THE INTERNATIONAL CONFERENCE PROGRESS IN URO-ONCOLOGY

5th Edition

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Neoadjuvant chemotherapy for bladder cancer:

fighting between evidence 1 level and real life.

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Introduction

- Radical cystectomy(RC)+ pelvic lymphadenectomy(LAD): gold standard.

- 5-yrs survival rate depends on T and N stage:
  - -52-77% for organ confined node negative (cT2N0M0)
  - -40-50% extravescical extension of primary (cT3-4)
  - -15-35% node positive disease (anyT)

- 50% develop distant metastasis within 2 yrs

- BC is the most expensive diagnosis for lifetime among all cancer

Improve outcomes!

improve surgical techniques

perioperative sistemic therapy

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Advantages of NAC

- Evaluate response to chemotherapy upfront.
- Better tolerance pre surgery.
- Downstaging local tumor for better resectability
- Early targeting of micrometastasis
- Make possible preoperative pCR
- Improve survival.

Disadvantages of NAC

- Potential disease progression in chemo resistant.
- Overtreat pts upstaged
- Delay surgery for toxicity.
- Possible increase in post surgical complications

ABC Meta-analysis Collaboration:

update on 11 trials, 3005 pts

HR 0.86; 14% risk death. Absolute Surv benefit 5%; 50% 5yrs

Table 1. List of neoadjuvant chemotherapy trials included in the 2005 ABC meta-analysis

Author/year	No. patients	Stage	NC regimen	Definitive treatment	OS benefit
Wallace/1991[29]	159	T2-4NXM0	Cisplatin 100 mg/m²	45-50 Gy in 22F	No
Raghavan/1991[30]	96	T2-4NXM0	Cisplatin 70 mg/m²	65 Gy in 22F + RC + pelvic lymphadenectomy	No
Martinez-Pineiro/1995[31]	122	T2-4ANX-2M0	Cisplatin 100 mg/m²	RC + pelvic lymphadenectomy	No
Malmstrom/1996[32]	325	T1 (grade3) T2-4A NXM0	Cisplatin 70 mg/m² Doxorubicin 30 mg/m²	20 Gy in 5F + RC + pelvic lymphadenectomy	Yes for T3-T4 (p=0.03)
Abol-Enein/1997[33]	196	T2-4ANXM0	Carboplatin 300 mg/m² Methotrexate 50 mg/m² Vinblastine 4 mg/m²	RC + pelvic lymphadenectomy	Not reported
Bassi/1999[34]	206	T2-4N0M0	Cisplatin 70 mg/m² Methotrexate 30 mg/m² Vinblastine 3 mg/m²	RC + pelvic lymphadenectomy	Not reported
International Collaboration/1999,[7] updated 2011[8]	976	T2 (grade 3) T3-T4A NO,NXM0	Cisplatin 100 mg/m² Vinblastine 4 mg/m² Methotrexate 30 mg/m²	60 Gy in 30F (or) 20 Gy in 5F + RC (or) RC and pelvic lymphadenectomy	Yes on 2011 update (p=0.037)
Sherif/2002[35]	317	T2-4ANXM0	Cisplatin 100 mg/m² Methotrexate 250 mg/m²	RC + pelvic lymphadenectomy	No
Sengelov/2002[36]	153	T2-T4b N0NX M0	Cisplatin 100 mg/m² Methotrexate 250 mg/m²	60 Gy in 30F (or) RC	No (p=0.76)
Cortesi/unpublished	171	T2-4N0M0	Cisplatin 70 mg/m² Methotrexate 30 mg/m² Vinblastine 3 mg/m² Epirubicin 40 mg/m²	RC	Not reported
Grossman/2003[9]	317	T2-T4A NXM0	Methotrexate 30 mg/m² Vinblastine 3 mg/m² Doxorubicin 30 mg/m² Cisplatin 70 mg/m²	RC	No (p=0.06)

Eur Urol. 2005 Aug;48(2):202-5

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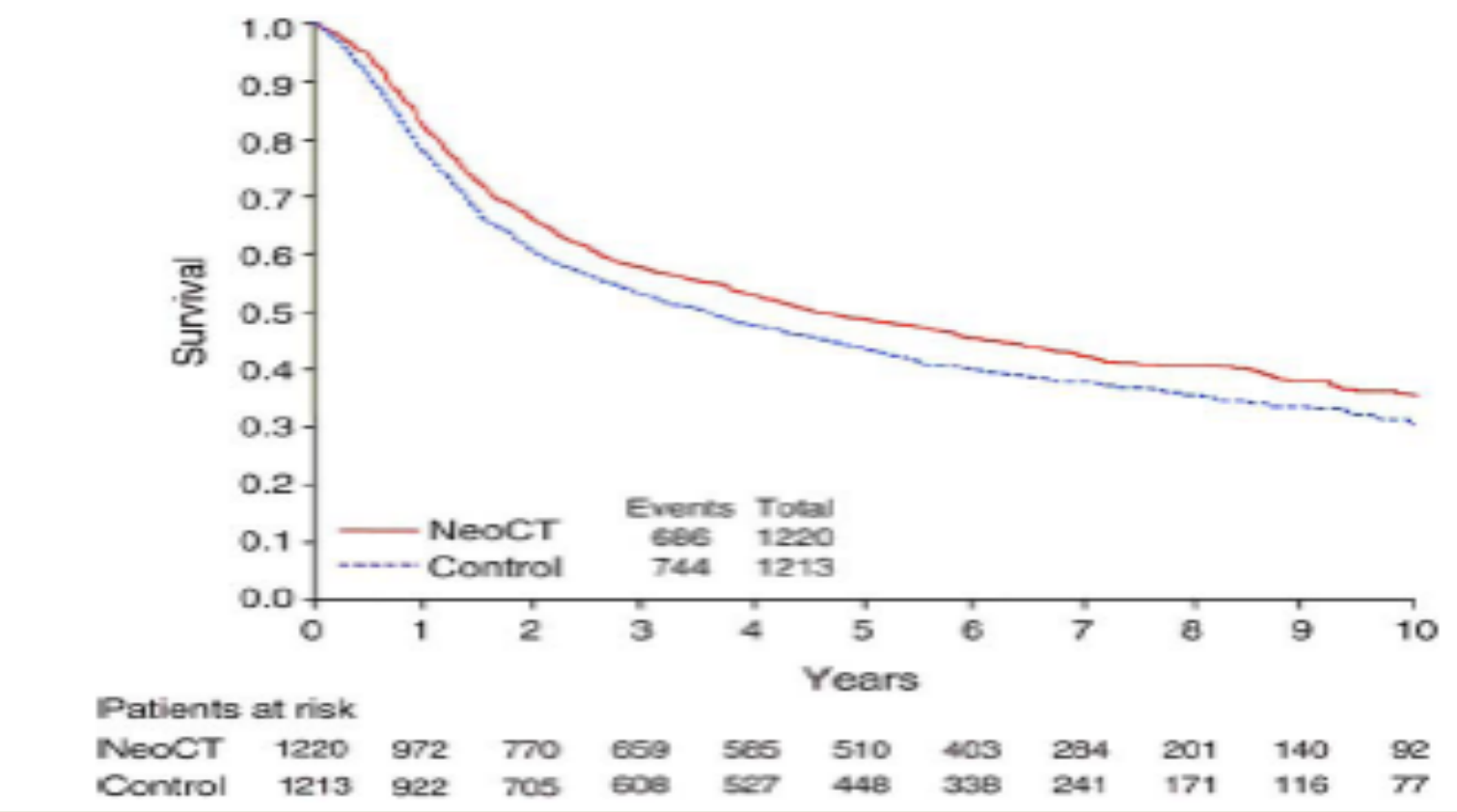
ABC Meta-analysis Collaboration:
update on 3005 pts

Survival curve (platinum based combination trials only)



Eur Urol. 2005 Aug;48(2):202-5

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This fit all?

- review of inclusion criteria and pts characteristics on the 3 major trials (EORTC, SWOG and Nordic)
- 1913/3005→ 64%
- Compared with SEER database.
- No data on >80 years old pts
- No data on PS 2-3.

- In pts >70 years old the probability of PS <1→ 13%
- In pts >70 years old the probability of Cr Cl < 50 ml/min→ 47%

- Pts > 70 years old are almost 1/3 of bladder pts

Take home message on NAC

- NAC is feasible with level I evidence data.

- Careful patients selection:
  - T2-T4a N0-x
  - ECOG 0-1
  - Creatinine clearance > 50 ml/min

- Adequate pre treatment staging and clinical evaluation

- pCR: 30-40% and correlate with survival (less benefit with GC but less toxicity)

Take home message on NAC

- NO platinum in monotherapy: no benefit
- NO Regimen other than cisplatinum based

- Optimal regimen unknown (MVAC; ddMVAC; GC)
- 4 cycles before surgery

•UC of the upper tract or urethra and mixed squamous and/or glandular differentiation can be considered

National Cancer Database (NCDB)

David et al. J Urol. 2007:

1998-2003 on 7161 pts (stage III).

11.6% perioperative CT

10.4% AC- 1.2% NAC

40388 pts after metanalysis (Fedeli and Coll, 2013):

NAC 2003 → 2007

6% → 13%

5692 pts after metanalysis (Zaid and Coll, 2014):

NAC 2006 → 2010 (overall use: 16.9%)

10.2% → 20.9%

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Trends in the Utilization of Neoadjuvant Chemotherapy in Muscle-invasive Bladder Cancer: Results From the National Cancer Database

Harras B. Zaid, Sanjay G. Patel, C. J. Stimson, Matthew J. Resnick, Michael S. Cookson, Daniel A. Barocas, and Sam S. Chang. Urology 2014

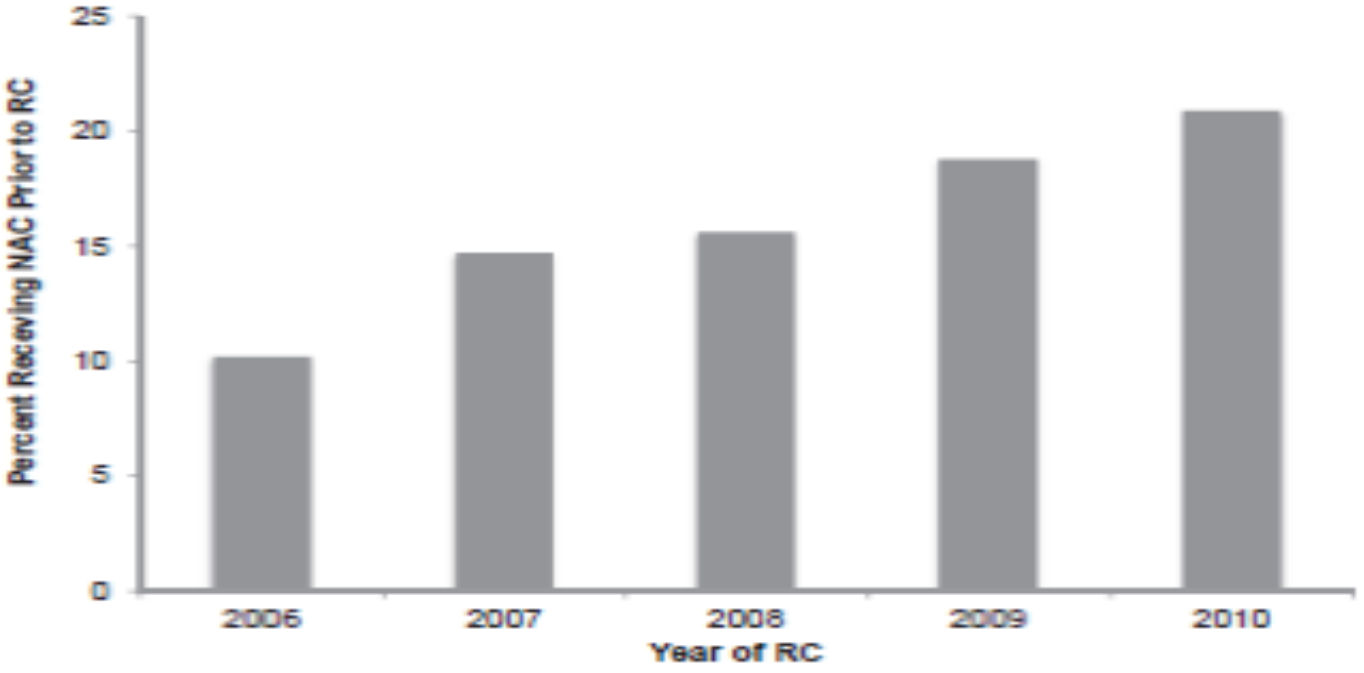

Figure 1. Use of neoadjuvant chemotherapy (NAC) increased with time for patients undergoing radical cystectomy (RC). The difference between 2006 (7.6%) and 2010 (20.9%) reached significance ($P < .01$).

Zaid et Al J. Urol, 2013

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Indipendent factors in receiving NAC

- Younger age
- Higher clinical stage
- Lower comorbidity

- Married status
- North est location (USA)
- Higher income

- Academic or tertiary structure

Zaid et Al J. Urol, 2013

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Understanding Avoidance, Refusal, and Abandonment of Chemotherapy Before and After Cystectomy for Bladder Cancer

Shabnam Rehman, Alice Crane, Rakeeba Din, Syed Johar Raza, Yi Shi, Gregory Wilding, Ellis G. Levine, Saby George, Roberto Pili, Donald L. Trump, and Khurshid A. Guru, 2013

Increasing Utilization of Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer in the United States

Kirk A. Keegan & Harras B. Zaid & Sanjay G. Patel & Sam S. Chang, Curr Urology 2014

Neoadjuvant Chemotherapy Use in Bladder Cancer: A Survey of Current Practice and Opinions

N. G. Cowan,[1] Y. Chen,[2] T. M. Downs,[3] B. H. Bochner,[4] A. B. Apolo,[5] M. P. Porter,[6] J. C. La Rochelle,[1] C. L. Amling,[1] and T.M. Koppie[1], Advances in Urology 2014

Cost-effectiveness of neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer .

Scott M.Stevenson,M.D.,MatthewR.Danzig,B.S.,RashedA.Ghandour,M.D., ChristopherM.Deibert,M.D.,M.P.H.,G.JoelDecastro,M.D.,M.P.H.,MitchellC.Benson,M.D., JamesM.McKiernan,M.D.* Urologic Oncology 2014

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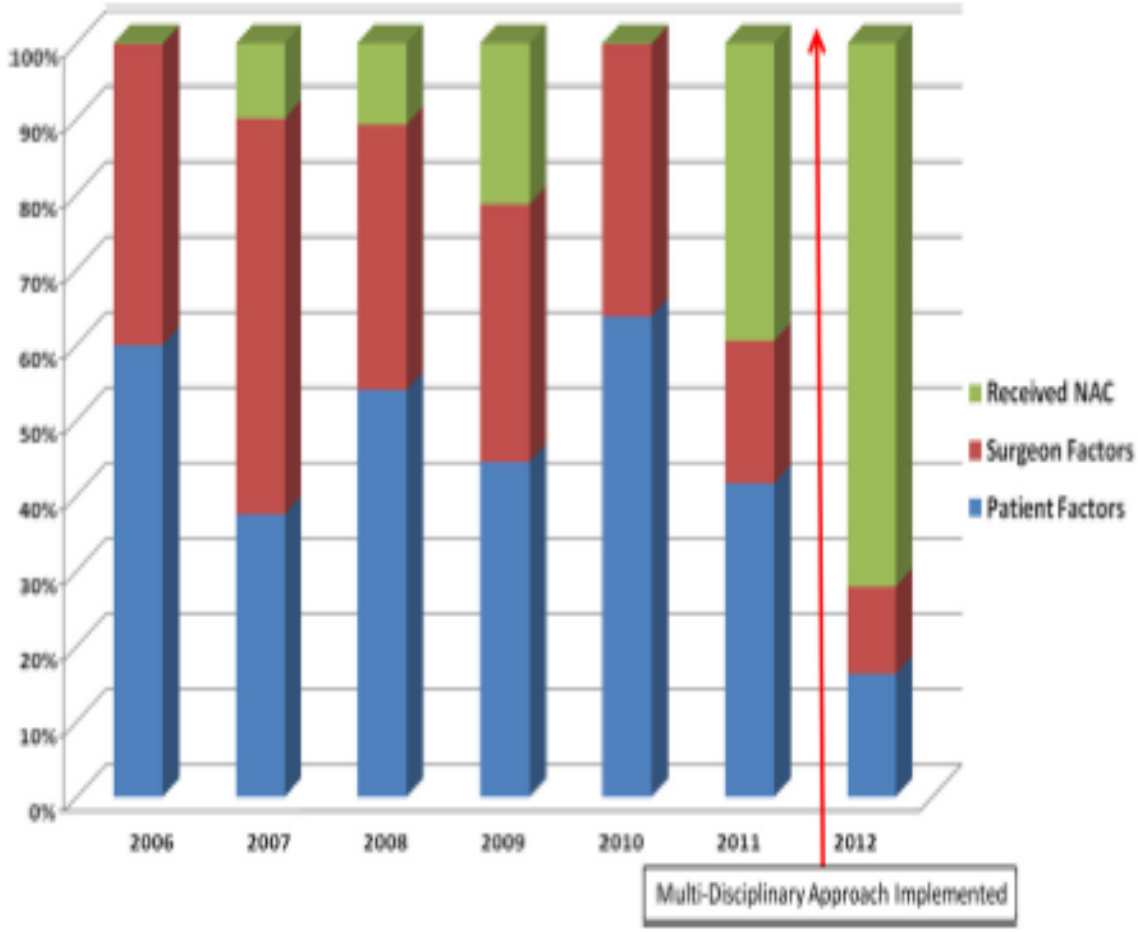

Figure 2. Yearly proportions of patients who received neoadjuvant chemotherapy (NAC) and patients in the non-NAC group, who were not referred to medical oncology due to patient or surgeon factors. (The year 2005 was omitted from the *x*-axis due to surgeon's brief initial tenure at the institution.)

Rehman et Al J. Urol, 2013

First: try to understand

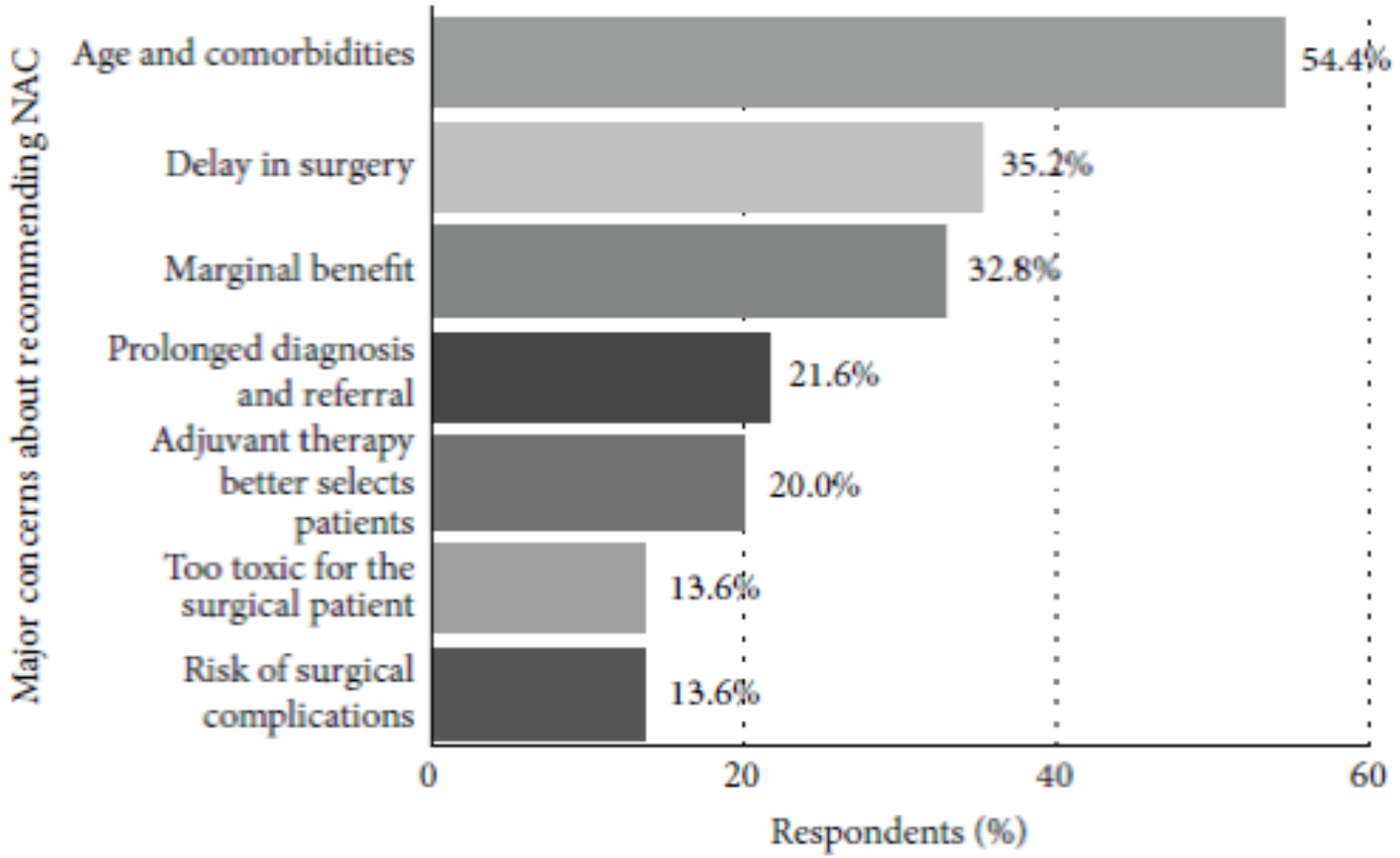

FIGURE 5: "What are your major concerns about recommending NAC? (Select all that apply.)"

Cowan et Al Advances in Urology, 2014

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Clarifying doubts:

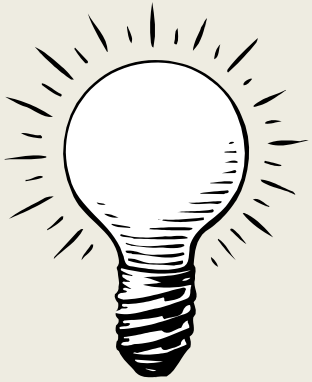
- Age should not be an exclusion criteria on its own.

- Similar mean time from diagnosis to RC (3.3 mons RC alone vs 3.8 mons in NAC+RC)
- No increase in perioperative complications.

- The % of pts excluded for comorbidity is similar in NAC and surgery arm.

- High probability to achieve pCR and so to improve survival.

- T2G3: high probability to be upstaged at surgery.



Enhace multidisciplinarity

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Stringent multidisciplinary approach

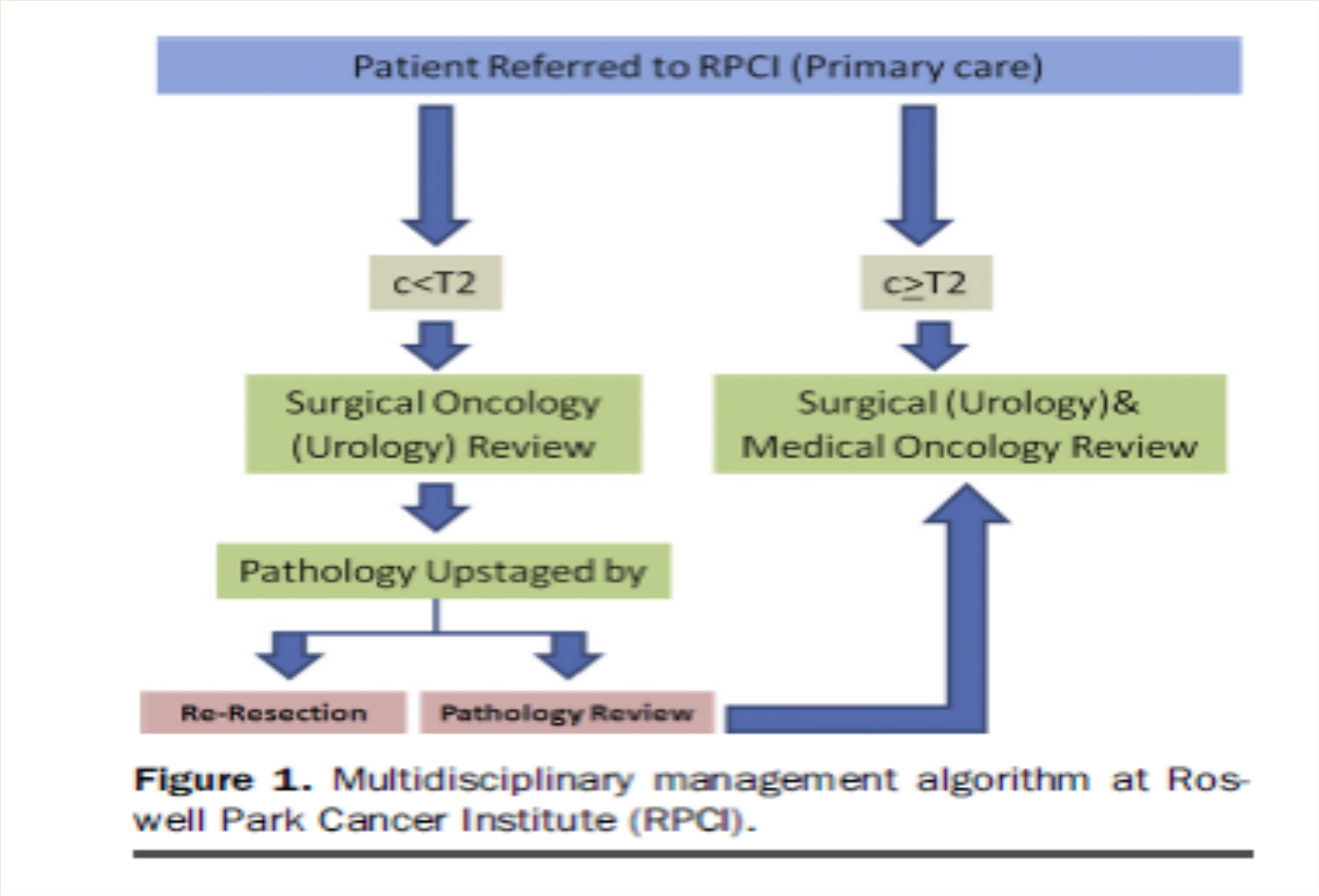

Figure 1. Multidisciplinary management algorithm at Roswell Park Cancer Institute (RPCI).

Rehman et Al J. Urol, 2013

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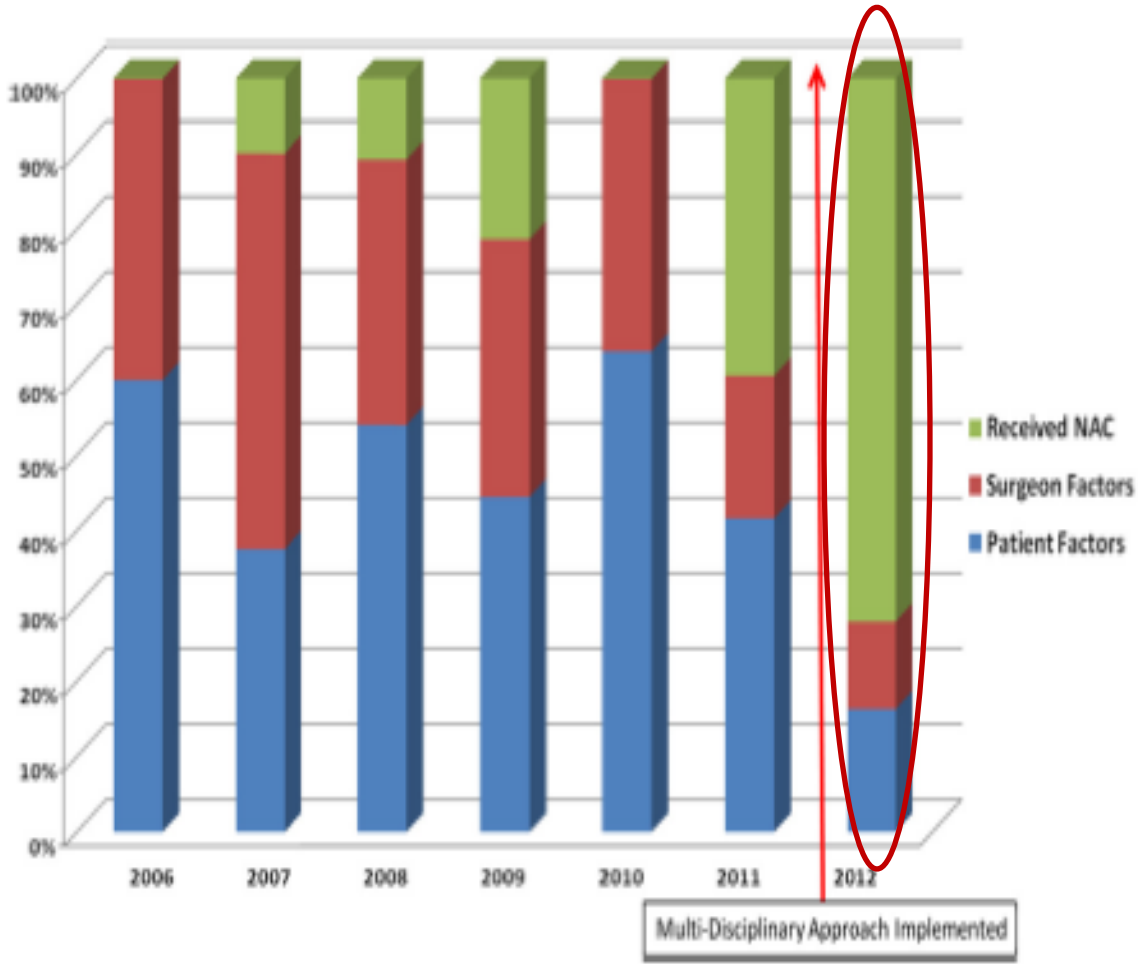

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Rehman et Al J. Urol, 2013

…About cost effectivness

Table 4
Survival and summary of costs

	Radical cystectomy	Neoadjuvant chemotherapy	*P* value
n	119 (65.4%)	63 (34.6%)	
Median follow-up, mo	22.3	29.6	
Percentage who died during follow-up	52.9%	42.9%	
Median survival, mo			
Unadjusted	26.6	46.2	0.027
QALY	21.9	40.4	0.029
5-Y overall survival			
Unadjusted	31.7%	42.5%	0.034
QALY	21.9%	42.9%	0.021
Mean total cost	$42,890	$52,429	0.005
Percentage of total			
Radical cystectomy	35.8	17.7	
Early surgical complications	11.8	3.0	
Related hospital admissions	22.9	24.3	
Neoadjuvant chemotherapy	0	26.2	
Outpatient visits/procedures	20.6	26.4	
Adjuvant/salvage chemotherapy	8.9	1.7	

Stevenson, Urolonc, 2014

To cut a long story short

Underutilization and disparities in NAC represent an opportunity to improve multidisciplinarity.

Implement dedicated programs and discuss every case together can be the right way.

Educate community doctors towards best practice and evidence based practice guidelines.

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Thanks for your attention!

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