder cancer or upper-tract urothelial cancer
  - Outcome
    - Disease free survival, Overall Survival
  - Exclusion
    - *Positive surgical margin*
  - Inclusion
    - *Resected Node positive*

Problems with Current Trial Design

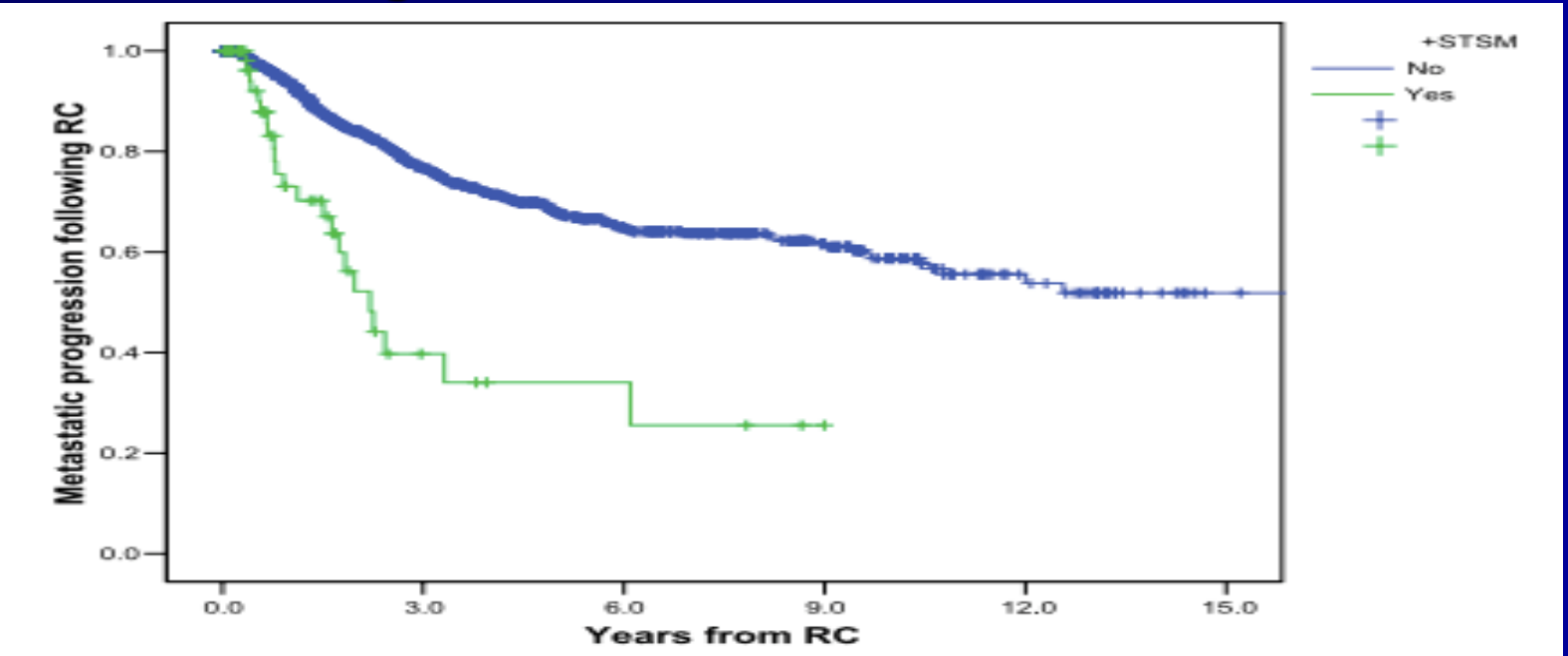
- Positive surgical margins are often not inadequate or poorly performed surgery
  - Reflect aggressive disease
  - Caveat is T2 tumors with positive surgical margins
- Patients with positive margins
  - Most to gain from adjuvant therapy

Positive Surgical Margins in Soft Tissue Following Radical Cystectomy for Bladder Cancer and Cancer Specific Survival

Zohar A. Dotan, Kathryn Kavanagh, Ofer Yossepowitch, Matt Kaag, Semra Olgac, Machele Donat and Harry W. Herr*

From the Departments of Urology (ZAD, KK, OY, MK, MD, HWH) and Pathology (SO), Memorial Sloan-Kettering Cancer Center, New York, New York

- 1589 patients RAC at MSKCC
  - 4.2% overall positive margin rate
  - 0% in T2 or less disease
  - 9% T3 or greater
- Positive margin associated worse DSS and mets

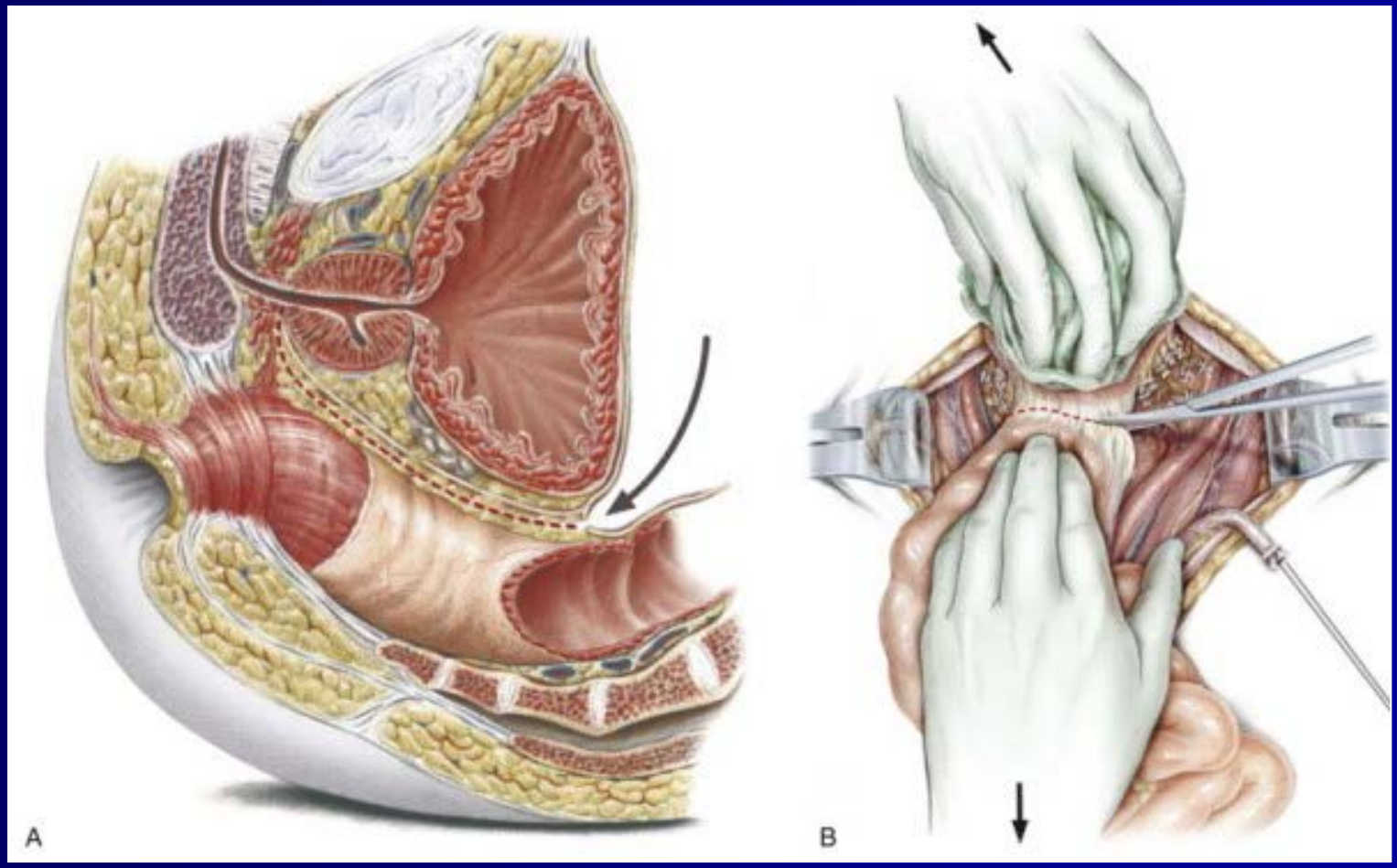


Impact of surgical margin status on the outcome of bladder cancer treated by radical cystectomy: a meta-analysis

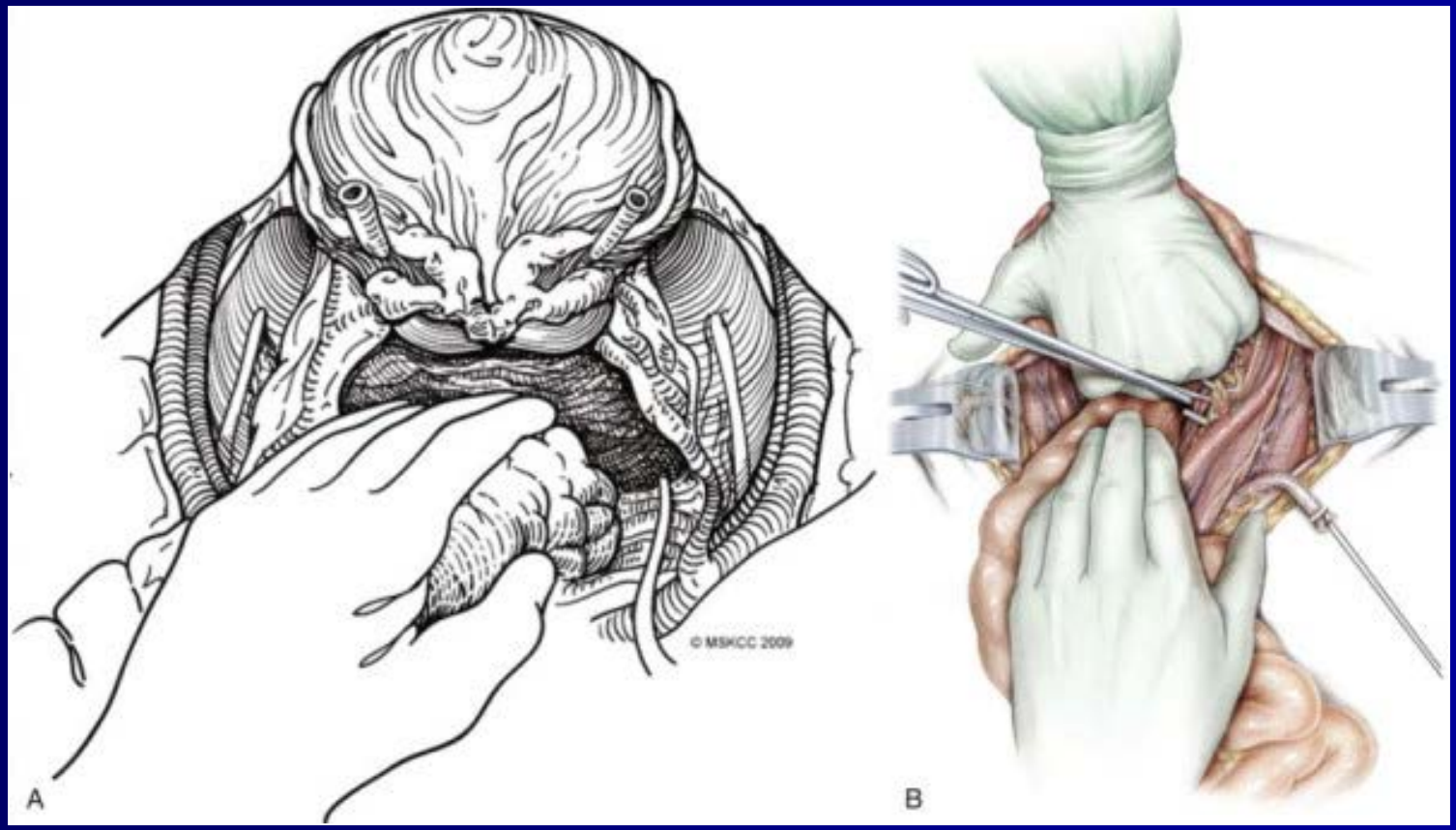
Xuwei Hong[1,*], Tieqiu Li[2,*], Fengsheng Ling[1,*], Dashan Yang[1], Lina Hou[3,*], Fei Li[1,*] and Wanlong Tan[1,*]

- Objective:
  - Determine impact of PSM in bladder cancer
- Meta-analysis
  - 36 articles
  - 38,384 patients
    - 4354 PSM
- Results (multivariable analysis)
  - Cancer Specific Survival (HR 1.82; 95% CI 1.6-2.0)
  - Overall Survival (HR 1.68; 95% CI 1.58-1.80)
- Conclusion
  - PSM associated with worse cancer specific and overall survival

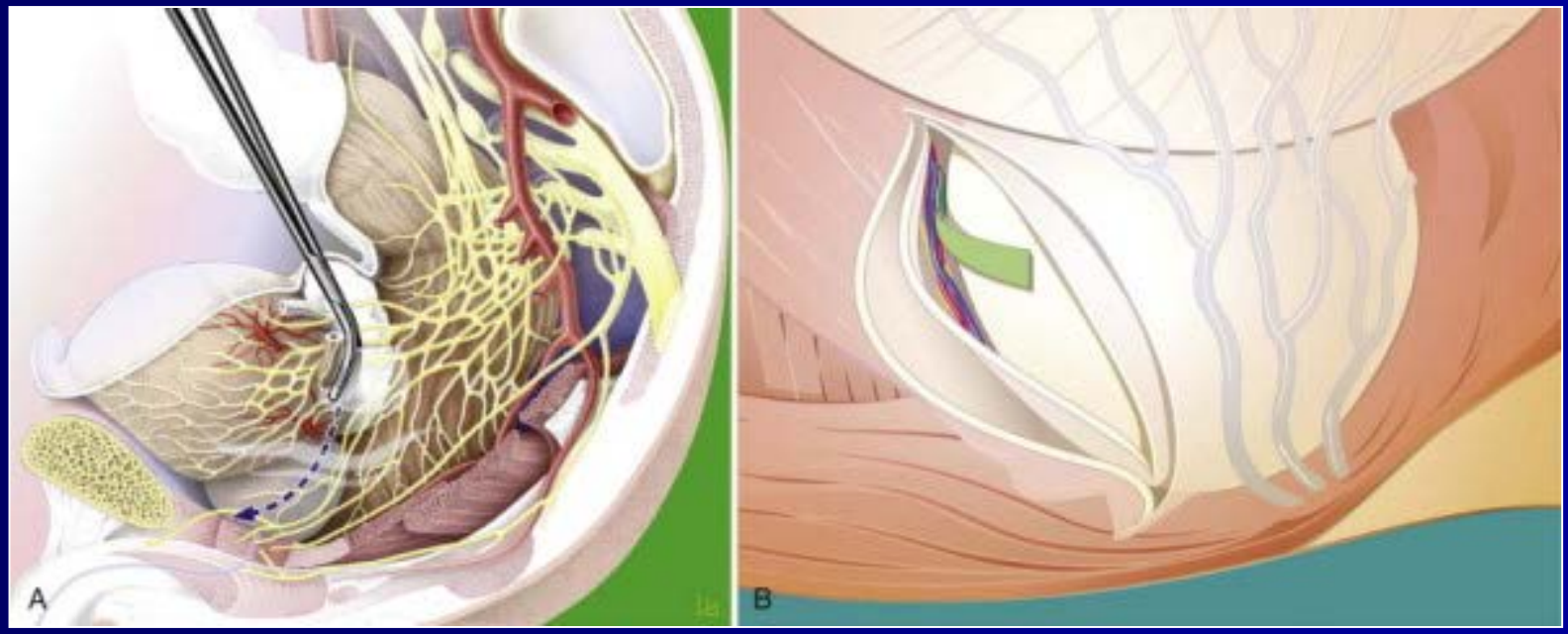
Radical Cystectomy



Radical Cystectomy

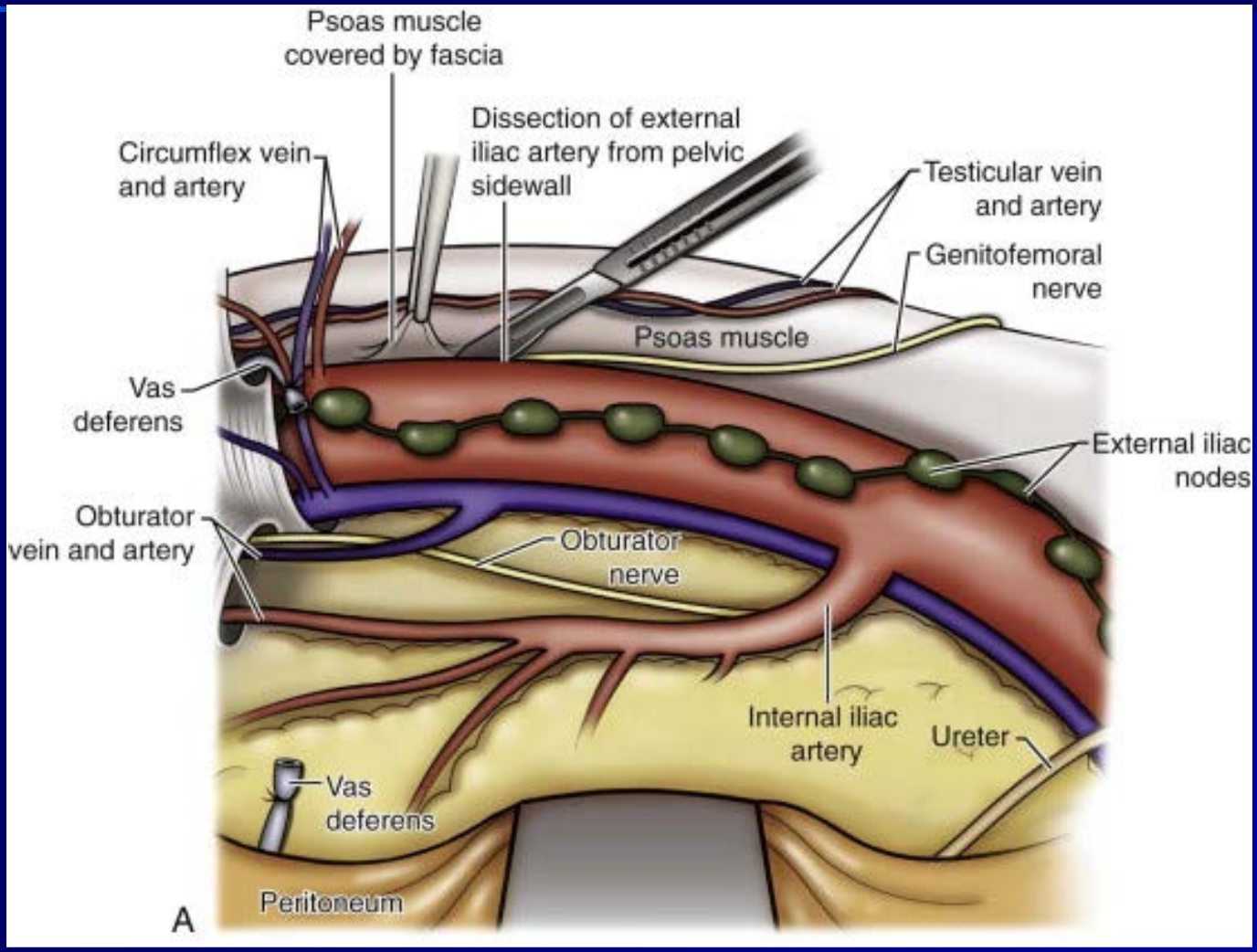


Radical Cystectomy



Separation of plane between prostatic capsule and neurovascular bundle

Adequate Lymph Node Dissection

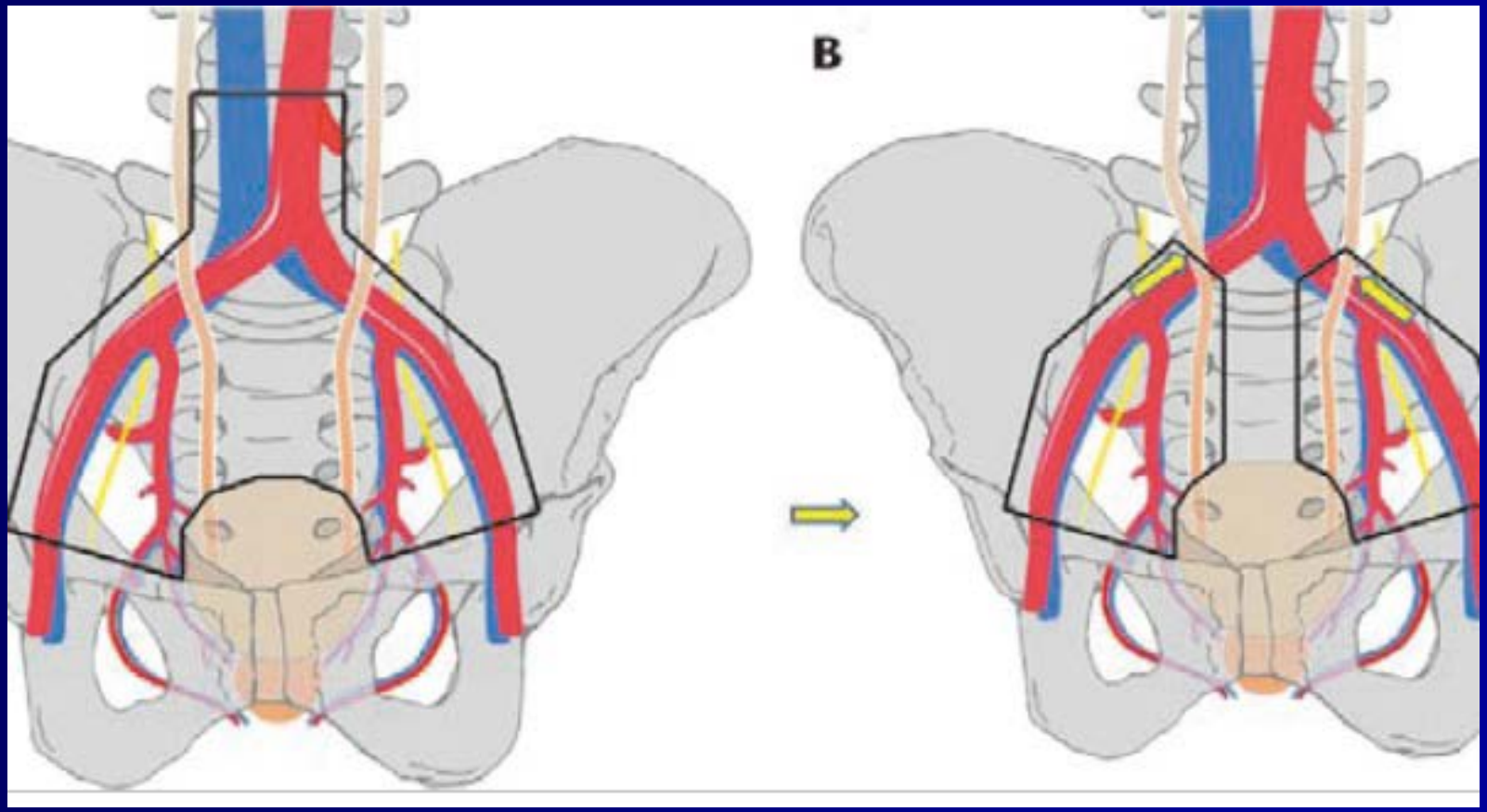


Adequate Lymph Node Dissection

- Classic Boundaries
  - Proximal: Midportion Common Iliacs
  - Lateral: Genitofemoral Nerve
  - Medial: Bladder wall
  - Distal: Circumflex Iliac Vein
  - Posterior: Hypogastric Vessels
    - Includes: Obturator Fossa, Pre-Sciatic and Presacral Lymph Nodes

Stein et al 2006 BJU 97:232

Pelvic LND Templates



Zhender et al 2011 J Urol 186

Extended Pelvic LND

Extended vs. Standard LND

- Preferred Template Unknown
  - No level 1 data
- Current RCTs
  1. SWOG S1011
     - Phase 3 comparing standard vs. extended LND
     - Primary Endpoint
       - Disease Free Survival
  2. German Association of Urologic Oncology
     - Phase 3 comparing standard vs. extended LND
     - Primary Endpoint
       - Recurrence Free Survival

Limited versus extended pelvic lymphadenectomy in patients with bladder cancer undergoing radical cystectomy: Survival results from a prospective randomized trial (LEA AUO AB 25/02).

- Extended (n=183)
  - Median LN 31 ($p<0.01$)
  - 5 yr RFS 67% ($p=0.64$)
- Standard (n=190)
  - Median LN 19
  - 5 yr RFS 61%
- T2 patients favors Extended (NAC pts excluded)
  - 5 yr RFS (62.5% vs. 85%), $P<0.01$
  - 5 yr OS (59.1 vs. 79.8%), $P<0.05$
- Conclusion
  - Failed to show statistically significant benefit
  - Benefit seen on post-hoc analysis
  - Results potentially limited by trial design

How many Lymph Nodes are Enough?

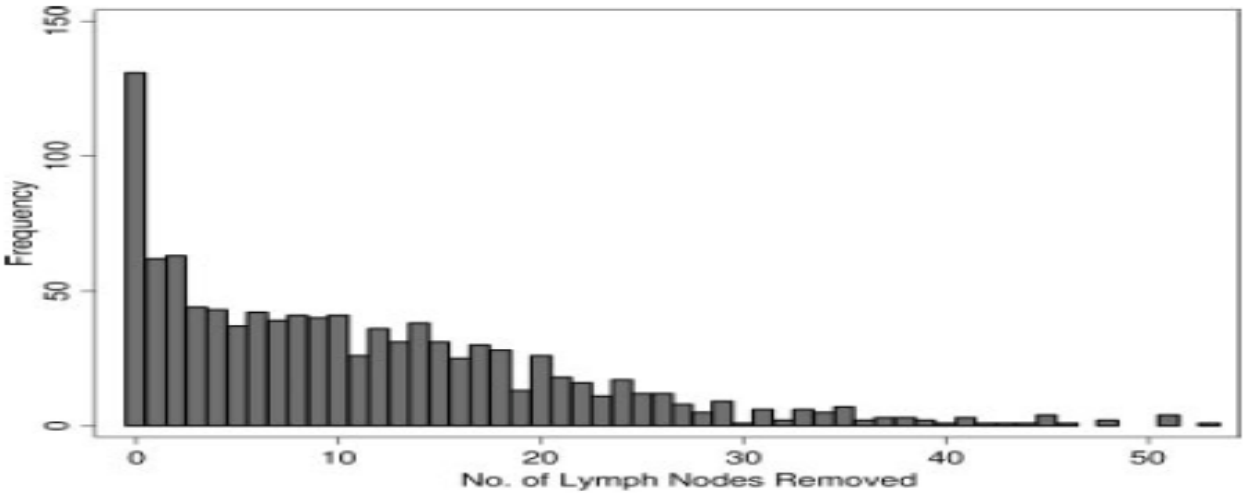


FIGURE 1. Histogram of the number of lymph nodes removed.

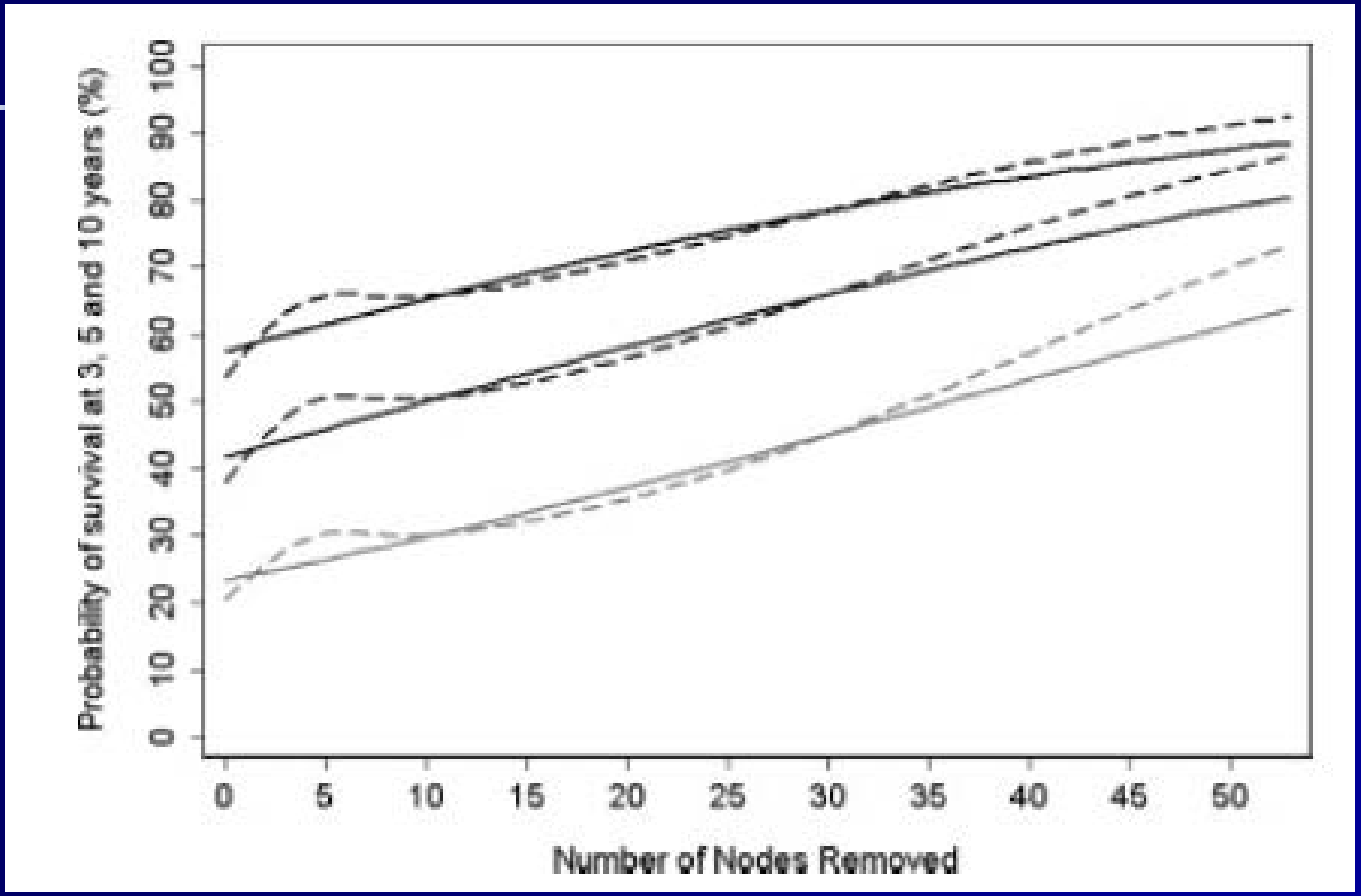
TABLE 2
Multivariable Regression Model for Overall Survival

Variable	Hazards ratio	95% CI	*P*
Lymph nodes removed (per lymph node)	0.973	0.960–0.986	<.0005
Stage pT2 or above	2.305	2.04–2.57	<.0005
ASA classification 3 or 4	1.513	1.28–1.74	<.0005
Age per year	1.012	1.001–1.024	.034

95% CI indicates 95% confidence interval; ASA, American Society of Anesthesiologists' patient classifications.

Koppie et al 2006 Cancer 2006

How many Lymph Nodes are Enough?



Koppie et al 2006 Cancer 2006

Impact of RC on Timing of Adjuvant Chemotherapy

Potential Impact of Postoperative Early Complications on the Timing of Adjuvant Chemotherapy in Patients Undergoing Radical Cystectomy: A High-Volume Tertiary Cancer Center Experience

S. Machele Donat[a,*], Ahmad Shabsigh[a], Caroline Savage[a], Angel M. Cronin[c], Bernard H. Bochner[a], Guido Dalbagni[a], Harry W. Herr[a], Matthew I. Milowsky[b]

Impact of RC on Timing of Adjuvant Chemotherapy

- Background
  - Adjuvant chemotherapy best given between 6-12 weeks
- Objective
  - Impact of complications on the timing of adjuvant chemotherapy
- Study Design
  - Retrospectively evaluated 1142 RC patients
  - All RC performed by high volume surgeons
  - Assessed 90 D complications
- Conclusion
  - 30% of patients had Clavien Grade 2-5 complications in 6-12 week range
  - These patients would have delay or possible inability to receive therapy

Urinary Diversion Impact

- Barriers for Adjuvant Chemotherapy
  - Renal function
  - Metabolized by kidneys
- Immunotherapy
  - More patients may be eligible for adjuvant therapy because less complications
  - Not metabolized by kidneys

Surgery is Synergistic with Immunotherapy?

- Hypothesis
  - Surgery causes cell injury and cell death releases tumor neoantigens
  - Innate and Adaptive T-cell Response
  - Induction of Tumor PDL-1
  - Check Point Inhibitor Therapy
  - ? Abscopal Effect

Conclusions

- Positive Surgical Margins in locally advanced tumors should not preclude enrollment in adjuvant trials
- High quality RC and standardized pelvic LND need to be further refined
- Immunotherapy is likely to be better tolerated in adjuvant setting than chemotherapy