Enhanced Recovery After Surgery

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Enhanced recovery after surgery

- **Goal of modern ERAS:**
  - Make a positive impact from diagnosis, through surgery, to return of normal function
  - Not exclusively dependent on one measure

- **Full ERAS adoption**
  - Reduces complications by up to 50%
  - Decreases length of stay by 30%
  - Decreases readmissions
  - Reduces cost

ERAS is a pathway

• No single intervention is adequate

• Includes components of
  • Pre-operative
  • Intra-operative
  • Post-operative
  • Post-discharge

• Requires ‘buy-in’ from patients, surgeons, anesthesiologists, and nursing

• Requires education and monitoring
ERAS is a pathway

- ERAS as a continuum of care
- Encourage engagement with stakeholders
ERAS is a not just a pathway but also a process

- Requires analysis and data tracking
- Patient care dashboards
- Continuous improvement
Enhanced recovery after cystectomy

• Pre-operative
  • Patient counseling, expectations, education
  • Preadmission nutritional support
    • Treatment of hypoalbuminemia and anemia
    • SIM (specialized immunonutrition)
    • Improvements in 2 weeks
  • Plan for post-discharge care
Enhanced recovery after cystectomy

- **Pre-operative**
  - Carbohydrate-rich fluid intake
    - Specialized formulas or sports drinks
  - Avoid mechanical and antibiotic bowel preparation
  - Smoking cessation
  - Exercise
Nutritional deficiency = preoperative albumin < 3.5, BMI < 18.5, weight loss > 5% body weight

90-day mortality 16.5% vs 5.1% (p<0.01)
Sarcopenia in Patients With Bladder Cancer Undergoing Radical Cystectomy

Impact on Cancer-Specific and All-Cause Mortality

Sarah P. Psutka, MD; Alonso Carrasco, MD; Grant D. Schmit, MD; Michael R. Moynagh, MD; Stephen A. Boorjian, MD; Igor Frank, MD; Suzanne B. Stewart, MD; Prabin Thapa, MS; Robert F. Tarrell, MS; John C. Cheville, MD; and Matthew K. Tollefson, MD

- Sarcopenia = skeletal muscle wasting
- Assess skeletal muscle index at level of L3
  - Quantify using imaging software from CT scan
SARCOPENIA AND OUTCOMES AFTER RC

- Associated with increased risks of cancer death and all-cause mortality on multivariate analysis
  - Noted as early as 90-day ACM (7.8% vs 1.6%)

Psutka SP et al, Cancer 2014
WHAT CAN BE DONE PREOPERATIVELY TO “OPTIMIZE” PATIENTS FOR RC? PREHABILITATION

Optimizing a frail elderly patient for radical cystectomy with a prehabilitation program

- Exercise program prior to surgery
- Patients provided with specialized immunonutrition (arginine, fish oil, vit A, and nucleotides) prior to surgery
  - 33% decreased risk of complications
  - 39% decreased risk of infection
Enhanced recovery after cystectomy

- **Intra-operative**
  - Minimization of intraoperative fluids
    - Vasopressors instead
  - Minimally invasive approach
    - RARC with intracorporeal diversion
  - Limited narcotics for pain control
    - Regional anesthesia
    - Improved local anesthesia
  - Efficient operation
    - Target operative time less than 4 hours
    - Reduce need for transfusion

Wuethrich et al. Eur Urol 2014
Parekh et al. AUA 2017
BLOOD TRANSFUSION AT RC

- Given in up to 60% of cases
- Costly
  - Each unit $1500-$2000 at Mayo
- Risk of transfusion reaction
- Risk of infectious transmission
- Adverse cancer consequences?

Shabsigh et al, Eur Urol 2009
Linder et al, Eur Urol 2013
The Impact of Perioperative Blood Transfusion on Cancer Recurrence and Survival Following Radical Cystectomy

Brian J. Linder, Igor Frank, John C. Cheville, Matthew K. Tollefson, R. Houston Thompson, Robert F. Tarrell, Prabin Thapa, Stephen A. Boorjian

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tumor recurrence</th>
<th></th>
<th></th>
<th>Death from bladder cancer</th>
<th></th>
<th>All-cause mortality</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p value</td>
<td>HR</td>
<td>95% CI</td>
<td>p value</td>
<td>HR</td>
</tr>
<tr>
<td>Age at surgery</td>
<td>1.00</td>
<td>0.99–1.01</td>
<td>0.87</td>
<td>1.01</td>
<td>1.00–1.01</td>
<td>0.20</td>
<td>1.03</td>
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<tr>
<td>Gender (ref. female)</td>
<td>1.19</td>
<td>0.98–1.45</td>
<td>0.08</td>
<td>1.22</td>
<td>1.01–1.47</td>
<td>0.04</td>
<td>1.33</td>
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<tr>
<td>Body mass index</td>
<td>0.96</td>
<td>0.88–1.05</td>
<td>0.34</td>
<td>0.97</td>
<td>0.88–1.06</td>
<td>0.44</td>
<td>1.02</td>
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<td>ECOG performance status</td>
<td>1.06</td>
<td>0.93–1.20</td>
<td>0.37</td>
<td>1.28</td>
<td>1.15–1.44</td>
<td>&lt;0.0001</td>
<td>1.40</td>
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<tr>
<td>Preoperative hemoglobin level</td>
<td>0.96</td>
<td>0.92–1.01</td>
<td>0.12</td>
<td>0.90</td>
<td>0.86–0.94</td>
<td>&lt;0.0001</td>
<td>0.89</td>
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<tr>
<td>Receipt of PBT</td>
<td>1.20</td>
<td>1.01–1.42</td>
<td>0.04</td>
<td>1.31</td>
<td>1.10–1.57</td>
<td>0.003</td>
<td>1.27</td>
</tr>
<tr>
<td>Pathologic tumor stage</td>
<td>2.16</td>
<td>1.84–2.54</td>
<td>&lt;0.0001</td>
<td>3.04</td>
<td>2.55–3.62</td>
<td>&lt;0.0001</td>
<td>1.83</td>
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<tr>
<td>(pT2–4 compared with ≤pT1)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>pN+</td>
<td>1.91</td>
<td>1.54–2.37</td>
<td>&lt;0.0001</td>
<td>1.78</td>
<td>1.45–2.18</td>
<td>&lt;0.0001</td>
<td>1.68</td>
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<tr>
<td>Total no. nodes removed</td>
<td>0.98</td>
<td>0.97–0.99</td>
<td>0.0005</td>
<td>0.99</td>
<td>0.98–0.99</td>
<td>0.002</td>
<td>0.99</td>
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<tr>
<td>Positive radial margin</td>
<td>0.97</td>
<td>0.86–1.08</td>
<td>0.53</td>
<td>1.00</td>
<td>0.98–1.02</td>
<td>0.65</td>
<td>1.00</td>
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<tr>
<td>Receipt of perioperative chemotherapy</td>
<td>1.03</td>
<td>0.82–1.29</td>
<td>0.82</td>
<td>1.31</td>
<td>1.06–1.62</td>
<td>0.01</td>
<td>1.07</td>
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<tr>
<td>Year of cystectomy</td>
<td>1.00</td>
<td>0.99–1.01</td>
<td>0.77</td>
<td>1.00</td>
<td>0.99–1.02</td>
<td>0.59</td>
<td>1.00</td>
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<tr>
<td>Early complication</td>
<td>1.05</td>
<td>0.90–1.23</td>
<td>0.51</td>
<td>1.04</td>
<td>0.88–1.21</td>
<td>0.66</td>
<td>1.09</td>
</tr>
</tbody>
</table>

Each unit transfused → 7% increased risk of death from bladder cancer
SOLUTIONS TO PROBLEM OF BLOOD TRANSFUSION AT RC?

• More restrictive threshold Hb for transfusion
  • Non-inferior to liberal transfusion strategy among patients undergoing cardiac surgery
    
  *Mazer CD et al, N Engl J Med 2018*

• Identify at-risk patients/pre-operative iron supplementation

• Robotic cystectomy

• Tranexamic Acid
TRANEXAMIC ACID

• Lysine analog
• Given as IV infusion during surgery
• Prevents clot breakdown
• No demonstrated increased risk of thromboembolic events
• Shown to reduce need for transfusion in cardiac and orthopedic surgeries
  • 21% reduction in transfusion for RRP
  Crescenti et al, BMJ 2011
• Cost-effective ($60-80/case at Mayo)
• N=103 – open RC patient treated with tranexamic acid (TXA) as intraoperative infusion

• Matched 1:2 to (historic control) patients who did not receive TXA during RC, based on:
  • Age
  • Preoperative Hb
  • Receipt of NAC
  • Pathologic T and N stage
DECREASED RATE OF BLOOD TRANSFUSION WITH TXA

Table 2. Receipt of PBT stratified by preoperative hemoglobin: (A) Overall cohort; (B) Baseline anemia; (C) Normal baseline hemoglobin. Furthermore, timing of PBT for the 115 control and 32 TA-treated patients who received a PBT with RC is depicted in (D)

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 200)</th>
<th>Received TA (n = 103)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Overall PBT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PBT</td>
<td>19 (42.5%)</td>
<td>71 (68.9%)</td>
<td>.0001</td>
</tr>
<tr>
<td>+PBT</td>
<td>115 (57.5%)</td>
<td>32 (31.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>(B) PBT with preoperative Hgb &lt;13.5 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PBT</td>
<td>19 (20.7%)</td>
<td>26 (51.0%)</td>
<td>.0012</td>
</tr>
<tr>
<td>+PBT</td>
<td>73 (79.3%)</td>
<td>25 (49.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>(C) PBT with preoperative Hgb ≥13.5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PBT</td>
<td>66 (61.1%)</td>
<td>45 (86.5%)</td>
<td>.003</td>
</tr>
<tr>
<td>+PBT</td>
<td>42 (38.9%)</td>
<td>7 (13.5%)</td>
<td></td>
</tr>
</tbody>
</table>

DECREASED TRANSFUSION RISK, REGARDLESS OF PREOPERATIVE Hb

Zaid HB et al, Urology 2016
IS TXA SAFE?

• No adverse events attributable to TXA usage
  • In particular:
    • No increased risk of DVT/PE within 30 days of RC (p=0.52)

• Caveat = do not use if:
  • Preoperative history of DVT/PE
  • History of cardiac stenting

Zaid HB et al, Urology 2016
## COMPARATIVE COST ANALYSIS OF TXA

### Table 4. Comparative institutional cost data of tranexamic acid and red blood cell transfusion

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cost†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tranexamic acid</strong></td>
<td></td>
</tr>
<tr>
<td>Bolus and 5 hour infusion for a 70 kg patient with normal renal function</td>
<td>$40</td>
</tr>
<tr>
<td>Pharmacy handling or overhead</td>
<td>$227</td>
</tr>
<tr>
<td><strong>Total</strong> (Tranexamic acid)</td>
<td>$267</td>
</tr>
<tr>
<td><strong>Red blood cell transfusion</strong></td>
<td></td>
</tr>
<tr>
<td>Direct cost of 1 unit</td>
<td>$270</td>
</tr>
<tr>
<td>Overhead cost of 1 unit</td>
<td>$1034</td>
</tr>
<tr>
<td>Compatibility testing</td>
<td>$125</td>
</tr>
<tr>
<td>Administration cost</td>
<td>$109</td>
</tr>
<tr>
<td><strong>Total</strong> (Red blood cell transfusion)</td>
<td>$1538</td>
</tr>
</tbody>
</table>

* Administered as a 10 mg/kg bolus, then 2 mg/kg/hour maintenance infusion for normal renal function.
† All costs rounded down to nearest dollar.
Enhanced recovery after cystectomy

• **Post-operative**
  - No post-operative nasogastric tube
  - Early feeding (gastro-colic reflex)
    - POD 1 – clear liquids
    - POD 2 – general diet
    - Chewing gum/hard candy throughout
  - Alvimopan
  - Aggressive ambulation
    - 6-8 times daily
  - VTE thromboprophylaxis (30 days)
The Question of Alvimopan

Alvimopan Accelerates Gastrointestinal Recovery After Radical Cystectomy: A Multicenter Randomized Placebo-Controlled Trial


- μ-opioid receptor antagonist
- Among 277 patients randomized to alvimopan vs. placebo
  - Time to GI recovery (5.5 vs. 6.8 days, p<0.0001)
  - Ileus related morbidity (8.4% vs. 29.1%, p<0.001)
  - Length of stay (7.4 vs. 10.1 days, p=0.0051)
Alvimopan Points

• Needs to be started before surgery
  • 12 mg BID
  • Not effective once patients develop ileus

• Should not be used beyond 7 days post-op

• Unclear if there is a cost advantage
  • Bowel-related costs vs. overall costs

• Alone does not equal ERAS
  • Neither 10.1 nor 7.4 day hospitalization is in accord with modern paradigms

Kauf et al. J Urol 2014
Enhanced recovery after cystectomy

- **Post-discharge**
  - Continue VTE prophylaxis 30 days
  - Maintain hydration
  - **Keep in contact**
    - Intervene if not progressing
    - Evaluate for readmission rate
    - ET nurse visit
  - Audit compliance
    - Understand variance
    - Evaluate new techniques
    - Ensure ‘buy-in’ from whole team
INSTITUTIONAL PRACTICE CHANGES TO EXTENDED DURATION PROPHYLAXIS

Extended duration enoxaparin decreases the rate of venous thromboembolic events after radical cystectomy compared to inpatient only subcutaneous heparin.

- Extended duration prophylaxis decreased 90-day rate of VTE: 12% → 5% (p=0.024)
- No increase in transfusions
- Extended outpatient chemoprophylaxis reduces venous thromboembolism after radical cystectomy

Multivariable analysis for 90 day DVT: Extended prophylaxis
- HR 0.22 (95% CI 0.06-0.89) p=0.03
- No increase in hemorrhage

Table 3. Multivariate logistic regression of risk factors for VTE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin (ref: heparin)</td>
<td>0.33</td>
<td>0.14–0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>Female (ref: male)</td>
<td>1.10</td>
<td>0.51–2.39</td>
<td>0.802</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>0.66</td>
<td>0.22–1.97</td>
<td>0.453</td>
</tr>
<tr>
<td>CCI (per unit increase)</td>
<td>1.13</td>
<td>0.94–1.37</td>
<td>0.201</td>
</tr>
</tbody>
</table>

J Urol 2017

Urol Oncol 2018
ERAS: Current State

• ERAS is evidenced-based
  • Plethora of data in the literature
  • Within urology, cystectomy is best studied
  • Need for ongoing evaluation, especially of individual features

• Compliance with ERAS associated with:
  • Shorter hospitalization
  • Improved bowel recovery
  • Earlier return to normal activity
  • Similar rate of re-admission
  • Fewer complications
    • Rate of complications inversely associated with compliance with pathway
Barriers to ERAS Implementation

• Majority of RC is performed at low-volume centers
  • Slower adaption of protocols

• Different provider and health care incentives

• Patient perception
  • Not being ‘kicked to the curb’
  • Need for ongoing engagement

• Need better evaluation of total costs of care
  • ERAS requires resources
  • Post-discharge requirements beyond readmission
Conclusions

• ERAS represents a continuum of evidence-based care improvements

• Recovery after major surgical procedures can be improved with ERAS pathways
  • Pathways are multifactorial in scope
  • Focus on safe recovery, not just length of stay
  • Require engagement from patients, surgeons, anesthesia and nursing

• Standardized pathways and consistent evaluation of outcomes should be encouraged
Thank you!

Email: frank.igor@mayo.edu

https://youtu.be/AkX2ipPFipM