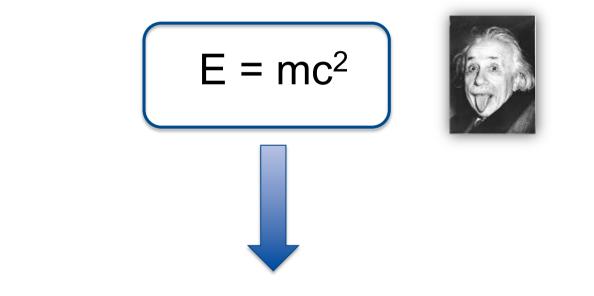




14.00 - 15.30 SIMPOSIO AIRO-SIUrO Approccio multidisciplinare nel Carcinoma della Vescica Moderatori: C. Magno, L. Tomio

Il punto di vista del Chirurgo - G. Conti Il punto di vista del Radio-Oncologo - M. Orsatti Il punto di vista dell'Oncologo - D. Amoroso

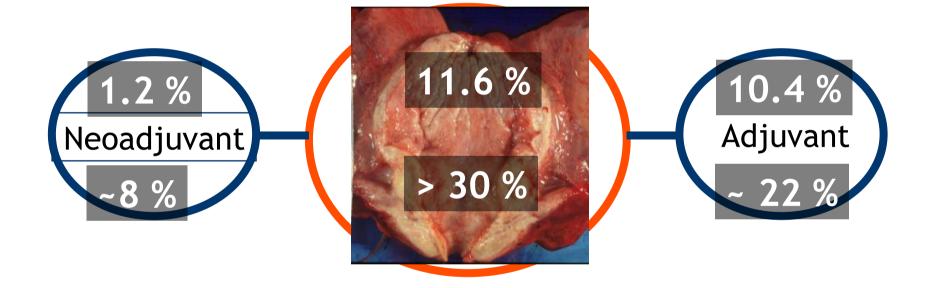
Il punto di vista dell'urologo



MIBC = Cistectomia immediata

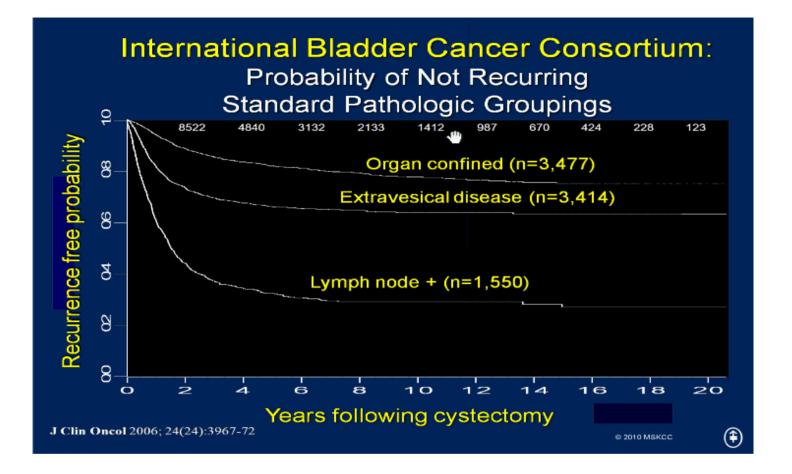
On average, roughly 12% of some 5000 MIBC patients undergoing cystectomy annually in Europe are considered for NCT.

Bladder Cancer: Perioperative Chemotherapy



Neoadjuvant vs. Adjuvant 2003 - 2007

Courtesy by A. Stenzl-2012



Radical Cystectomy is still the best treatment for MIBC. Long-term CSS and OS are low after RC single treatment for extravesical disease and N+ pathologic stages

Survival Outcomes Cystectomy Series

| | | | | | Surviva | al |
|--------|------|--------------|--------|-----|---------|------|
| Series | Year | Treatment | Stage | n | 5yr | 10yr |
| Padua | 1999 | Cystectomy | P2-P4a | 258 | 44% | - |
| USC | 2001 | Cystectomy + | P2-P4a | 633 | 48% | 32% |
| MSKCC | 2001 | Cystectomy + | P2-P4 | 184 | 36% | 27% |

Stein JCO 2001, Dalbagni J Urol 2001, Bassi J Urol 1999

Neo-Adjuvant Chemotherapy Rationale

- Increasing T stage and extravesicular cancer
- Metastatic disease present at diagnosis

Chemotherapy in 2011

| Conclusions | LE |
|---|-----------|
| Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival by 5-7% at 5 years, irrespective of the type of definitive treatment used. | 1a |
| Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations. | |
| | |
| | GR |
| 5.2 Recommendations for neoadjuvant chemotherapy Recommendations Neoadjuvant cisplatin-containing combination chemotherapy should be considered in muscle- invasive bladder cancer, irrespective of further treatment. | GR |

EAU Guidelines on Bladder Cancer Muscle-invasive and Metastatic. **2011**



Chemotherapy in 2013

6.4 Conclusions and recommendations for neoadjuvant chemotherapy

| Conclusions | LE |
|---|----|
| Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival. | 1a |
| Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations. | |
| In current routine clinical practice, it is difficult to select patients who will respond to neoadjuvant chemotherapy due to the lack of a widely applicable test. In the future, genetic markers, in a 'personalised medicine' setting, will make it easier to select patients for treatment and to differentiate responders from non-responders. | |

| Recommendations | GR |
|---|----|
| Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatinum-based combination therapy. | A |
| Neoadjuvant chemotherapy is not recommended in patients with PS \geq 2 and/or impaired renal function. | В |

EAU Guidelines on Bladder Cancer Muscle-invasive and Metastatic. **2013**



First-line treatment for "fit" patients: Cisplatin-containing combination chemotherapy

Gemcitabin/Cispaltin CMV MVAC HD-MVAC

[Grade of raccomandation A]

EAU Guidelines, European Association of Urology 2013



Open Question

What is the current role of neoadjuvant chemotherapy for bladder cancer?

Is EBM data sufficient in order to recommend this kind of treatment?

| Trial | Patients,n | Regimen | Survival benefits | FU Years |
|-----------------------|------------|-------------------------|----------------------|----------|
| BA 06 30894 | 976 | CMV x3 | 5% | 8 |
| SWOG/US intergroup | 317 | MVAC x3 | 5% | 5 |
| ABC meta-analysis | >3000 | Cisplatinum based CT | 5% | 5 |

For what clinical stage do you recommend NCT as an elective treatment?

All patients undergoing radical cystectomy, only cT2 or only \geq cT3?

Carcinoma della vescica: chemioterapia neoadiuvante

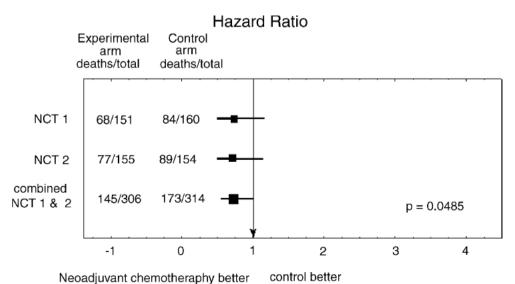
European Urology

European Urology 45 (2004) 297-303

Neoadjuvant Cisplatinum Based Combination Chemotherapy in Patients with Invasive Bladder Cancer: A Combined Analysis of Two Nordic Studies

Amir Sherif^{a,*}, Lars Holmberg^{b,c}, Erkki Rintala^d, Oddvar Mestad^e, Jonas Nilsson^b, Sten Nilsson^f, Per-Uno Malmström^a other co-workers in the Nordic Urothelial Cancer Group

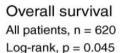
- riduzione del rischio di morte del 20% (HR: 0.80)
- sopravvivenza globale a 5 aa del 56% vs 48%
- riduzione del rischio assoluto di morte del 8%.

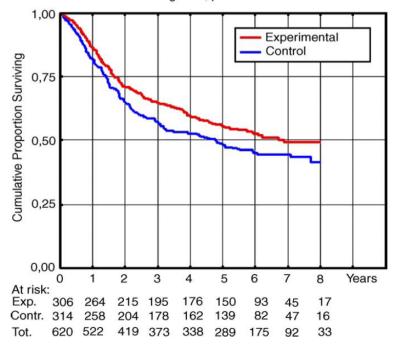


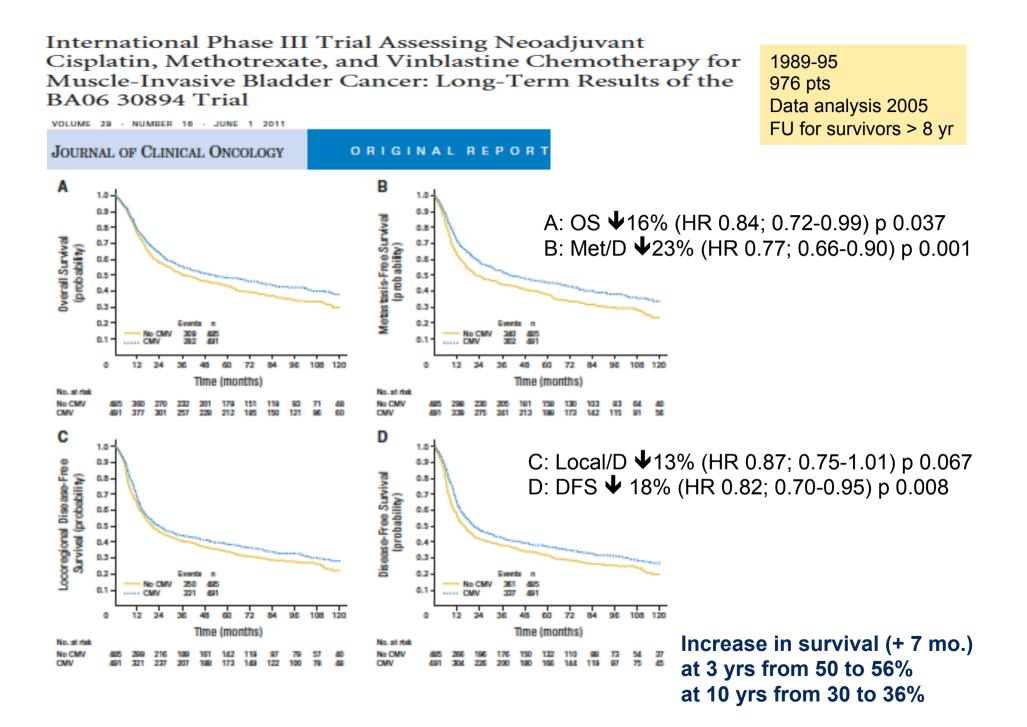
Courtesy Dr. C. Ortega

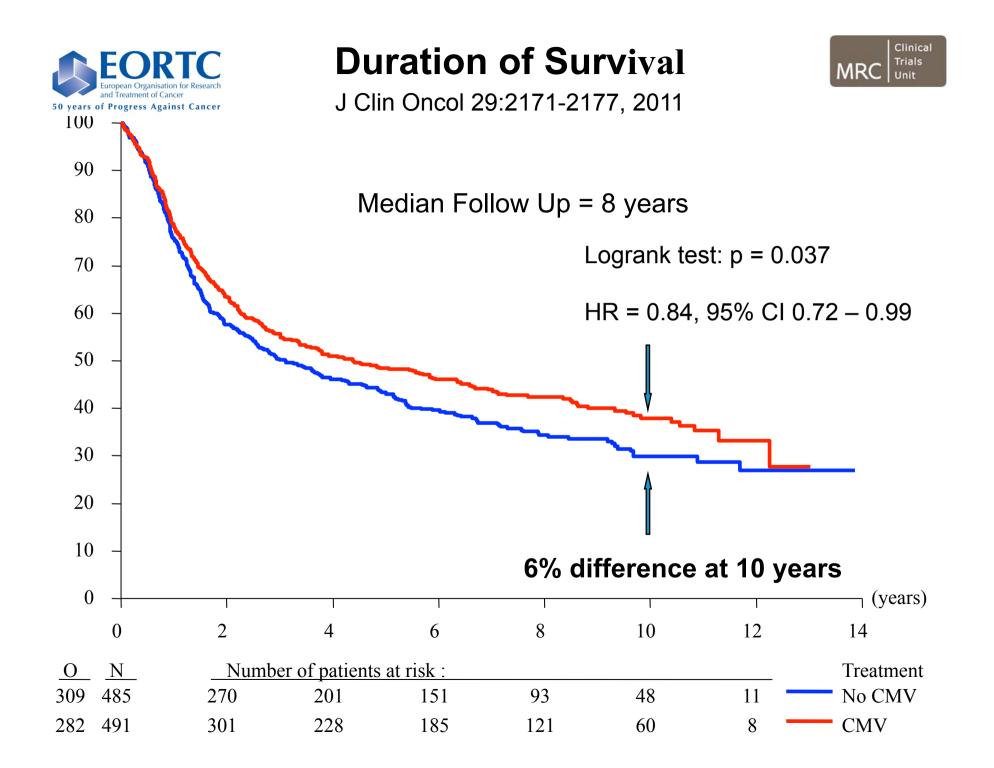
620 pazienti T1G3, T2–T4aNXM0 arruolamento: **1985–1997**

CDDP + ADM (Nordic I) CDDP + MTX (Nordic 2)









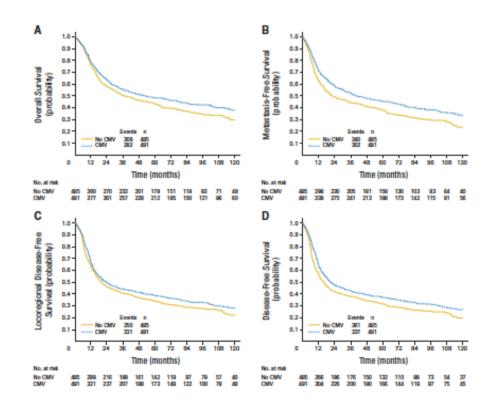
International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial



VOLUME 29 - NUMBER 16 - JUNE 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



NNT: 17
No difference comparing RC and RT

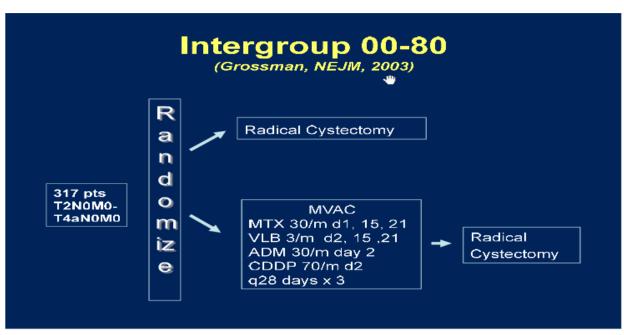
1999 Interim report: NB for MVC arm

2002 Update from ASCO (7.4 year F-U: significant improvement in survival in MVC arm (HR: 0.85; 95% CI 0.72-1.0)

1989-95 976 pts Data analysis 2005 FU for survivors > 8 yr Increase in survival (+ 7 mo.) at 3 yrs from 50 to 56% at 10 yrs from 30 to 36%

Predefined end point: 10% improvement in survival. Not reached

Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *Grossman HB, NEJM 349: 859-66, 2003* Aug 28, 2003): 859-66.

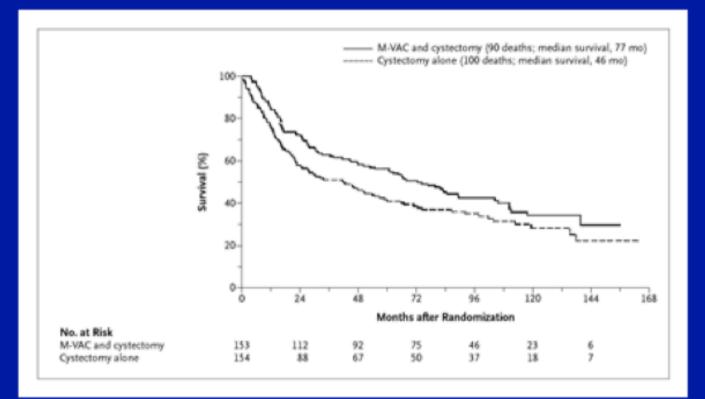


a)154 PtsT2-T4a treated by RC alone b)153 Pts (3)M-VAC and RC

Estimated reduction of risk of death: 25%
 NC did not adversely impact the ability to proceed with RC

Median FU: 8.7 years: a)Median survival: 77 mo. b)Median survival: 43 mo. P=0.06

SWOG Intergroup Overall Survival (n=307)

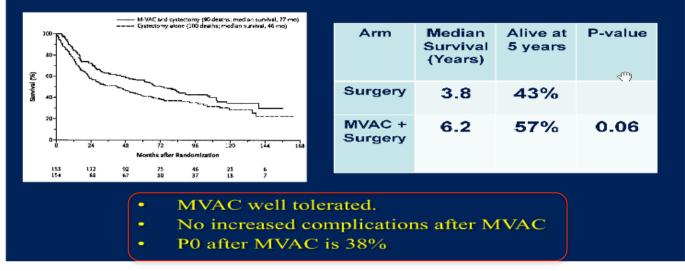


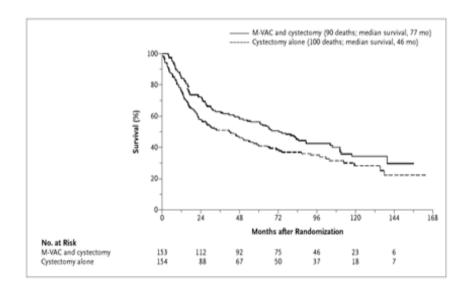
43% vs. 57% 5 yr survival <u>p=0.06</u>, 2-sided borderline significance) HR: 1.33 (95% Cl 1.0- 1.76)

Grossman HB, NEJM 349: 859-66, 2003



(Grossman, NEJM, 2003)





43% vs. 57% 5 yr survival <u>p=0.06</u>, (2-sided borderline significance) HR: 1.33 (95% CI 1.0- 1.76)

Grossman HB, NEJM 349: 859-66, 2003

META-ANALYSIS STUDIES

| | 10 PRT (but SWOG) <i>rival benefit at 5-y</i> the risk of death) | 2688 Pts | 5% |
|--|---|----------------|------|
| absolute surv | 11 PRT vival benefit at 5-y e-free survival at 5 y of 9% | 3005 Pts %) | 5% |
| <u>J Urol 2004</u> absolute overall | 16 PRT survival benefit | 3315 Pts | 6.5% |



European Urology 48 (2005) 202-206

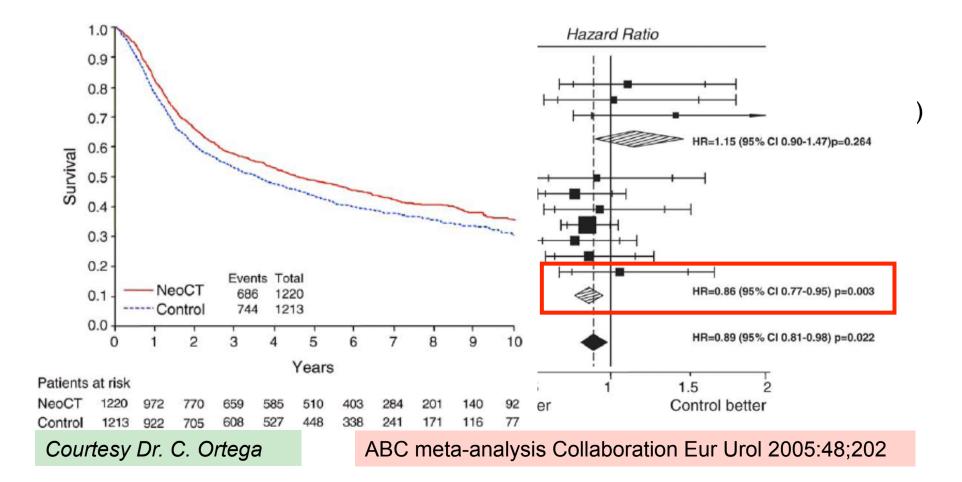
Review—Bladder Cancer

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration



chemioterapia neoadiuvante + trattamento locale (radioterapia o cistectomia) vs trattamento locale.







- Il beneficio clinico complessivo è del 5% a 5 anni e fornisce la miglior stima di effetto in tutte le categorie;
- Tuttavia l'interpretazione di questo beneficio ha impatti differenti in funzione della differente prognosi considerata per categoria:
- a 5 anni la terapia neoadiuvante migliora la sopravvivenza

(vantaggio relativo: VR):

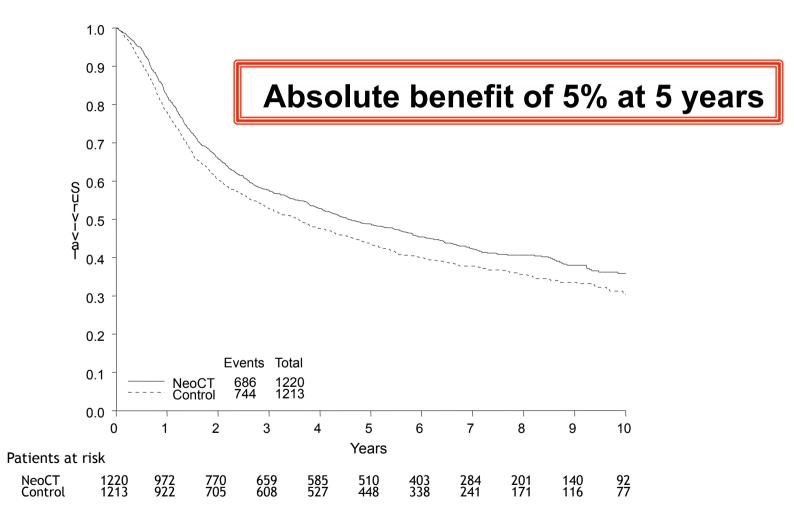
- dal 55% al 60% nei pazienti con malattia T1–2 \rightarrow (VR 9%)
- dal 40% al 45% nei pazienti con malattia T3 \rightarrow (VR 12,5%)
- dal 25% al 30% nei pazienti con malattia T4 \rightarrow (VR 20%)

Adapted, Courtesy Dr. C. Ortega

ABC meta-analysis Collaboration Lancet 2003:361;1927

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

Platinum-based combination chemotherapy trials only Overall survival



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

Neo-Adjuvant Chemotherapy

Neo-adjuvant Chemotherapy prior to cystectomy shows a real benefit

There is consistent data to prove the benefit

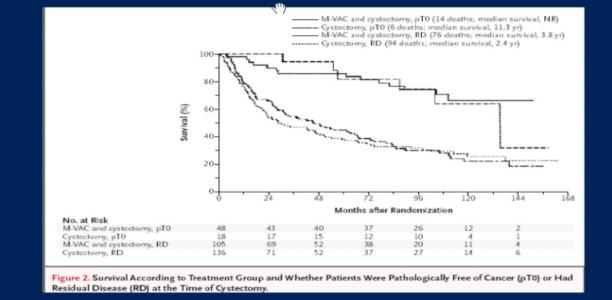
Courtesy by Cora sternberg



Open Question

Are we able to state conclusively that patients who achieve pT0 after NC represent the best subgroup in terms of long term oncologic outcomes? Shell we consider the surrogate pT0 end point universally accepted? What is the NC regimen that, at now, has proved to achieve the highest pT0 rate?





The survival benefit of neoadjuvant M-VAC appears to be strongly related to downstaging of the tumor to **pT0**: 38 percent of the patients in this group had no evidence of cancer at cystectomy, as compared with 15 percent of the patients in the cystectomy group (P<0.001); the respective five-year survival rates were 85 and 82 percent.

Grossman HB, NEJM 349: 859-66, 2003

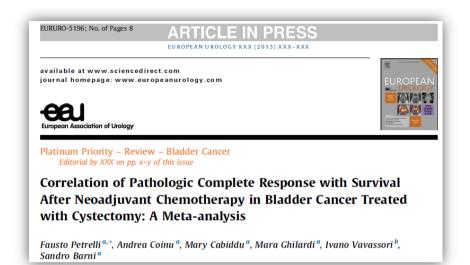


with Cystectomy: A Meta-analysis

Fausto Petrelli^{a,*}, Andrea Coinu^a, Mary Cabiddu^a, Mara Ghilardi^a, Ivano Vavassori^b, Sandro Barni^a

| | pCF | 2 | no pC | R | | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|--------|-------|--------|------------------------|----------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl Yea | r M-H, Fixed, 95% Cl |
| Dreicer 1993 | 0 | 6 | 0 | 9 | | Not estimable 199 | 3 |
| Herr 1994 | 2 | 12 | 7 | 14 | 3.7% | 0.33 [0.08–1.31] 199 | ↓ — - |
| Hatcher 1994 | 0 | 15 | 10 | 17 | 5.6% | 0.05 [0.00-0.84] 199 | 1 |
| Sagaster 1996 | 3 | 17 | 15 | 37 | 5.4% | 0.44 [0.15–1.31] 199 | ĵ − •+ |
| Scattoni 1996 | 1 | 6 | 25 | 61 | 2.5% | 0.41 [0.07-2.50] 199 | j <u> </u> |
| Sternberg 1999 | 2 | 13 | 15 | 31 | 5.0% | 0.32 [0.08–1.20] 199 | a — • – • |
| Matsui 2005 | 3 | 21 | 36 | 98 | 7.2% | 0.39 [0.13–1.14] 200 | 5 |
| Sonpavde 2009 | 23 | 46 | 52 | 69 | 23.7% | 0.66 [0.48-0.91] 200 | 3 🗕 |
| Ghadjar 2010 | 3 | 9 | 13 | 21 | 4.4% | 0.54 [0.20–1.44] 201 |) |
| Kaneko 2011 | 0 | 10 | 0 | 12 | | Not estimable 201 | |
| Rosenblatt 2012 | 6 | 51 | 84 | 174 | 21.7% | 0.24 [0.11-0.52] 201 | 2 |
| Meijer 2013 | 15 | 33 | 62 | 79 | 20.8% | 0.58 [0.39–0.86] 201 | 3 - |
| Total (95% CI) | | 239 | | 622 | 100.0% | 0.45 [0.36-0.56] | • |
| Total events | 58 | | 319 | | | | |

Fig. 2 – Forest plot of pooled relative risk for overall survival from eligible studies reporting outcome associated with achieving a pathologic complete response (pCR). Horizontal lines represent 95% confidence intervals (CIs). The area of each square represents the weighting, and the positions of each square demonstrate the risk ratio point estimate. M-H = Mantel-Haenszel; df = degrees of freedom.



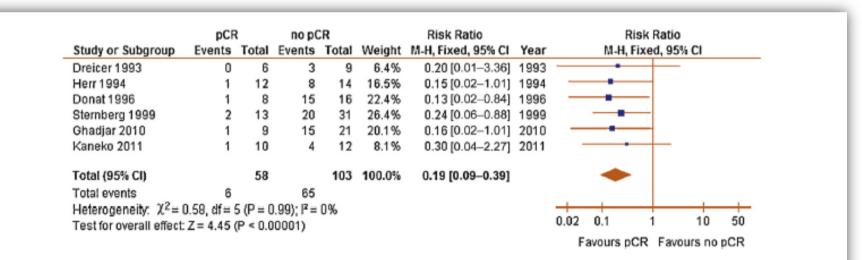
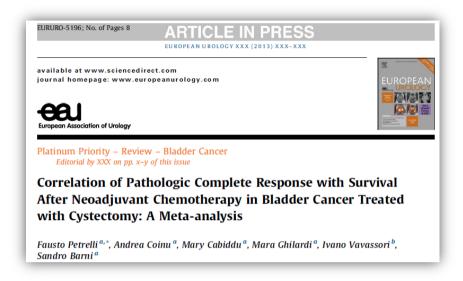


Fig. 3 – Forest plot of pooled relative risk for recurrence-free survival from eligible studies reporting outcome associated with achieving a pathologic complete response (pCR). Horizontal lines represent 95% confidence intervals (CIs). The area of each square represents the weighting, and the positions of each square demonstrate the risk ratio point estimate. M-H = Mantel-Haenszel; df = degrees of freedom.



4. Conclusions

As we await further molecular prognostic factors and predictors of sensitivity to medical therapy for UC, achieving pCR in both the bladder and lymph nodes after neoadjuvant chemotherapy and RC for BCa is associated with an impressively better outcome.

Neo - Adjuvant Chemotherapy

- 12% at leading academic US institutions
- SEER national data even less
- Consultation by MDT prior to surgery
- 5 yr survival rates 40-60% after cystectomy, no better than 80% pT2
- Transition to systemic disease paradigm breast and colon cancers (26% colon cancer)



Open Question

Can we definitively state today that NC doesn't increase the rate of complications after radical cystectomy? This may be of crucial importance for the attitude of surgeons in favor of NC

SWOG 8710: Randomized Trial of Neo-Adjuvant Chemotherapy Followed by Cystectomy vs. Cystectomy Alone

| | (N=124) | lone | M-VAC and Cystectomy (N=126) | | |
|------------|---|--|---|---|---|
| Grade 3 | Grade 4 | Grade 5 | Grade 3 | Grade 4 | Grade 5 |
| | | number o | f patients | | |
| 0 | 0 | 0 | 3 | 0 | 0 |
| | | | | her or no | ot |
| nt chei | mothera | apy was | given | | |
| 0 | 0 | 0 | 3 | 0 | 0 |
| 3 | 0 | 1 | 2 | 1 | 0 |
| 0 | 0 | 0 | 3 | 0 | 0 |
| 1 | 0 | 0 | 3 | 0 | 0 |
| 0 | 1 | 0 | 0 | 0 | 0 |
| 2 | 1 | 0 | 2 | 0 | 0 |
| 2 | 0 | - | 1 | 1 | 0 |
| | Grade o ication nt che o 3 o 1 o 2 | Grade Grade O O ications were nt chemothera O O 3 O 1 O 1 O 1 O 2 1 | Grade Grade Grade 5 number of 0 ications were the same nt chemotherapy was 0 0 0 3 0 1 0 0 0 1 0 0 1 0 2 1 0 | Grade 3Grade 4Grade 5Grade 300030003ications t chemotherapy 000000330120003100310032102 | Grade 3Grade 4Grade 5Grade 3Grade 400030ications ications t chemotherapy 30300003030121000301003021000 |

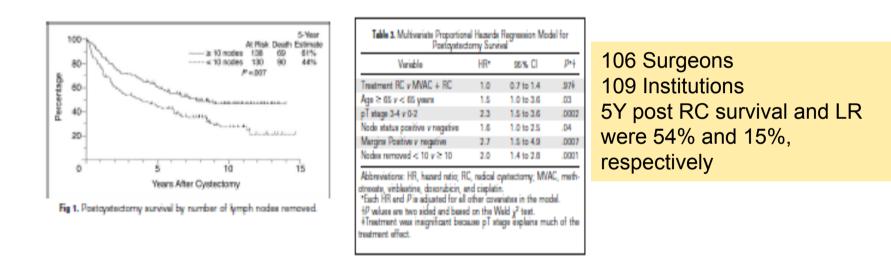
Grossman, NEJM 2003

Surgical Factors Influence Bladder Cancer Outcomes:

A Cooperative Group Report

Harry W. Herr, James R. Faulkner, H. Barton Grossman, Ronald B. Natale, Ralph deVere White, Michael F. Sarosdy, and E. David Crawford

J Clin Oncol 22:2781-2789. © 2004 by American Society of Clinical Oncology



Preictors of LR: positive margins and < 10 nodes removed

Surgical factors influence bladder cancer outcomes after cystectomy, after adjustment for pathologic factors and neoadjuvant chemotherapy usage. [LE 2]



Open Question

If we accept the surrogate pT0 status after NC as a reasonable end point, should we expect that the inclusion of new drugs [bevacizumab, sorafenib, avastin, sunitinib] in the NC regimen may increase this end point achievement?

At now, there is no prove that novel combination regimens provide increased pT0s rather than increased toxicity

Clinical trial setting: novel agents

• Sunitinib as first line:

PS 0-1 Creat 30-60 ml/min median age 75 (range 70-80 yrs) Locally advance or metastatic UC

Bellmunt J. et al Annals of Oncology 2011

• Carboplatin / Gemcitabine / Bevacizumab:

KPS >60%, creat <2,0 or GFR>30ml/min [MSKCC; NCT00588666]

Neoadjuvant Dasatinib (oral multi-BCR/ABL and Src family TKI):

miUCB (T2-T4a,N0,M0), Creat <2 x ULN, PS 0/1: 19/6

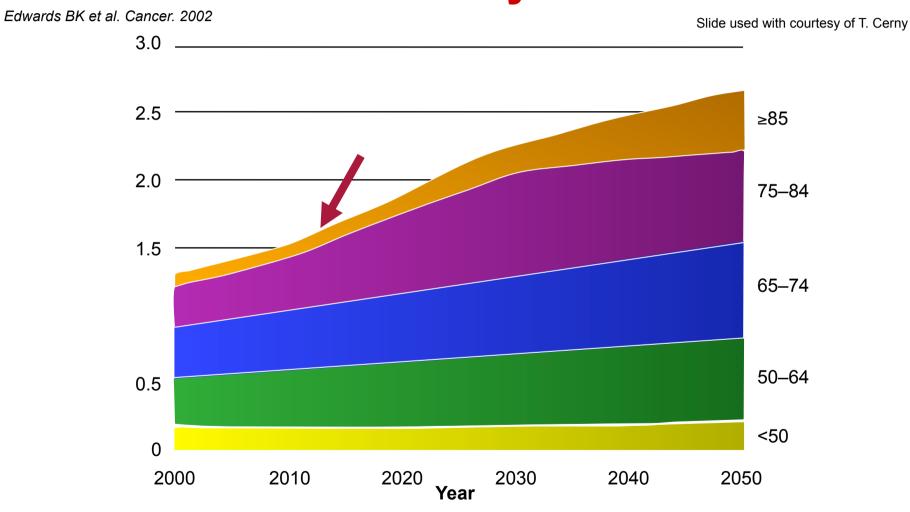
Unsuitable or unwilling to CDDP (relevant concomitant disease:tumors, cardiac failur, uncontrolled arythmia or hypertension) [Hoosier, NCT00706641]

Hann N M et al ASCO 2012

Neoadjuvant lpilimumab:

T1-T3N0M0, CrCl < 40ml/min, ECOG 0-1 [MD Anderson, NCT00362713]

The burden of cancer is shifting to the elderly



UNFIT DEFINITION

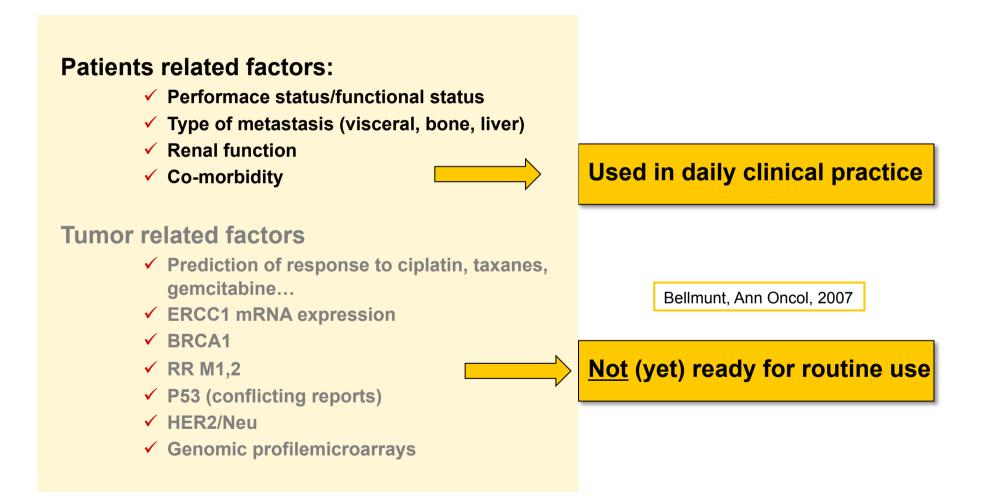
 At least on e of the following criteria □ WHO/ECOG PS 2; KPS: 60-70% □ Creatinine clearence (calculated or measured) less than 1 mL/s □ CTCAE version 4: grade 2 or above audiometric hearing loss CTCAE version 4: grade 2 or above peripheral neuropathy NYHA Class III

Galsky M et al J Clin Oncol 2011

EORTC Definition of "fit" and "unfit" for cisplatin (2011)

| "Unfit" | | |
|------------------------------------|--|--|
| GFR < 60 ml/min | | |
| and /or | | |
| PS ≥2 | | |
| ≥ grade 2 audiometric hearing loss | | |
| ≥ 2 peripheral neuropathy | | |
| NYHA Class III heart failure | | |
| NYHA Class III heart failure | | |
| ≥ 2 peripheral neuropathy | | |
| | | |

Patients selection, individualized treatment

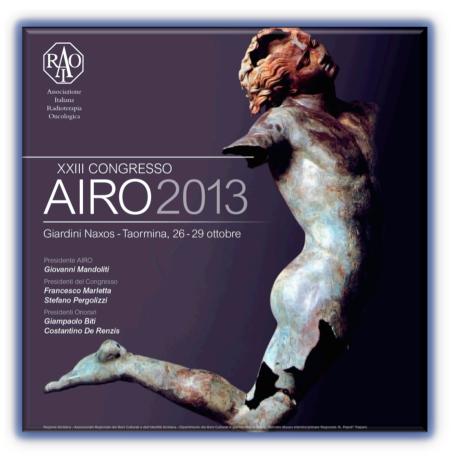


Options for "unfit" patients with......

PS 0-1 and organ function impairments

Performance status ≥ 2





Due to the discrepancy between clinical and pathologic complete response after NC, radical cystectomy cannot be obviated by response [grade B]

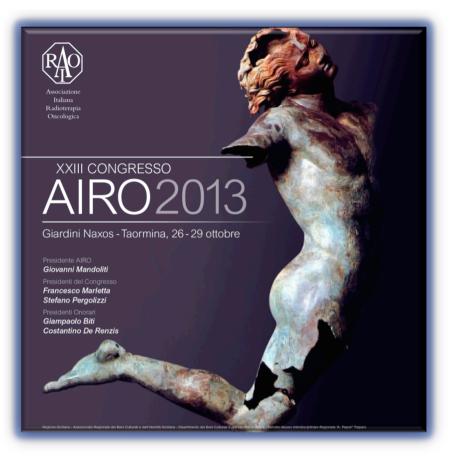
Toxicity and mortality associated with NC is acceptable [grade B]

The quality of radical cystectomy is a confounding factor in interpreting these studies [grade B]



Available data suggest that for average risk patient <cT2 the benefit of adding NC to local therapy is at best modest

■ Likewise, all available studies support much more substantial benefit for patients with high risk disease such as **cT2 -cT3b** or those with **N+** status [grade B]



All three major drugs regimens (M-VAC; GC; DD-MVAC), were proved to have a similar efficacy with a median survival of 15 mo with responses in 40-60%

Presence of squamous or glandular differentiation in locally advanced UC doesn't confer resistance to NC and at contrary may be an indicator for the use of NC [grade 3C]



There are no data from PRT supporting the use of **new drugs** and novel drug combination in NC setting (just within phase II trials)

At now is not possible to make a definitive statement about the role of gene expression profiling in the molecular prognostication on MIBC. (i.e.20-gene signature has been investigated as an independent predictor for N+ and p53 as well as Ki67)

Baseline tumor genomics appear promising as predictors of pCR however, limited small studies have been reported Why Neo-adjuvant Chemotherapy ?

- Neo-adjuvant chemotherapy should be the standard of care for eligible patients with muscle invasive bladder cancer !
- Challenge to incorporate a multidisciplinary approach!

MDT & adherence to guidelines

- MDT adherence to guidelines in 71% of cases
- Discordance mainly noted for:
 - older patients (70+)
 - borderline performance status
 - patients with co-morbidities

Multidisciplinary care and likelihood of undergoing AS in men with low risk PCa (1)

Aizer AA. Int J Radiat Oncol Biol Phys 2011:81(2 Suppl):S101-2(abs. 203)

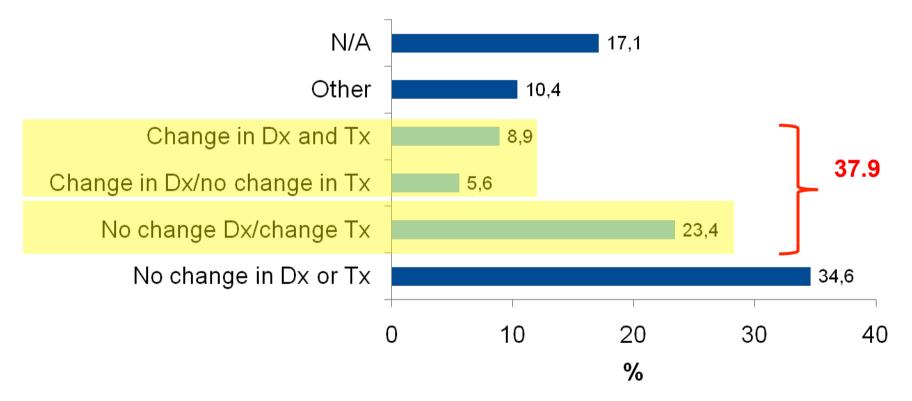
 Retrospective study; N=701 pts with <cT2b, GS<7, PSA<10 ng/ ml PCa (2009)

| | Multidisciplinary clinic (N=329) | Individual practitioners (N=462) | <i>P</i> -value |
|-------------------------|--|--|-----------------|
| # physicians seen (N) | 3.1 | 1.6 | |
| # specialities seen (N) | 2.8 | 1.4 | |
| AS (%) | 43 | 22 | <0.001 |
| RP (%) | 43 | 56 | |
| EBRT (%) | 7 | 11 | |
| BrachyT (%) | 7 | 10 | |

Multidisciplinary clinic: concurrent consultation with ≥2 of following: urologic oncologist, radiation oncologist, medical oncologist

A MDT approach influences diagnostic and treatment decisions

• 296 patients presented MDT with an outside diagnosis of a urologic malignancy

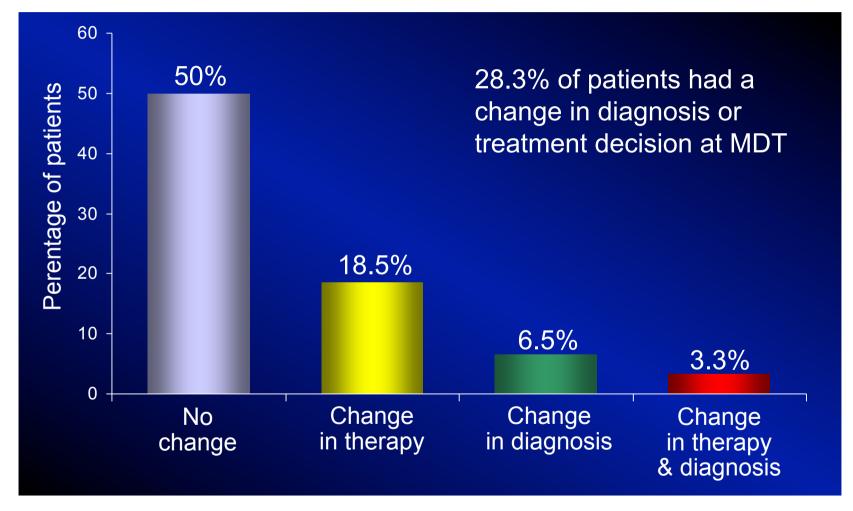


Dx: diagnostic decision; Tx: treatment decision

Kurpad R et al. Urol Oncol 2009 DOI: 10.1016/j.urolonc.2009.04.008 – B. Tombal Cury

2011

MDT in prostate cancer may change diagnosis and treatment decisions



92 consecutive patients with prostate cancer reviewed in MDT in a single institution

Enhancing Prostate Cancer Care Through the Multidisciplinary Clinic Approach: A 15-Year Experience

By Leonard G. Gomella, MD, Jianqing Lin, MD, Jean Hoffman-Censits, MD, Patricia Dugan, RN, Fran Guiles, RHIA, CTR, Costas D. Lallas, MD, Jaspreet Singh, DO, Peter McCue, MD, Timothy Showalter, MD, Richard K. Valicenti, MD, Adam Dicker, MD, and Edouard J. Trabulsi, MD ONCOLOGY Practice

Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Vol. 6, Issue 6 November 2010

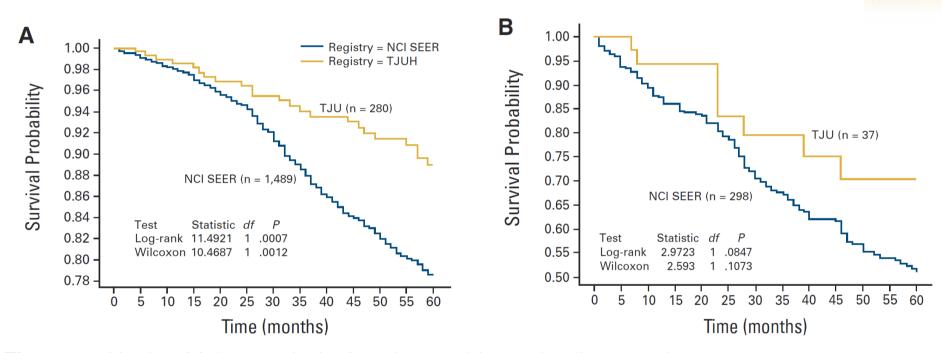
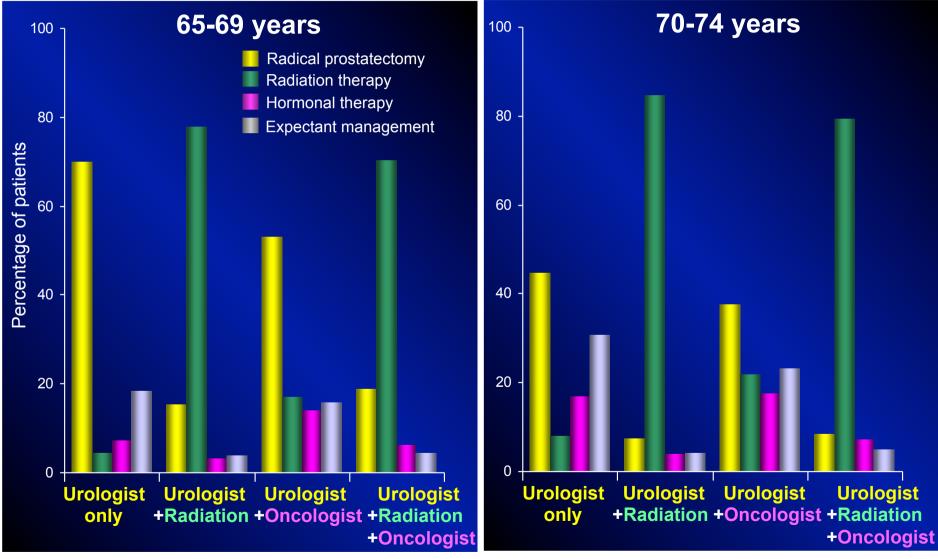
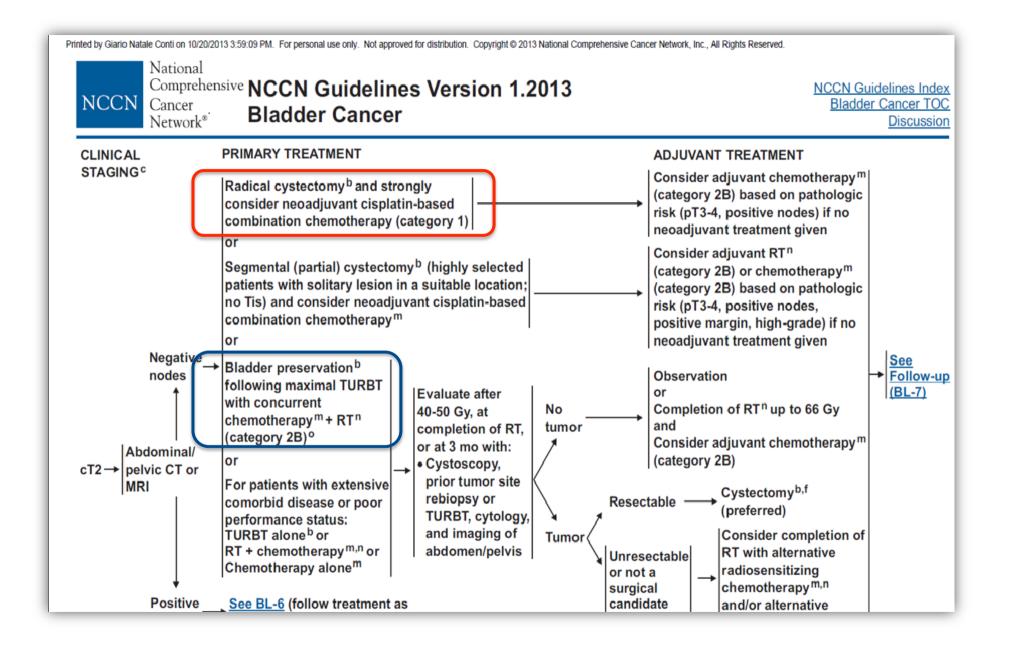


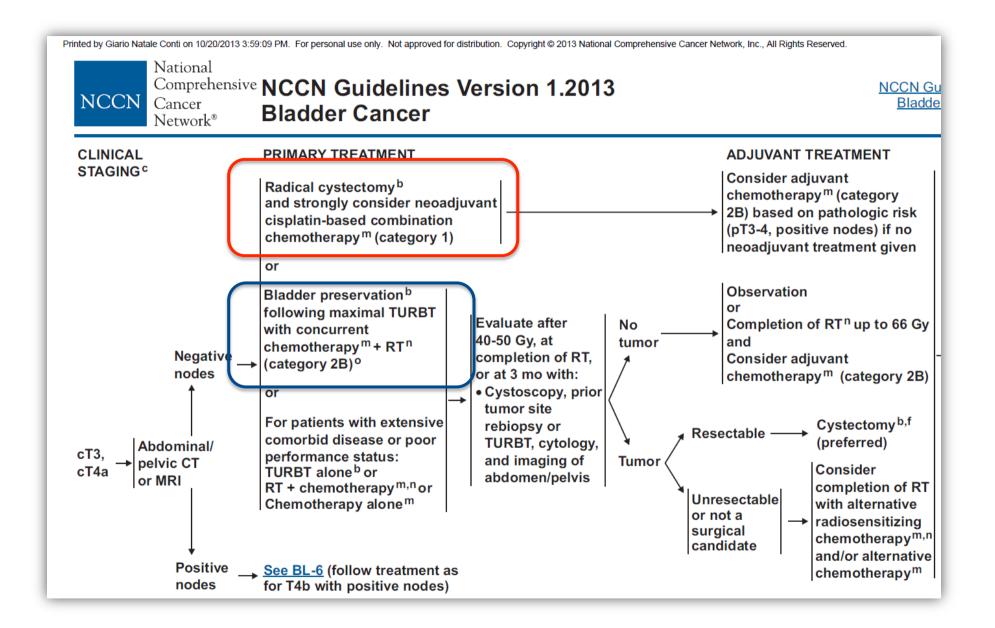
Figure 1. Kaplan-Meier survival of patients with newly diagnosed prostate cancer at the TJUH/KCC (1996-2008) and patients in NCI SEER (1997-2003). (A) Stage III (T3 N0 M0); (B) T4 N0 M0. TJUH, Thomas Jefferson University Hospital; KCC, Kimmel Cancer Center; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology, and End Results.

Strongest predictor of treatment is the type of specialist visited



Jang TL et al. Arch Int Med 2010, 170: 440-50







Società Italiana di Urologia Oncologica Italian Society of Uro-Oncology



Con il contributo incondizionato di



AZIENDA OSPEDALIERA OSPEDALE SANT'ANNA DI COMO

DIREZIONE GENERALE

Tel.: 031/585.9471 Telefax: 031/585.5739 e-mail: dir.gen@hsacomo.org

Deliberazione n. 762 del 18 ottobre 2013

OGGETTO: Istituzione del Gruppo Operativo Interdipartimentale Permanente "Prostat Cancer Unit".

L'anno 2013, addì del mese di ottobre in Como, nella sede dell'Azienda Ospedaliera Ospedale Sant'Anna di Como, il Direttore Generale Dr. Marco Onofri prende in esame l'argomento in oggetto e delibera quanto segue con l'assistenza del Direttore Amministrativo Dott. Salvatore Gioia e del Direttore Sanitario Dr. Giuseppe Brazzoli.

IL DIRETTORE GENERALE



Azienda Ospedaliera Ospedale Sant'Anna di Como

Allegato 5 GOIP

Approvato con deliberazione n. 669 del 13 novembre 2012



| GOIP | |
|---|--|
| Breast Unit | |
| Cardiopatia ischemica | |
| Epato - gastroenterologia | |
| Fisiopatologia Neurorespiratoria | |
| Medicina Nutrizionale, Dismetabolica ed Endocrinologica | |
| Percorso Nascita | |
| Prostate Unit | |
| Attività di Pronto Soccorso Pediatrico Aziendale | |
| Integrazione Soccorso Territoriale e Rete Emergenza Ospedaliera | |
| Attività di Pediatria Chirurgica Aziendale | |
| Radiologia Interventistica | |
| | |



Piano di Organizzazione Aziendale (P.O.A.)

Azienda Ospedaliera Ospedale Sant'Anna di Como Piano di Organizzazione Aziendale (P.O.A.)

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Il punto di vista dell'urologo

