YES
What is NAC?

• It is the treatment of cancer by chemotherapy as a **first step in a multimodality treatment** setting.

• It is something **to be added** to the definitive treatment, **not to replace** it.

• Evidence supports the benefit of NAC in several cancers’ treatment.
If it is evidence based, why is it unpopular?

- It may delay cystectomy resulting in upstaging.
- It may exhaust the patient and preclude his chance to have radical surgery.
- We can give adjuvant chemotherapy (after surgery) if we want.
- The benefit is too little.
- And who said there is evidence of benefit?
1. The Spark
A meta-analysis of ten randomized trials of NAC,

2,688 patients,

significant relative reduction in the risk of death (13%) and improved 5-year survival from 45% to 50% \((P = .016)\).
2. Eliminating the Concerns
Evidence #2, Eliminating the Concerns

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.


- Cited 999 times since 2003
- Result: median survival with surgery alone was 46 months, 77 months with combination therapy
Eliminating the concerns

• This study provided evidence that NAC does not prevent patients from undergoing cystectomy and does not increase the risk of perioperative complications

• No deaths were associated with neoadjuvant chemotherapy
Eliminating the concerns

- Cystectomy was performed as planned for **82%** of patients assigned to NAC & **81%** of those assigned to cystectomy alone.

- **38% of patients who** received NAC **had a** pathologic **complete response** at the time of surgery, and **85% of them** were alive at 5 ys.
3. Consolidating the Data
Neoadjuvant Chemotherapy for Transitional Cell Carcinoma of the Bladder: A Systematic Review and Meta-Analysis

February 2004 Volume 171, Issue 2, Part 1, Pages 561–569

• 2,605 patients
• **6.5%** absolute benefit in 5-year OS
• Chemotherapy can be *administered safely without adverse outcomes resulting in delayed local therapy*
• Further efforts to identify the patients most likely to benefit from neoadjuvant therapy are necessary to optimize its use.
4. The Long Term Effect
Evidence #4, The Long Term Effect

A controlled trial by the (MRC) and the (EORTC) randomly assigned 976 patients with T3 or T4a or high-grade T2 BC to undergo either definitive treatment immediately or preceded by NAC.
The Long Term Effect

- Definitive treatment included **cystectomy** (428 pt), **RTx** (403 pt), or **RTx + cystectomy** (66 pt).

- At a median **follow-up of 8 years**, OS was significantly greater in the arm of NAC.

- The survival benefit was **6%** absolute increase in the likelihood of being alive at 3 years (56% vs. 50%), 5 years (49% vs. 43%), and 10 years (36% vs. 30%). [**Level of evidence: 1A**]
You know what?

We can’t change our practice according to studies if they are not part of the guidelines!!!
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

Version 2.2014

NCCN.org
PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

Perioperative chemotherapy (neoadjuvant or adjuvant)

- Regimens
  - DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles\(^1,2\)
  - Gemcitabine and cisplatin for 4 cycles\(^3,4\)
  - CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles\(^5\)

- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.\(^1,6,7\)
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.\(^7\)
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.\(^2,8\) Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence showing equivalence to conventional MVAC in the setting of advanced disease.\(^4,8\)
• While there is still insufficient evidence for the routine use of adjuvant chemotherapy in clinical practice, it is likely that high-risk patients, (extravesical and/or lymph node +ve disease) that have not received NAC, will benefit most from adjuvant chemotherapy.
Urothelial Carcinoma of Bladder and Upper Tract

This practice algorithm has been specifically developed for M.D. Anderson using a multidisciplinary approach and taking into consideration circumstances particular to M.D. Anderson, including the following: M.D. Anderson’s specific patient population; M.D. Anderson’s services and structure; and M.D. Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

NOTE: Consider clinical trials as treatment options for eligible patients.

STAGE

T 2-4 (Muscle Invasion)

EUA¹

CXR

CT of abdomen and pelvis

CT of chest if positive CXR or clinical suspicion for metastasis

Bone Scan if elevated alkaline phosphatase or bone pain

Presence of poor risk factors:

1. Lymphovascular invasion
2. Inability to assess depth of invasion
3. Variant histology such as small cell
4. Hydronephrosis
5. Tumor involving bladder diverticulum

Patient accepts surgery?

Yes

No, M0

T2/3a

Neoadjuvant chemotherapy

Clinical trial

Assess response by cystoscopy/EUA¹/imaging, as indicated

Resectable?

Yes → Cystectomy → See Surveillance On Page 6

No → Salvage therapy

pT3a

Observation

pT3b

N+, margins positive or prostatic stromal invasion pT4a

Consider adjuvant cisplatin or ifosfamide-based chemotherapy (i.e.: DDMVAC, IAG, etc., refer to chemotherapy principles, Page 7)

Upstaged at surgery?

Yes → Cystectomy

No

Assess response by cystoscopy/EUA¹/imaging, as indicated

Resectable?

Yes → Cystectomy → See Surveillance On Page 6

No → Additional chemotherapy

¹EUA = exam under anesthesia

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Convinced yet?

What about some guidelines for urologists?
Guidelines on Muscle-invasive and Metastatic Bladder Cancer
### 6.4 Conclusions and recommendations for neoadjuvant chemotherapy

<table>
<thead>
<tr>
<th>Conclusions</th>
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<td>Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival.</td>
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<th>Recommendations</th>
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<td>Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatinum-based combination therapy.</td>
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Advantages?

• Chemotherapy is delivered at the earliest time-point, when the burden of MTs is low.
• Potential reflection of in-vivo chemosensitivity.
• Better tolerability of chemotherapy is expected.
• Patients might respond by negative LNs and surgical margins.
What on hell was I thinking when I opened that patient!!!!
What type of NAC?

- The standard is the MVAC
- The alternative is GEM/CIS
Pooled Analysis of Clinical Outcomes with Neoadjuvant Cisplatin and Gemcitabine Chemotherapy for Muscle Invasive Bladder Cancer

CONCLUSIONS: Neoadjuvant cisplatin and gemcitabine yield appreciable pathological response rates in patients with muscle invasive bladder cancer. Since pathological response has been implicated as a potential surrogate for survival in muscle invasive bladder cancer, these data suggest that neoadjuvant cisplatin and gemcitabine may warrant further prospective assessment.

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Where do we stand?

- We started a study last year in Assiut University **Urology and Nephrology Hospital** that recruited 21 patients, using GEM/CIS as a NAC.
- 12/21 (57.1%) patients had complete or partial response.
- 6 (28.6%) had stable disease, 3 (14.3) patients had progressive disease.
1. Male, 53 ys. T3b G3, with Lt HN.
Case 1 post NAC
Case 2

- Female 60 ys. T3b, G3.
Case 2 post NAC
Case 3

- Male 65ys, T3b G3
Case 3 post NAC
How many more prospective trials must we perform to effectively establish that NAC is indeed the standard of care?
شحبة