Η φιλοσοφία των πολυτροπικών θεραπειών

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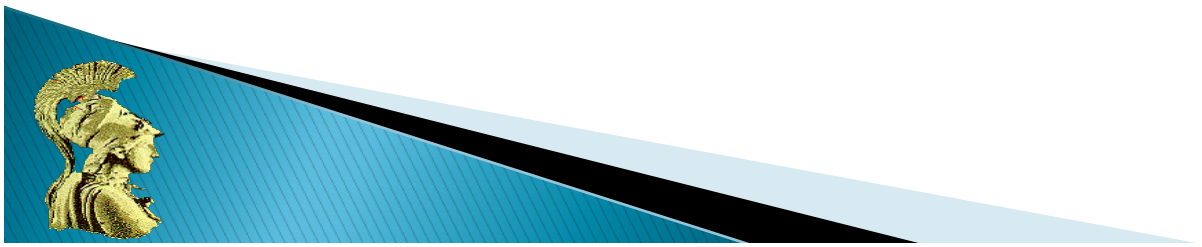
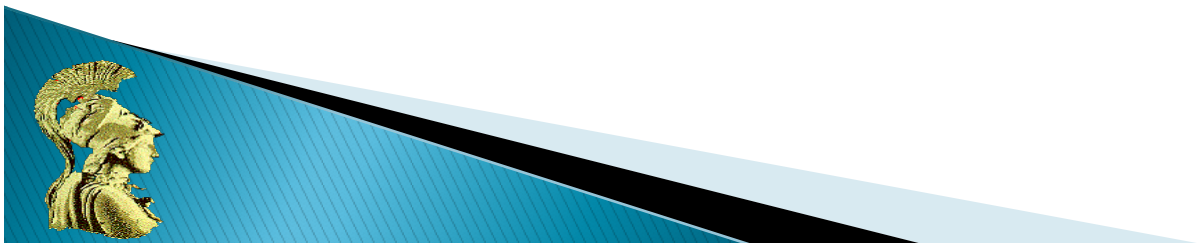
11ο UROSCHOOL 2018 ΣΧΟΛΕΙΟ ΟΥΡΟΛΟΓΙΑΣ

Σύγκρουση συμφερόντων

Ομιλητής/Προεδρείο: Astellas, Ferring, Sanofi



Πολυτροπική θεραπεία:
multimodality treatment




80's
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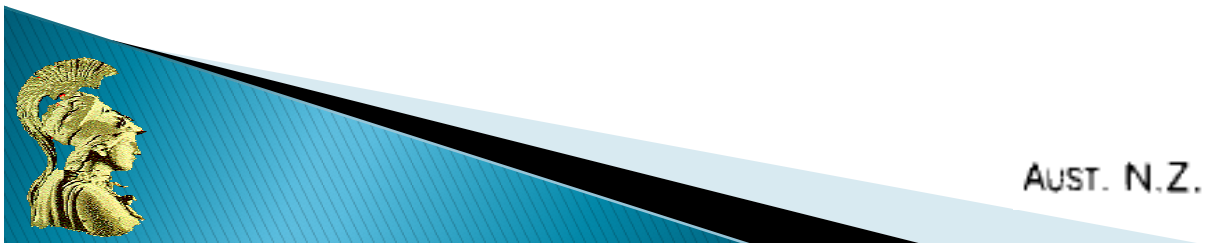
MULTIMODALITY TREATMENT OF CANCER

JOHN FREDERICK FORBES
Department of Surgery, University of Melbourne,

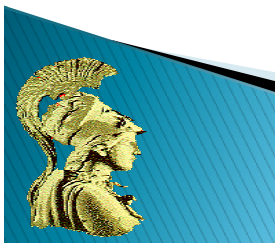
With these new developments the relationship between doctor and patient will be of greater importance. The potential for patient confusion will increase, and with it the need for all specialists to retain their close patient relationships. The great majority of patients are likely to continue to see a surgeon as their primary specialist, and this emphasises the requirement for surgeons to maintain an awareness of all relevant developments in all modalities of cancer therapy. Failure to do this will detract from the privileged oncology role that surgeons currently maintain and enjoy.



Aims of different modalities

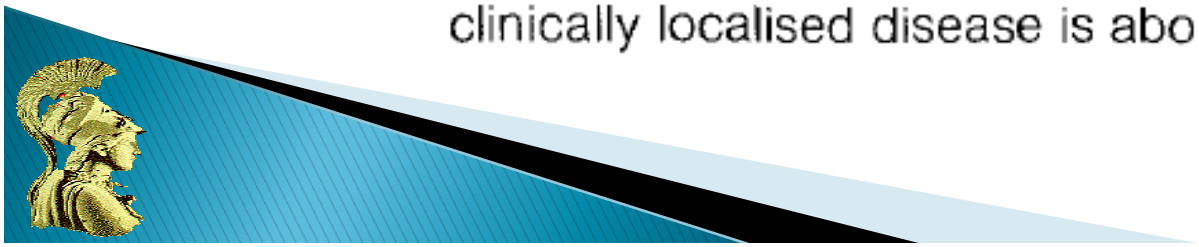
(a) "Curable" local disease (for example T1NoMo Breast Cancer)*	
Modality	**Aims**
Surgery alone	1. Tumour Removal — "cure" 2. Minimal morbidity
Radiotherapy alone	1. Tumour removal — "cure" 2. Minimal morbidity
Surgery plus radiotherapy	1. Equivalent tumour removal with *less* morbidity
(b) "Curable" local disease with occult spread (adjuvant therapy)	
Surgery	1. Local tumour removal 2. Minimal morbidity 3. Bulk reduction
Radiotherapy	1. Local tumour control 2. Minimal morbidity 3. Sterilization of "sanctuary sites" not inaccessible to chemotherapy
Systemic chemotherapy	1. Eradication of metastatic disease — "cure" 2. Improved local control

*Small breast cancer, up to two cm in diameter, no axillary gland involvement, no detectable metastases.



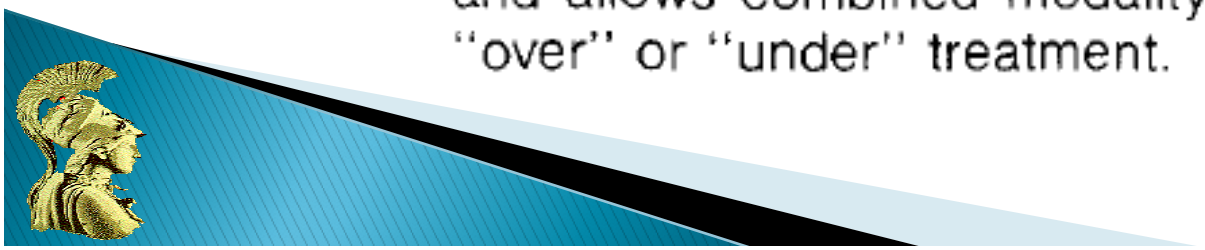
Principles of Combined Modality Approach

1. Local therapy, surgery or radiotherapy, can only treat localised disease. Neither modality will cure patients with metastases.
2. Systemic spread, even as occult metastases, requires systemic treatment (cytotoxic chemotherapy, or endocrine therapy) for adequate control or cure.
3. Surgery is a mechanical intervention — it cannot change the biology of the disease at the cellular or molecular level. Both radiotherapy and cytotoxic chemotherapy can.
4. Clinically overt metastases are usually incurable by systemic therapy (although important exceptions exist, such as metastatic teratoma, which can be cured by cis-platinum combination regimens).
5. The expectation of cure by local therapy alone for clinically localised disease is about 50%. Beyond



this, cure rates are directly proportional to the effectiveness of systemic therapies.

6. Optimal local treatment must consider both control of disease and local morbidity. If cure is not possible, regional morbidity has greater relevance. Locally recurrent disease may contribute to local morbidity, and it is not easy to balance the relative gains of surgery and radiotherapy. Effective systemic therapy can also assist local control, and must be considered when palliative treatment to reduce local control is planned.
7. Prognostic factors can be identified that allow selection of patients with early disease who have a high risk of developing (probably already having) metastatic disease. This allows adjuvant systemic therapy to be used more precisely for the groups where it is most likely to be beneficial, and allows combined modality therapy to avoid "over" or "under" treatment.



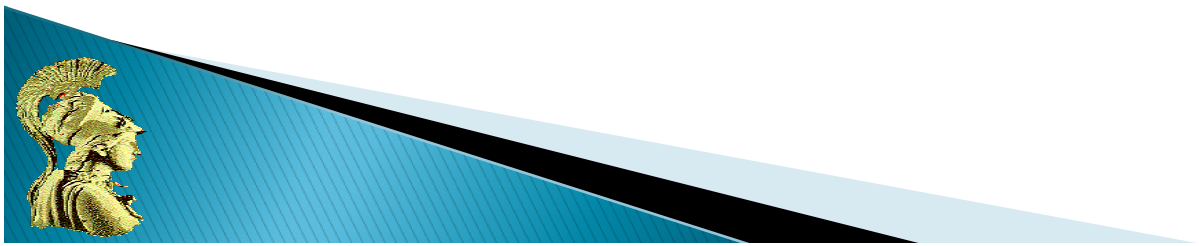
Does "Multimodal" Therapy For Cancer Really Work?

Walter Lawrence, Jr., M.D.

CA-A CANCER JOURNAL FOR CLINICIANS
VOL. 35, NO. 1 JANUARY/FEBRUARY 1985

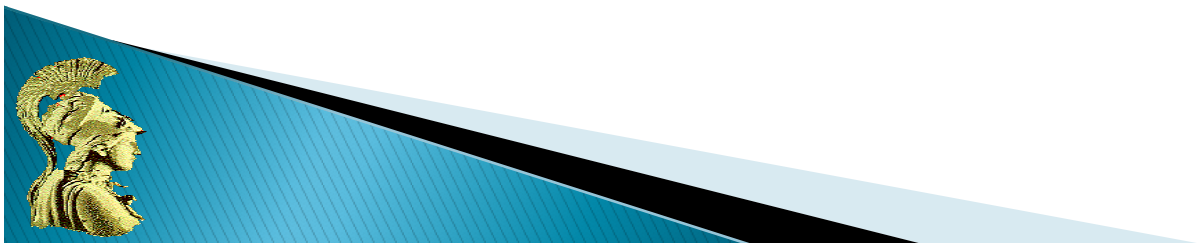
The list of cancers for which the benefit of adjuvant therapy has been established is, unfortunately, a relatively short one.

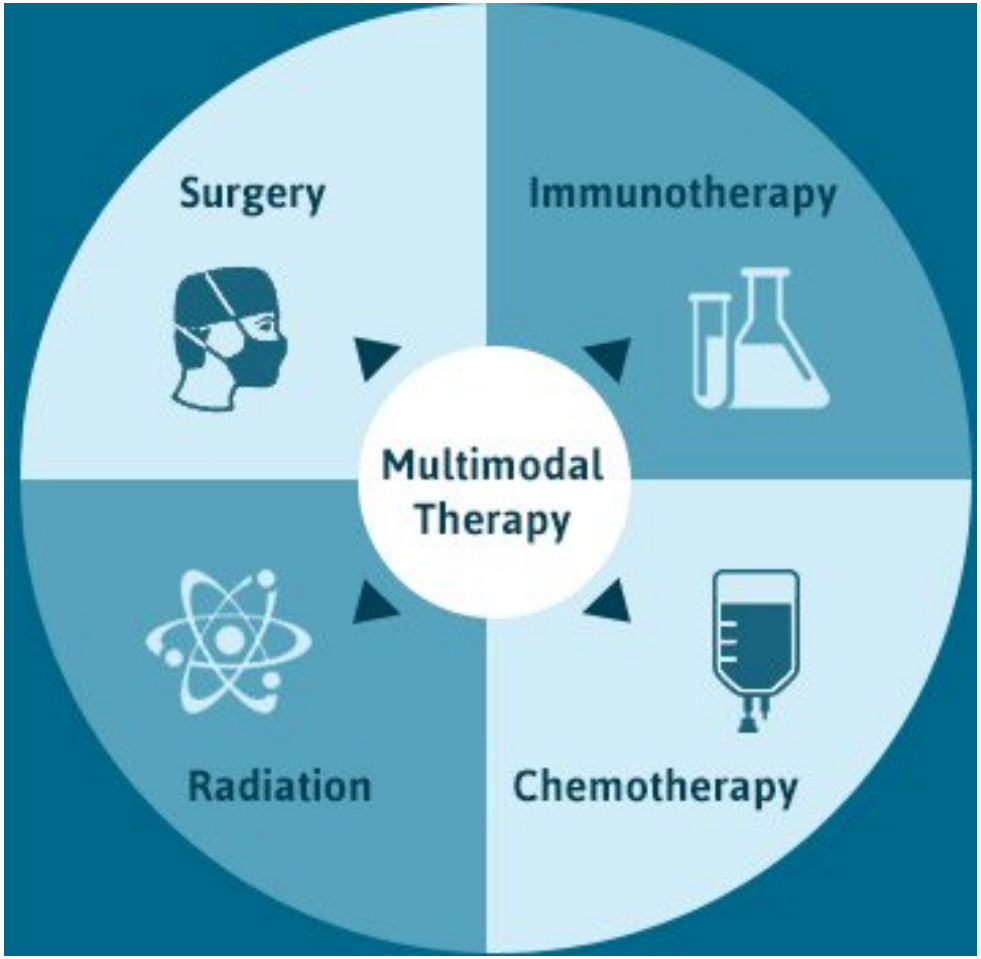
We must make the effort to include as many of our patients as possible in meaningful prospective clinical trials designed to define more effective combination therapy programs.



SURGICAL ADJUVANT THERAPY SCORE CARD

Benefit Established	Possible Benefit	No Benefit
Wilms' tumor	Head and neck cancer	Lung cancer
Childhood rhabdomyosarcoma	Gastric cancer	Esophageal cancer
Testicular cancer	Rectal cancer	Pancreatic cancer
Ovarian cancer	Osteogenic sarcoma	Colon cancer
Breast cancer	Soft tissue sarcoma	Bladder cancer
Carcinoma of anus		Prostate cancer
		Melanoma




Surgery
Immunotherapy
Multimodal Therapy
Radiation
Chemotherapy

Heterogeneity (molecular crosstalk mechanisms)

Τοπική νόσος, προχωρημένη (low vs high meta volume)

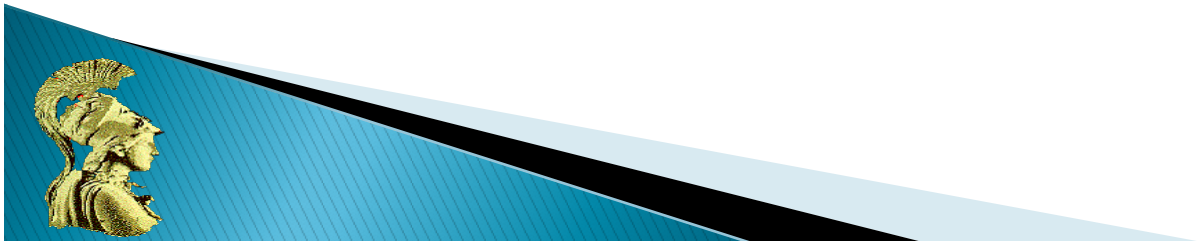
Occult/micro-/oligo- metastases

Organ preserving techniques

Novel RTx techniques and ChemoTx agents

Chemoradiotherapy protocols

Ολιγομεταστατική νόσος



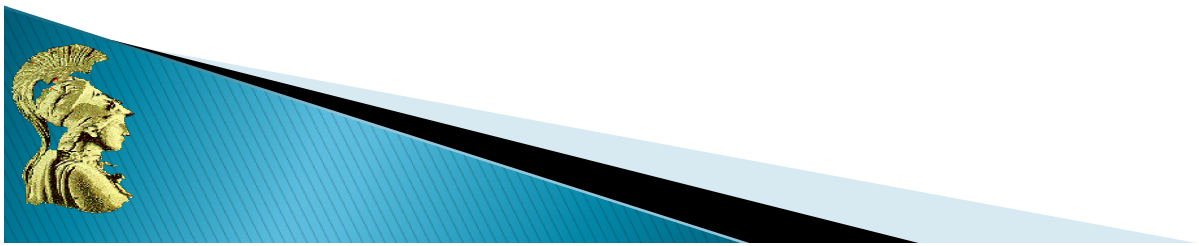
EDITORIAL

Oligometastases

Samuel Hellman
Ralph R. Weichselbaum
The University of Chicago
Chicago, IL

The number of metastases should reflect the biologic progression of the tumor. It will also determine the opportunities and the nature of potentially therapeutic interven-

Journal of Clinical Oncology, Vol 13, No 1 (January), 1995: pp 8-10



Radiation Delivery

- Conventional (3-5 beams)
  - 3-D conformal radiation therapy
  - Intensity modulated radiation therapy (IMRT)
    - Linac based radiation
    - Tomotherapy
- Stereotactic Radiation Therapy (10-12 beams)
  - Gamma Knife
  - Linac based (isocenter)
  - Cyberknife (non-isocenter)
- Proton Therapy (one beam repeated)

JOHNS HOPKINS
MEDICINE

Radiation: Fractionation

- Standard fractionation:
  - 1.8-2.0 Gy a day, 5 days a week for 25-30 treatments
- Conventional hypofractionation:
  - 3-5 Gy a day, 5 days a week for 10-15 treatments
- Stereotactic radiotherapy:
  - 15-25 Gy a day, 1-3 days a week for 1-5 treatments

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MEDICINE

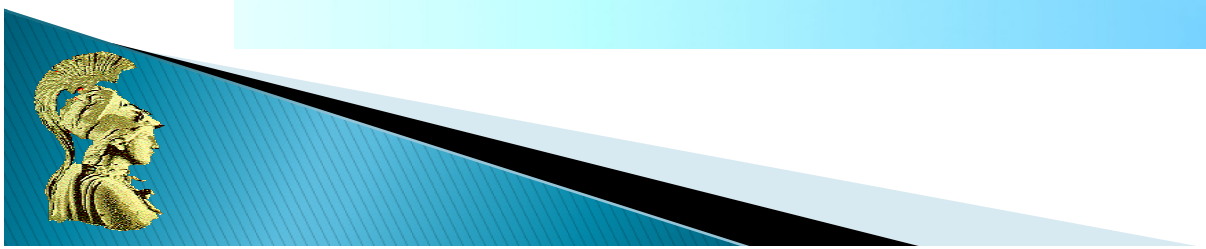
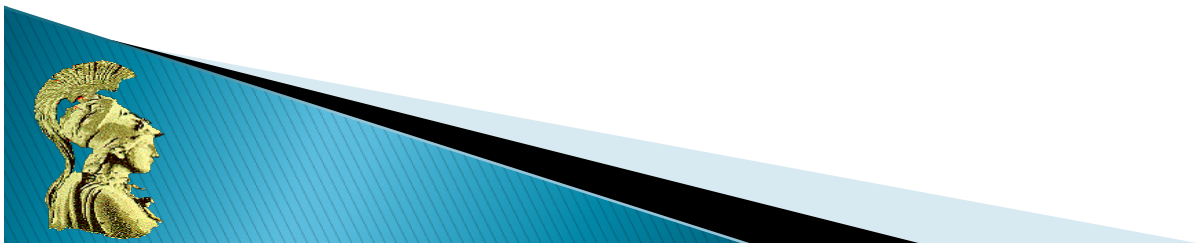


Table 1

Advantages and Disadvantages of SBRT

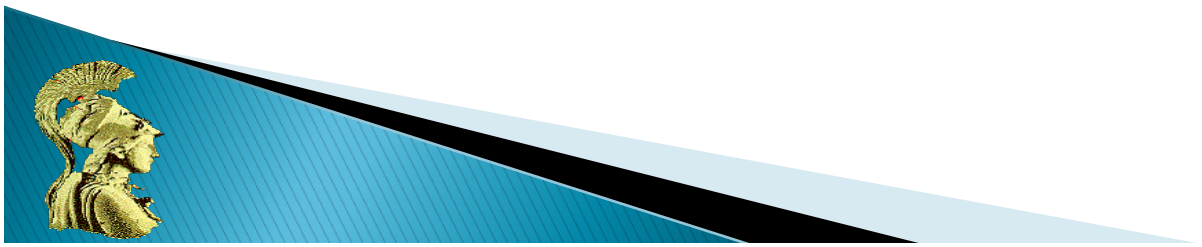
Advantages	Disadvantages
Shortened treatment course	Increased treatment time per fraction
Delivery of ablative dose	Difficult to use emergently
Reduced treatment volumes	Large fractional doses do not provide sparing for normal tissues
Potentially faster and more durable pain relief	Cannot be used for large lesions
Can be used for previously irradiated sites	Technology/methods are not universal/standardized
	More expensive
Large fractional doses affect "radioresistant" tumors	Does not treat subclinical disease
	Limited clinical experience leaves questions about safe and effective regimens

SBRT = stereotactic body radiation therapy.



Χήμειο- Άκτινο- θεραπεία

Αλληλεπίδραση



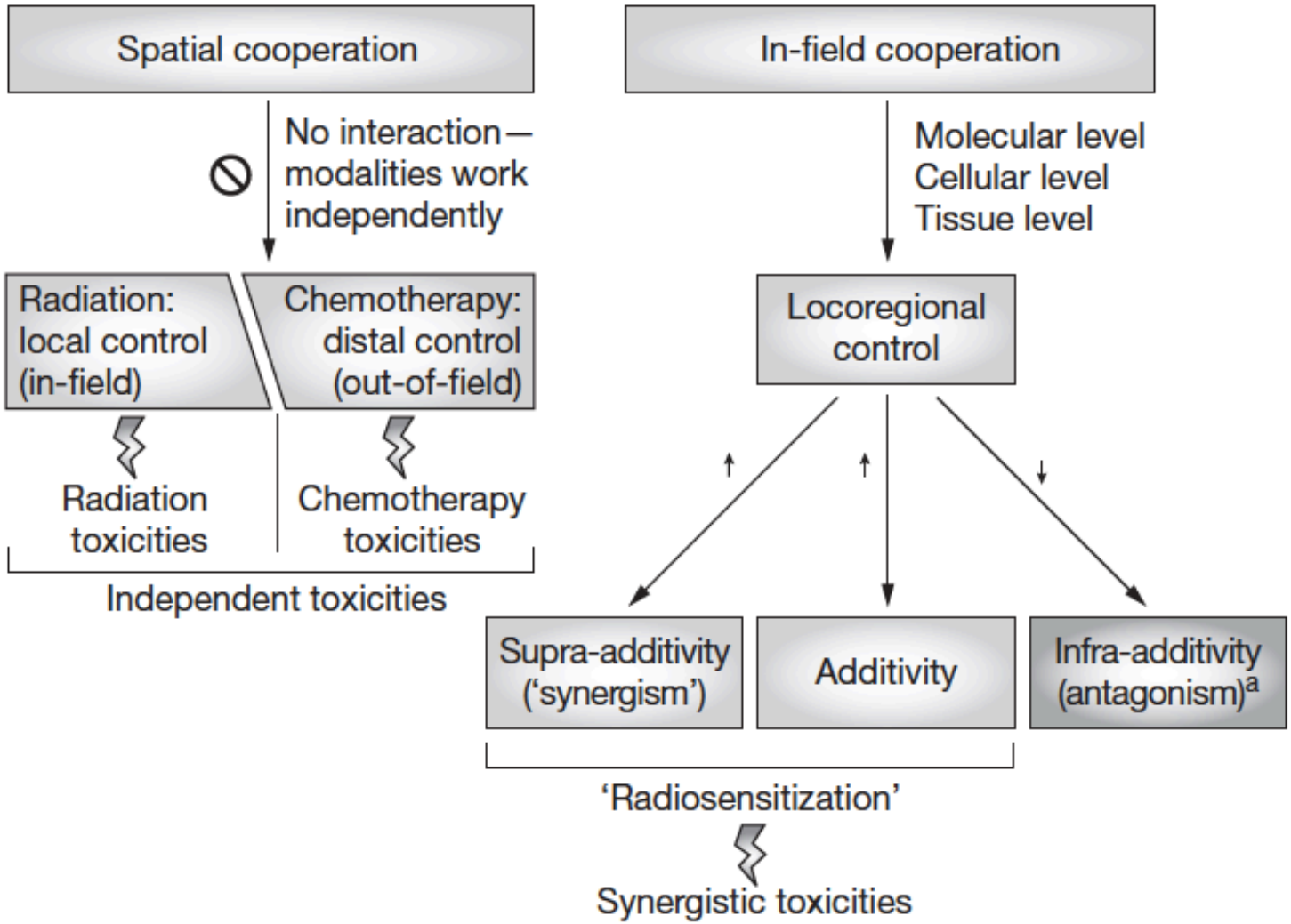


Figure 1 Rationale for adding chemotherapy to radiation. Spatial and in-field cooperation are the two idealized types of cooperation between radiation and chemotherapy. Both mechanisms can contribute synergistically to clinical benefit. [a]Usually not desirable as this could protect the tumor.

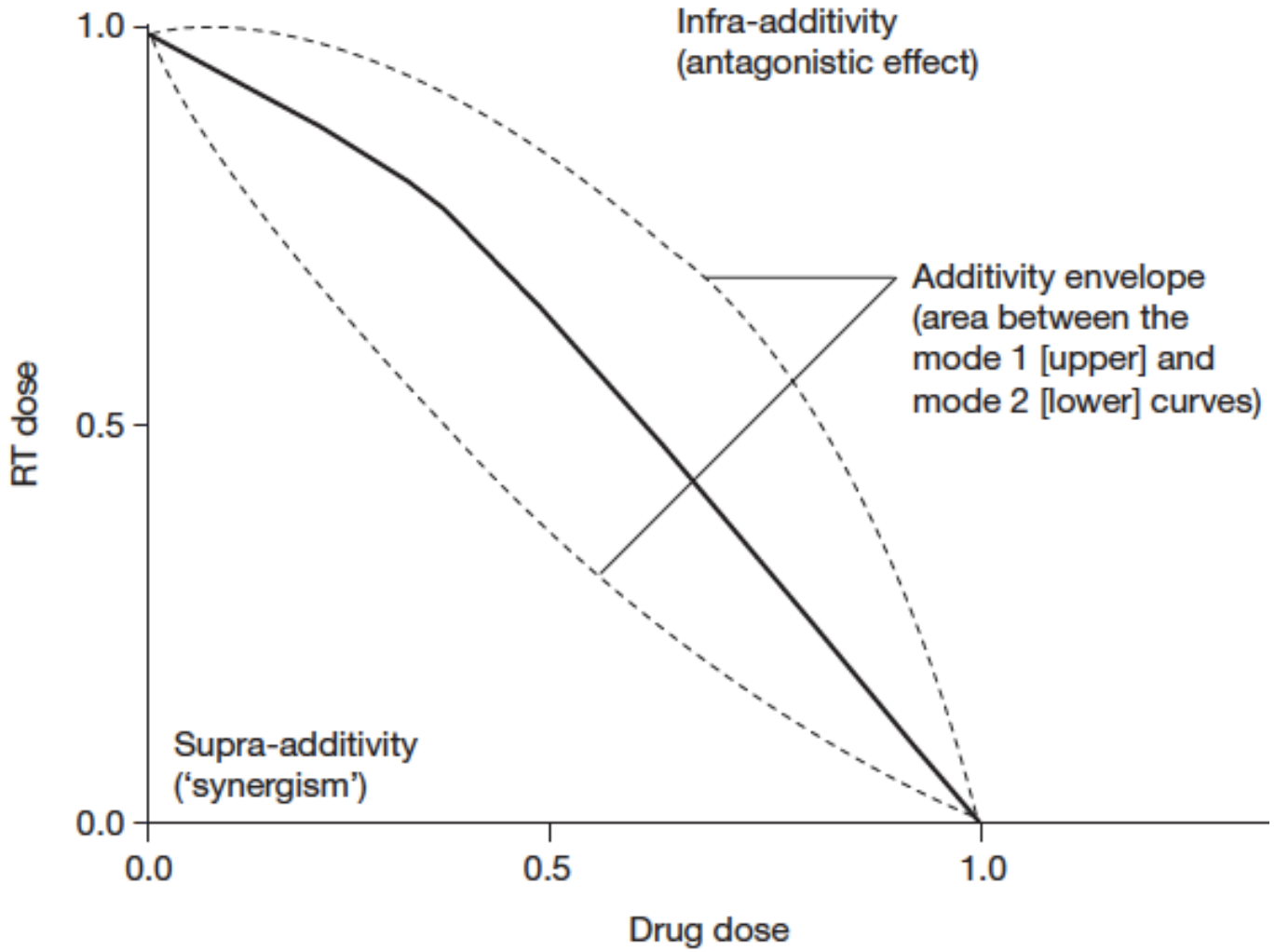


Figure 2 Schematic example of an isobologram depicting the combination of radiation and a systemic agent. The *x* and *y* axes show the isoeffective levels for radiation and drug. The thick line is the line of additivity, and the additivity envelope is based on the combined standard errors. Curves above the envelope represent antagonistic effects and curves below the envelope represent 'synergistic' effects.[1,41] Abbreviation: RT, radiotherapy.

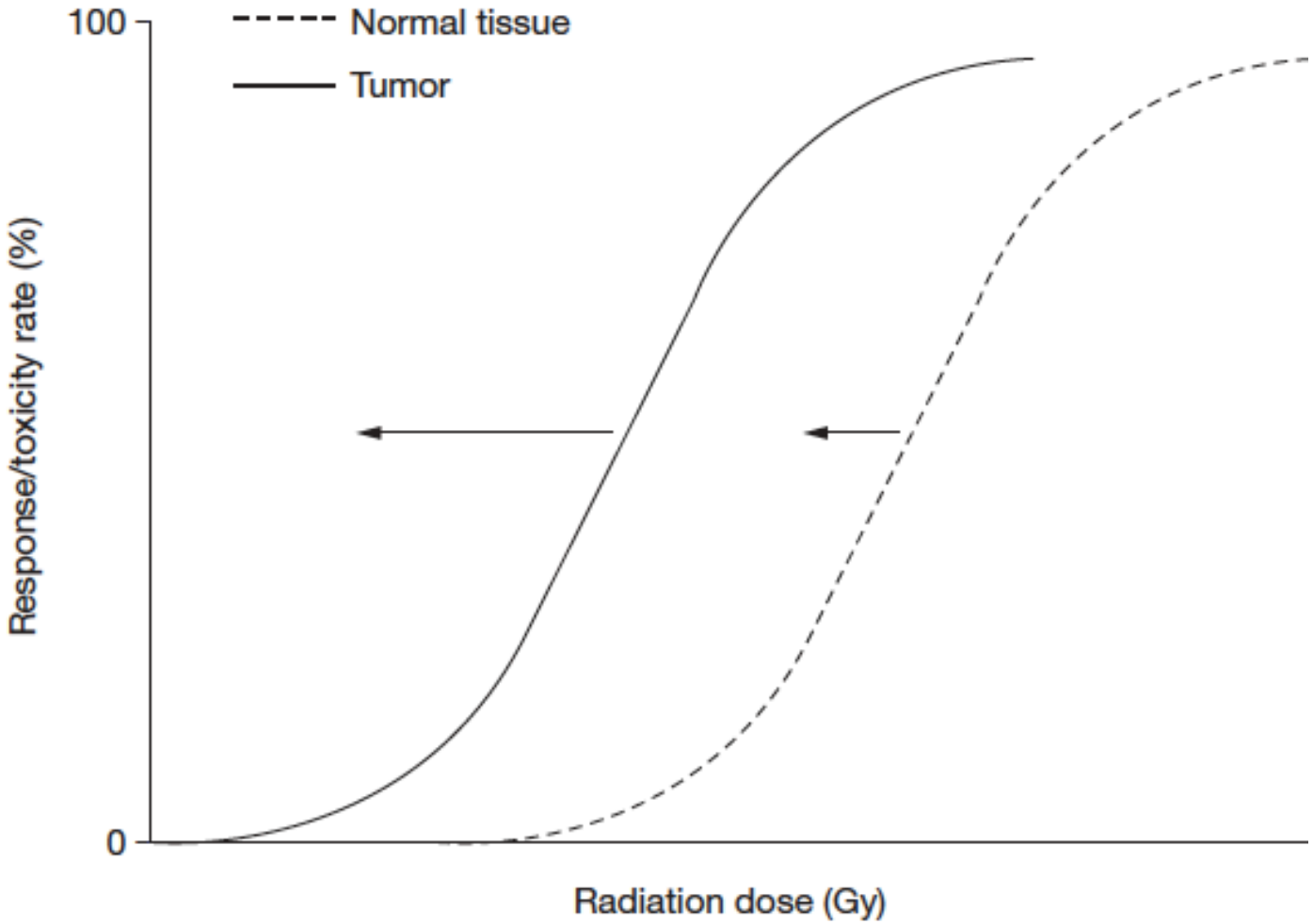
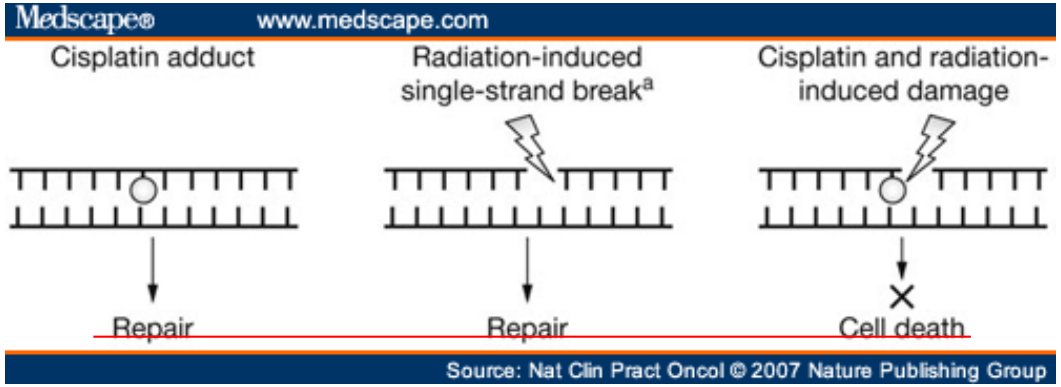


Figure 3 Schematic dose–response curves for tumor and normal tissue damage with radiation. The offset between the two curves indicates the therapeutic range. Chemoradiotherapy leads to a shift of both curves to the left, ideally with a stronger shift of the tumor curve (as indicated by the longer arrow), increasing overall efficacy of treatment (radiation enhancement).[120]

The concurrent chemoradiation paradigm general principles

Tanguy Y Seiwert*, Joseph K Salama and Everett E Vokes



KEY POINTS

- Concurrent chemoradiotherapy has improved cancer care during the past two decades in multiple diseases, and can be used in the neoadjuvant, primary (definitive), or adjuvant setting
- Chemotherapy or targeted agents can increase the efficacy of radiation
- Radiosensitizing effects (interaction within the radiation field) can be additive or supra-additive
- Multiple mechanisms underlie radiosensitizing properties of chemotherapeutic agents and include increased radiation damage, inhibition of DNA repair, cell-cycle synchronization, increased cytotoxicity against hypoxic cells, inhibition of prosurvival pathways, and abrogation of rapid tumor cell repopulation
- Radioresistance occurs through multiple mechanisms, such as a large tumor burden, hypoxia, rapid tumor cell repopulation, as well as the constitutive or acquired activation of radioresistance signaling pathways
- In addition to the classic chemotherapeutic agents with radiosensitizing properties (i.e. cisplatin and paclitaxel), several novel agents show promising interactions with radiation (e.g. EGFR inhibitors, pemetrexed, tirapazamine, and potentially several other targeted therapies)

NATURE CLINICAL PRACTICE ONCOLOGY

Table 2 Mechanisms of radioresistance.

Process affected	Mechanism
Large tumor cell burden	Tumor size is inversely correlated with tumor response. Radiation-induced cell kill is a random event—the higher the number of cells, the higher the chance of cells escaping a lethal hit.[121,122]
Tumor cell microenvironment/ hypoxia	Oxygen is needed to generate ROS and other radicals with radiation. ROS are thought to be essential to the cytotoxic effect from radiation (reviewed in Cook *et al.*[123]). Hypoxia is present for two reasons: 1. increased interstitial pressure may cause hypoperfusion, hypoxia and acidosis;[124–126] 2. cancer-related anemia contributes to local hypoxia (HIF1α is a marker of tumor hypoxia).
Inherent or acquired tumor cell resistance	Multiple mechanisms are thought to contribute, including mutated p53[29], DNA repair gene amplification, increased levels of ROS scavengers, activation of prosurvival/poor-prognosis oncogenes (EGFR,[100,101] c-MET[32]).
Repopulation	Regrowth of tumor cells between doses of radiotherapy or chemotherapy. Accelerated repopulation might lead to treatment failure and emergence of true radioresistance (see row above).[22]

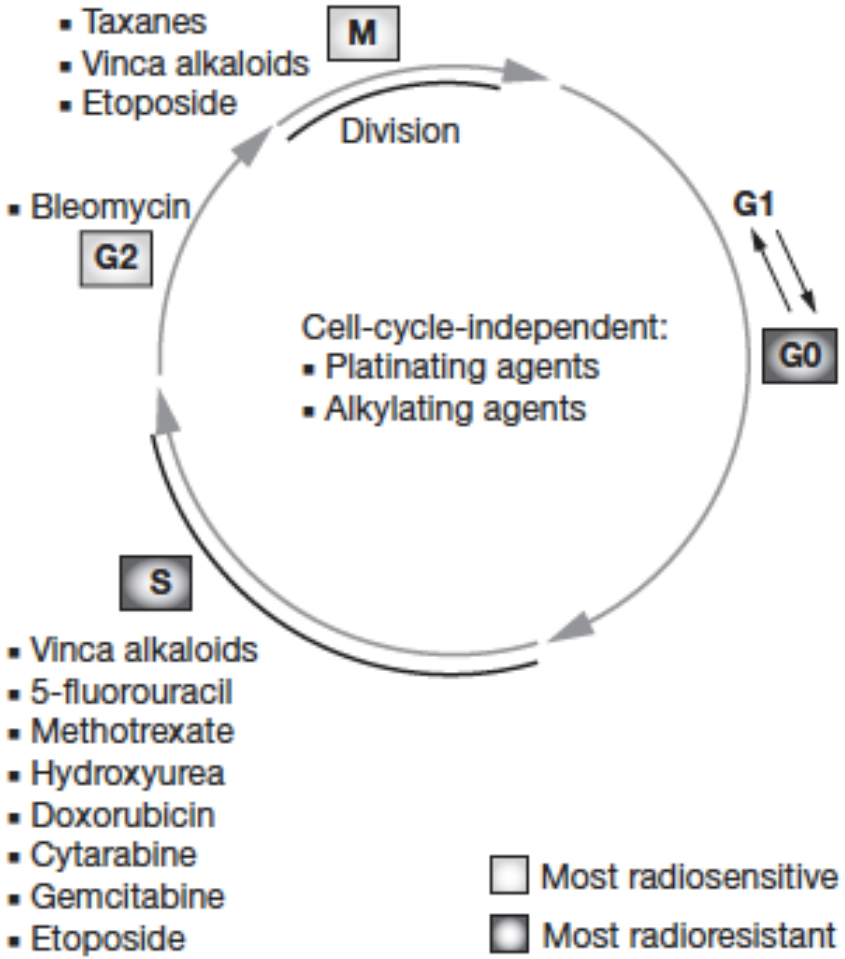
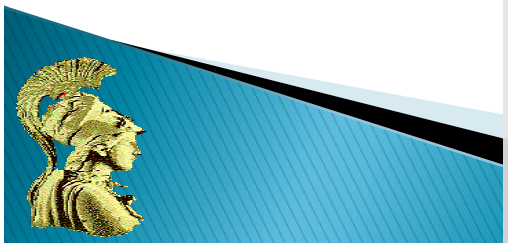


Figure 4 Cell-cycle schematic and respective sensitivity to chemotherapeutic agents.

Table 3 Mechanisms of chemotherapy and radiotherapy interaction.

Process affected	Mechanism[a]
Increased radiation damage[a]	Incorporation of chemotherapy drug into DNA/RNA
Inhibition of DNA repair process[a]	Interference with the DNA repair process after radiation
Cell-cycle interference (cytokinetic cooperation and synchronization)[a]	Most cytotoxic chemotherapies as well as radiation are cell-cycle-specific, and proliferating cells are most susceptible Accumulation of cells in the G2 and M phases (the most radiosensitive phases) Elimination of radioresistant cells in the S phase
Enhanced activity against hypoxic cells[a]	Reoxygenation second to tumor shrinkage. Hypoxic cells are 2.5–3.0 times less radiation-sensitive than normoxic cells[18,44] Chemotherapy can help to eliminate hypoxic cells
Radiotherapy enhancement by preventing repopulation[a]	Systemic therapy can slow or stop rapid proliferation, which could otherwise be the basis for repopulation phenomenon
Inhibition of prosurvival and 'poor prognosis' markers[a]	Targeted therapies (best demonstrated for EGFR inhibition) block signaling pathways that might be responsible for radioresistance and poor prognosis
Hyperradiation sensitivity[b]	HNSCC cells resistant to standard-fraction CRT can be resensitized to CRT by using smaller fraction sizes (<1 Gy) more frequently



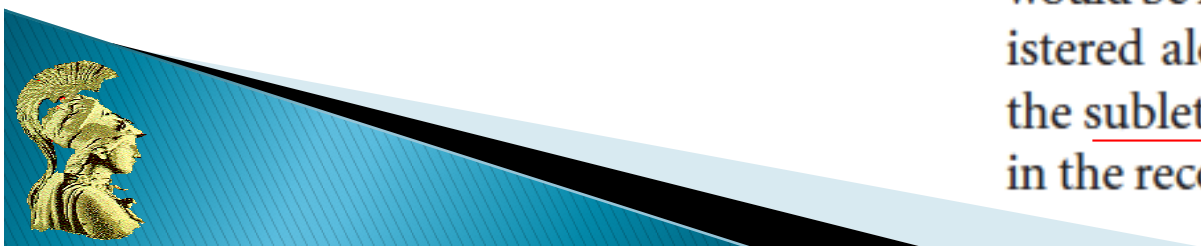
Specific mechanisms of chemotherapy and radiotherapy interaction

Platinum analogs

Cisplatin is one of the most commonly used drugs for concurrent chemoradiotherapy.

that radiation induces free radicals and subsequently the formation of toxic platinum intermediates, which increase cell killing.[52] Moreover, ionizing radiation can increase cellular uptake of platinum.[53] Damage to DNA by ionizing radiation that typically would be repairable can become fixed and lethal through cisplatin's free-electron-scavenging capacity. This inhibition of DNA repair (Figure 5)[54] leads to an increased incidence of cell-cycle arrest and apoptotic cell death after radiation.[41,55]

synergistic combination of cisplatin and radiation involves low doses of each, either of which would be insufficient to cause cell death if administered alone. Cisplatin would seem to inhibit the sublethal damage repair process implicated in the recovery of insufficiently radiated cells.[41]



Effect of mitochondrial metabolism-interfering agents on cancer cell mitochondrial function and radio/chemosensitivity

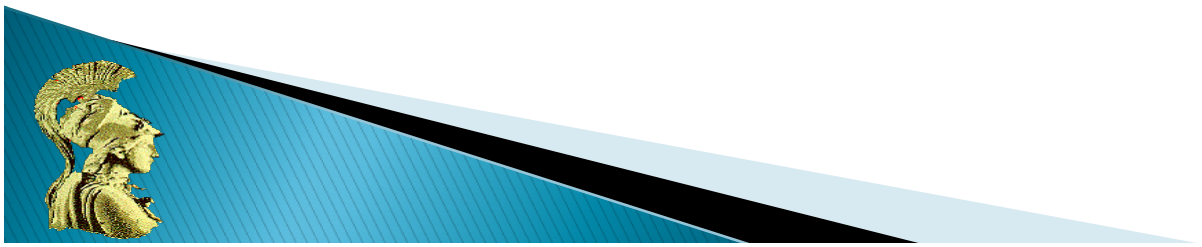
Achilleas G. Mitrakas, Dimitra Kalamida and Michael I. Koukourakis

Abnormal mitochondrial function is common in cancer cells and activates metabolic pathways suppressed in normal tissues. Experimental and clinical studies suggest that mitochondria might serve as targets for novel anticancer therapies. We investigated whether mitochondrial metabolism-interfering agents (MMIAs) available currently in clinical practice affect cancer cell mitochondrial metabolism and synergize with chemotherapy and radiotherapy. Two cancer cell lines A549 (lung cancer) and DU145 (prostate cancer) were treated with a variety of MMIAs (metformin, nimodipine, memantine, oxytetracycline, amiodarone, and sodium azide) and their response was assessed using a resazurin reduction method and confocal

Anti-Cancer Drugs 2014, 25:1182–1191

Πολυτροπική θεραπεία

(πρωταρχική, νεοεπικουρική, επικουρική)



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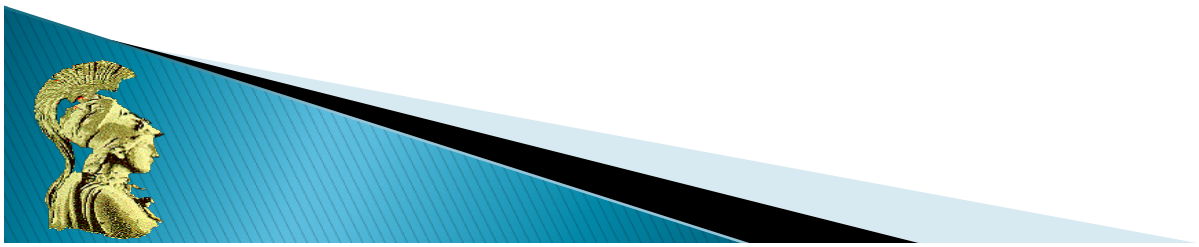
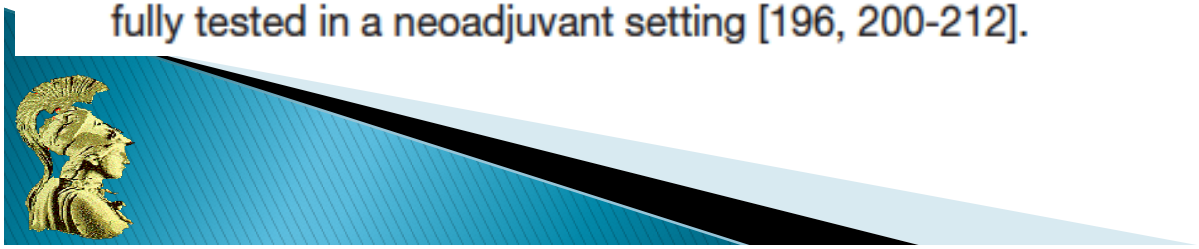


Neoadjuvant chemotherapy

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [194, 195], although published studies on the negative effect of delayed cystectomy only include chemonaive patients. There are no trials indicating that delayed surgery, due to NAC, has a negative impact on survival.
- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 post-operative complications was seen in both treatment arms [196]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm, 71% received all three chemotherapy cycles [197].
- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% [198, 199]. Overtreatment is a possible negative consequence.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [196, 200-212].



Trends in the Use of Perioperative Chemotherapy for Localized and Locally Advanced Muscle-invasive Bladder Cancer: A Sign of Changing Tides

Zachary D. Reardon [a,*], *Sanjay G. Patel* [b], *Harras B. Zaid* [a], *C.J. Stimson* [a], *Matthew J. Resnick* [a,c,d], *Kirk A. Keegan* [e], *Daniel A. Barocas* [a,c], *Sam S. Chang* [a], *Michael S. Cookson* [f]

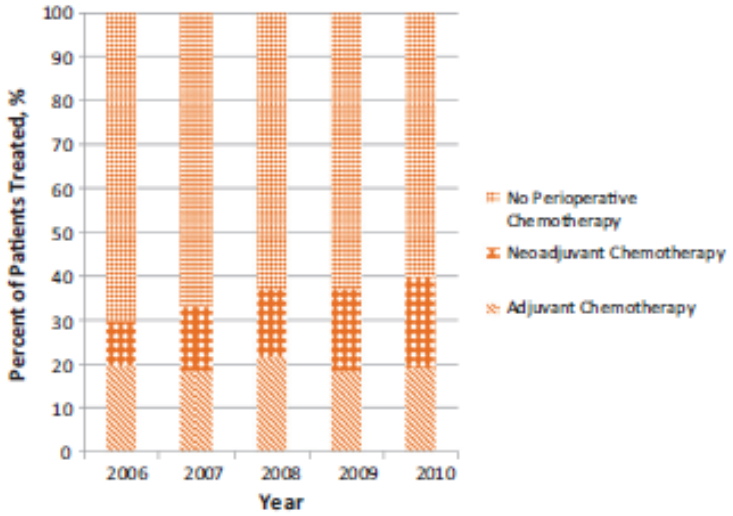


Fig. 1 – Change in perioperative chemotherapy use between 2006 and 2010. Neoadjuvant chemotherapy increased from 10.1% in 2006 to 20.8% in 2010 ($p = 0.005$), whereas adjuvant chemotherapy remained stable between 18.1% and 21.3% ($p = 0.68$).

Results and limitations: A total of 5692 patients met our inclusion criteria. POC use increased from 29.5% in 2006 to 39.8% in 2010 ($p < 0.001$). NAC use increased from 10.1% in 2006 to 20.8% in 2010 ($p = 0.005$); AC remained stable between 18.1% and 21.3%

Conclusions: POC use for MIBC increased from 2006 to 2010, with this increase disproportionately due to rising NAC utilization. Nonetheless, there is persistent variation

7.2.4 *Summary of evidence and guidelines for neoadjuvant chemotherapy*

Conclusions	LE
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (8% at five years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently, no tools are available to select patients who have a higher probability of benefitting from neoadjuvant chemotherapy (NAC). In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.	

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong

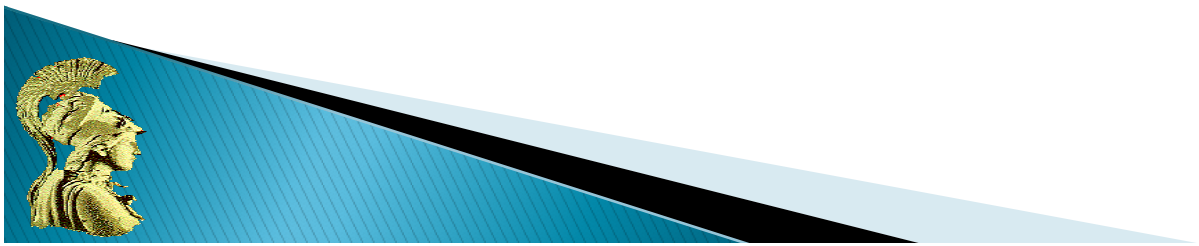
- 16% reduction in mortality risk;
- improvement in ten-year survival from 30% to 36% with neoadjuvant CMV;
- benefit with regard to distant metastases;

7.8.12 *Biomarkers*

Modest disease control rates with sporadic marked responses in some patients with UC have led to the investigation of biomarkers for assessment of post-operative prognosis and the potential value of peri-operative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most biomarkers are associated with tumour angiogenesis [522]. Small studies, usually retrospective, have investigated microvessel density, altered *p53* tumour expression [522], serum vascular endothelial growth factor [523], urinary and tissue basic fibroblast growth factor [524], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [525], and more recently, thrombospondin-1 [526], circulating tumour cells [527, 528], and multidrug resistance gene expression [529]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support their routine clinical use (LE: 3).

7.8.12.1 *Recommendation for the use of biomarkers*

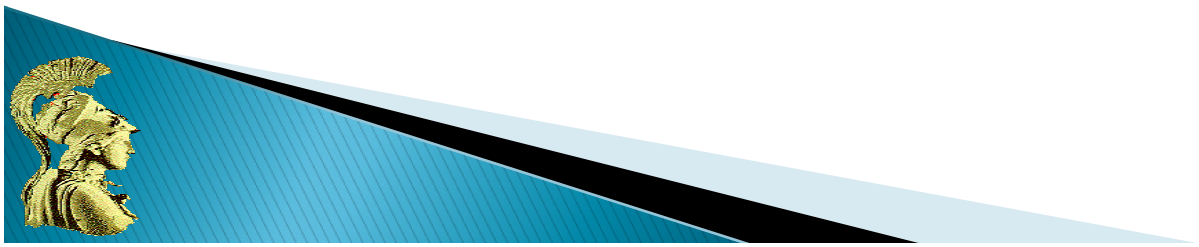
Recommendation	Strength rating
Do not use biomarkers in daily clinical practice since they have no impact on predicting outcome, treatment decisions, or monitoring therapy in muscle-invasive bladder cancer.	Strong



ICUD-EAU International Consultation on Bladder Cancer 2012: Radical Cystectomy and Bladder Preservation for Muscle-Invasive Urothelial Carcinoma of the Bladder

Georgios Gakis [a,*], *Jason Efstathiou* [b], *Seth P. Lerner* [c], *Michael S. Cookson* [d], *Kirk A. Keegan* [d], *Khurshid A. Guru* [e], *William U. Shipley* [b], *Axel Heidenreich* [f], *Mark P. Schoenberg* [g], *Arthur I. Sagaloswky* [h], *Mark S. Soloway* [i], *Arnulf Stenzl* [a]

[a] *Department of Urology, University Hospital Tuebingen, Tuebingen, Germany;* [b] *Department of Radiation Oncology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA;* [c] *Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA;* [d] *Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA;* [e] *Department of Urology, Roswell Park Cancer Institute, Buffalo, NY, USA;* [f] *Department of Urology, University Hospital Aachen, RWTH Aachen University, Aachen, Germany;* [g] *The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, MD, USA;* [h] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [i] *Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA*



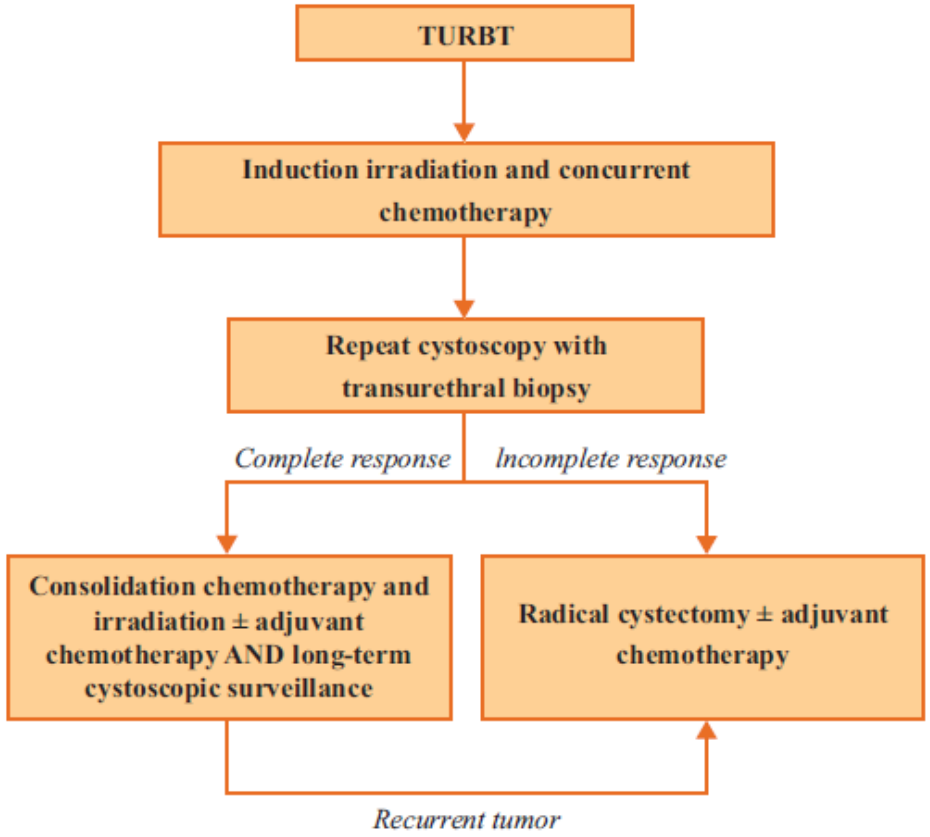


Fig. 2 – Current schema for trimodality treatment of muscle-invasive bladder cancer with selective bladder preservation. TURBT = transurethral resection of bladder tumor.

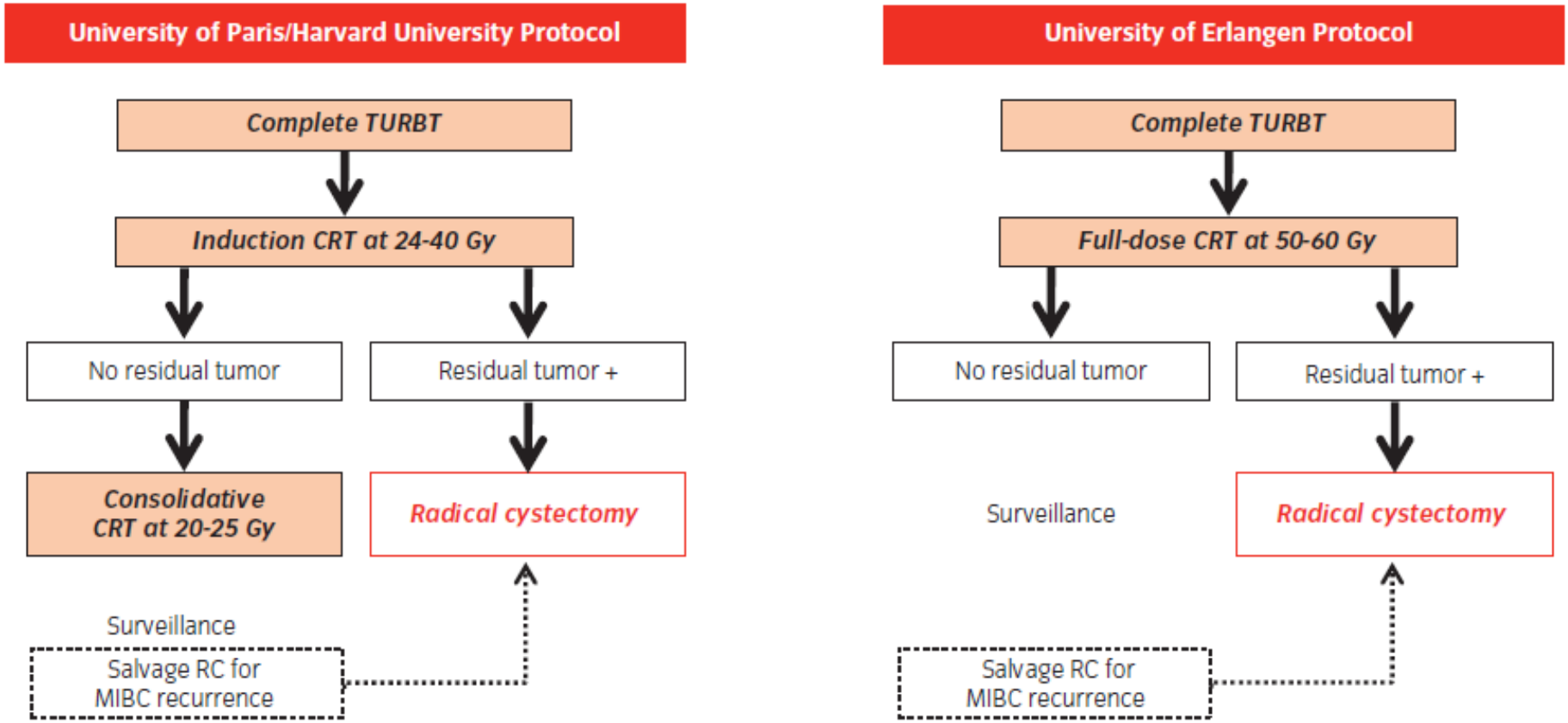


Fig. 1 Algorithms of two major trimodality bladder-sparing protocols at (a) University of Paris/Harvard University and (b) University of Erlangen.

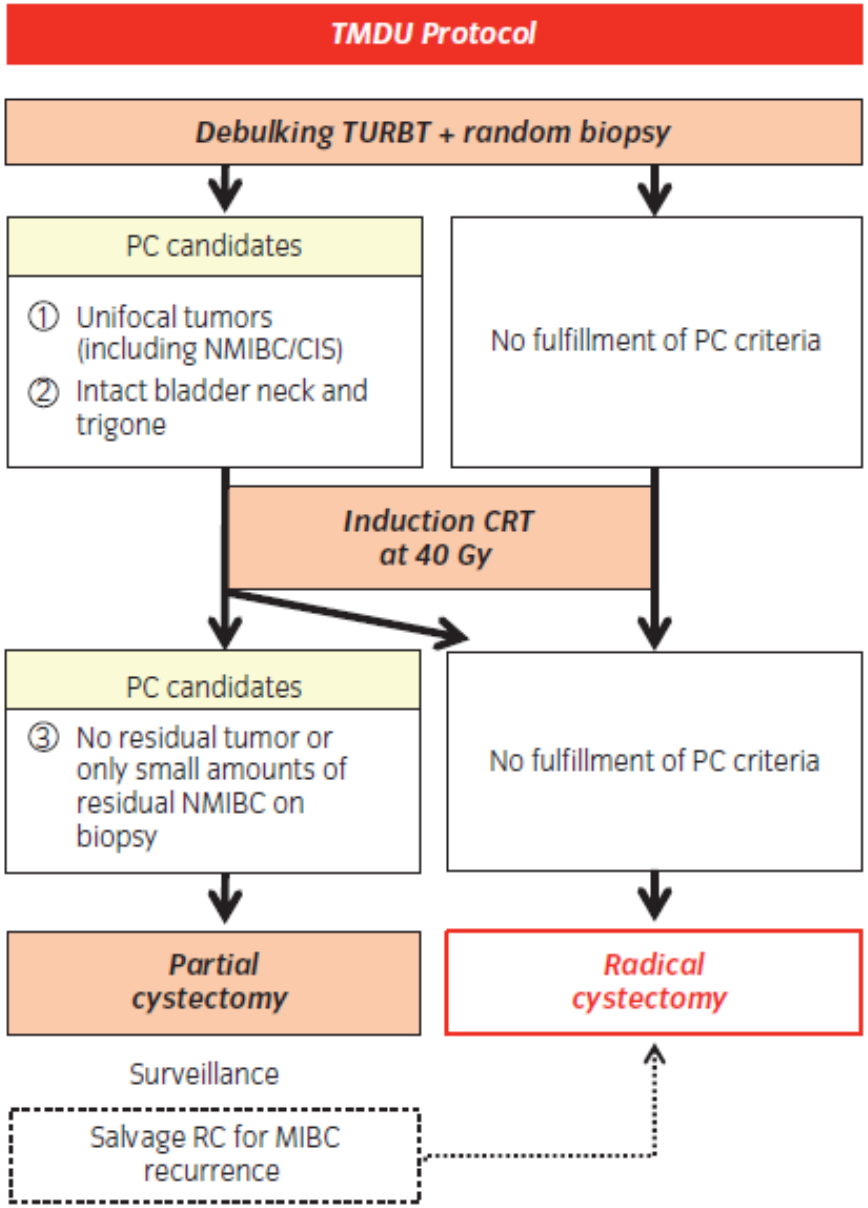
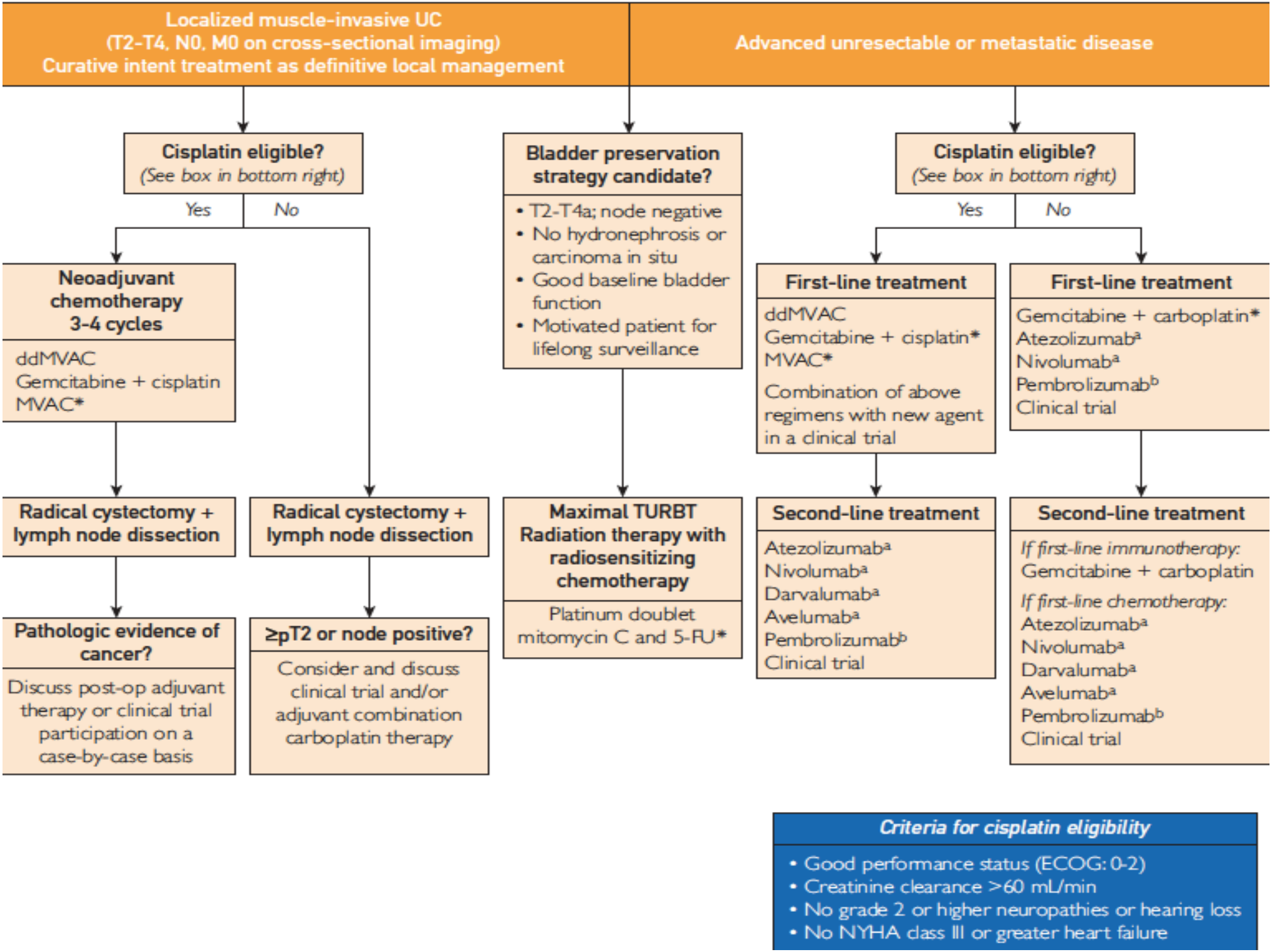


Fig. 2 Algorithm of bladder-sparing protocol incorporating partial cystectomy with PLND as consolidative therapy at TMDU.

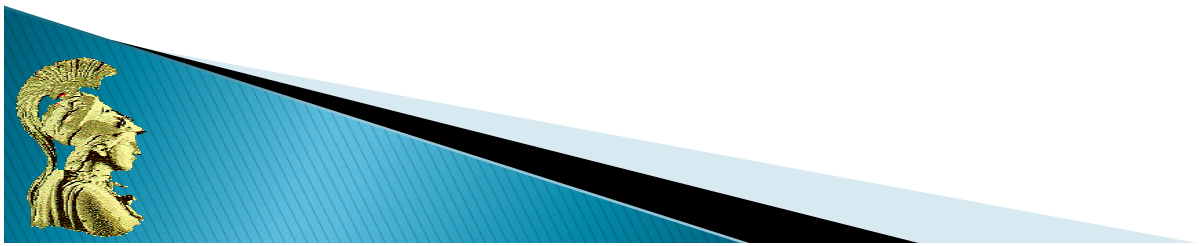

Localized muscle-invasive UC
(T2-T4, N0, M0 on cross-sectional imaging)
Curative intent treatment as definitive local management
Advanced unresectable or metastatic disease
Cisplatin eligible?
(See box in bottom right)
Yes
No
Neoadjuvant chemotherapy 3-4 cycles
ddMVAC
Gemcitabine + cisplatin
MVAC*
Radical cystectomy + lymph node dissection
Pathologic evidence of cancer?
Discuss post-op adjuvant therapy or clinical trial participation on a case-by-case basis
Radical cystectomy + lymph node dissection
≥pT2 or node positive?
Consider and discuss clinical trial and/or adjuvant combination carboplatin therapy
Bladder preservation strategy candidate?
• T2-T4a; node negative
• No hydronephrosis or carcinoma in situ
• Good baseline bladder function
• Motivated patient for lifelong surveillance
Maximal TURBT
Radiation therapy with radiosensitizing chemotherapy
Platinum doublet mitomycin C and 5-FU*
Cisplatin eligible?
(See box in bottom right)
Yes
No
First-line treatment
ddMVAC
Gemcitabine + cisplatin*
MVAC*
Combination of above regimens with new agent in a clinical trial
Second-line treatment
Atezolizumab[a]
Nivolumab[a]
Darvalumab[a]
Avelumab[a]
Pembrolizumab[b]
Clinical trial
First-line treatment
Gemcitabine + carboplatin*
Atezolizumab[a]
Nivolumab[a]
Pembrolizumab[b]
Clinical trial
Second-line treatment
If first-line immunotherapy:
Gemcitabine + carboplatin
If first-line chemotherapy:
Atezolizumab[a]
Nivolumab[a]
Darvalumab[a]
Avelumab[a]
Pembrolizumab[b]
Clinical trial
Criteria for cisplatin eligibility
• Good performance status (ECOG: 0-2)
• Creatinine clearance >60 mL/min
• No grade 2 or higher neuropathies or hearing loss
• No NYHA class III or greater heart failure

Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline

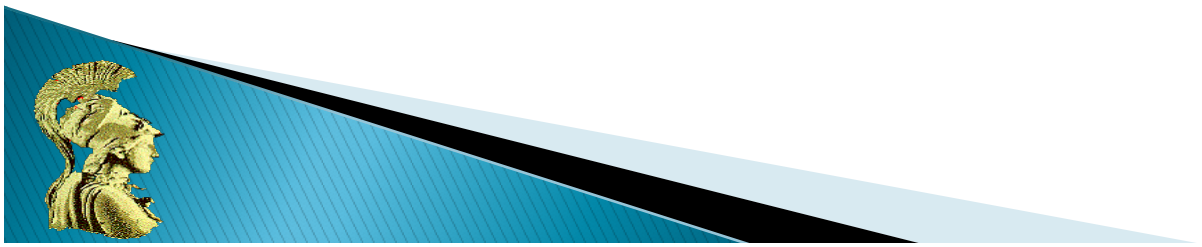
MULTIMODAL BLADDER PRESERVING THERAPY

25. Maximal transurethral resection of bladder tumor, chemotherapy combined with external beam radiation therapy, and planned cystoscopic re-evaluation
26. Radiation sensitizing chemotherapy regimens with cisplatin or 5- fluorouracil and mitomycin C
27. Surveillance of patients who elect bladder preservation

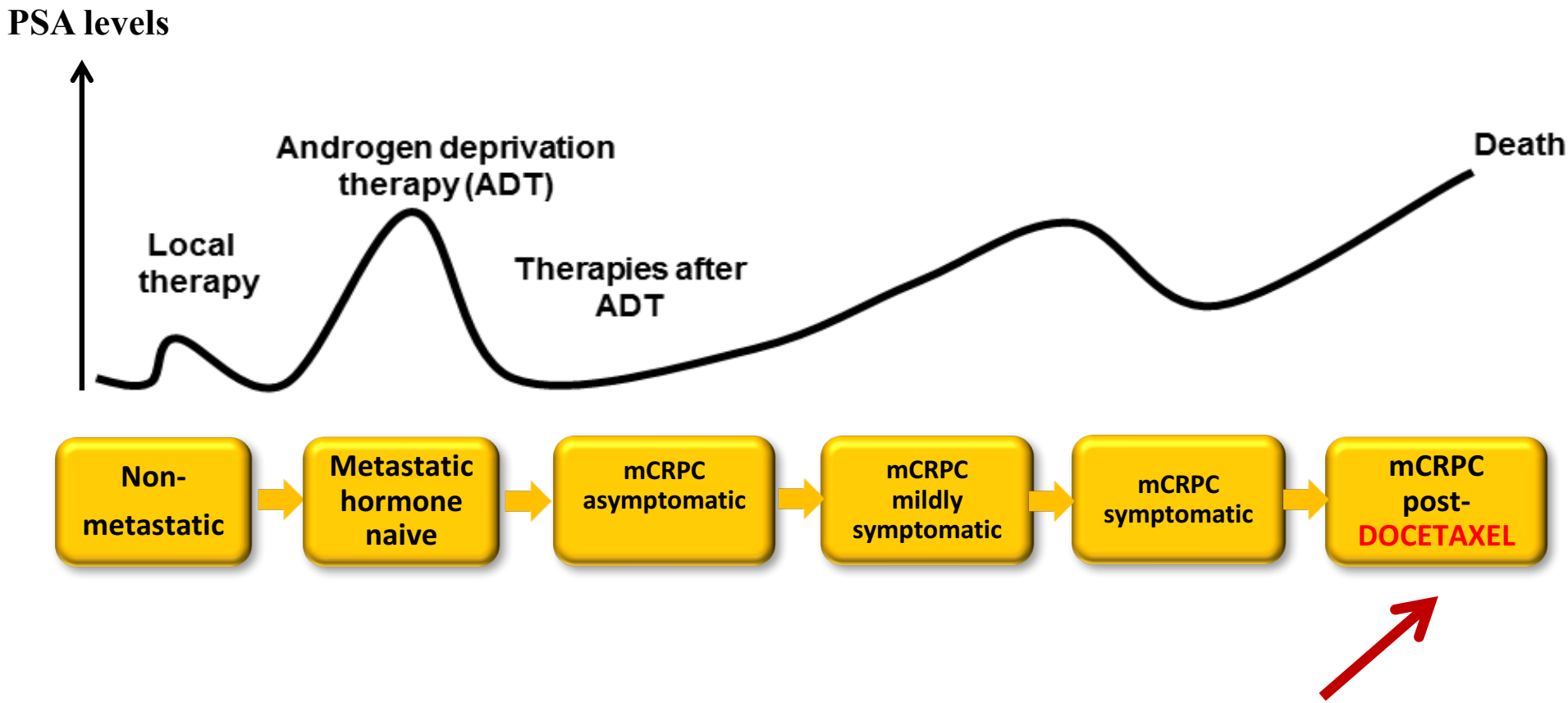
Those who are biopsy-proven complete responders to bladder preserving protocols remain at risk for both invasive and non-invasive recurrences as well as new tumors in the upper tracts. Recurrences may be successfully managed by prompt salvage therapy.



Προστάτης

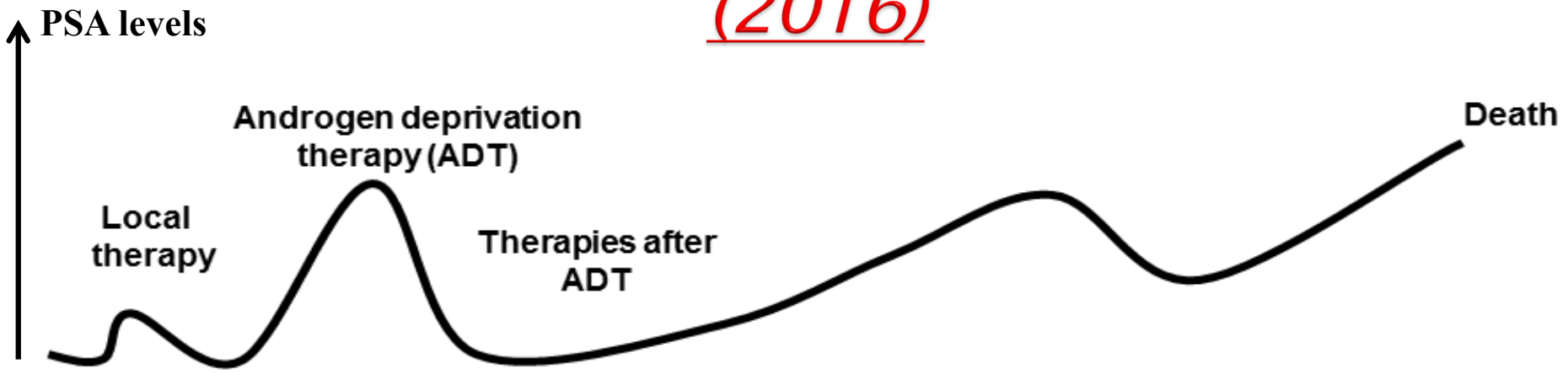


Εξέλιξη νόσου & Θεραπευτικές Επιλογές (2010)



ADT (Androgen Deprivation Therapy)

Θεραπευτικοί Επαναπροσδιορισμοί (2016)



Non-metastatic → Metastatic hormone naive → mCRPC asymptomatic (failed ADT) → mCRPC mildly symptomatic → mCRPC symptomatic → mCRPC post-docetaxel

Docetaxel

Docetaxel

Cabazitaxel

Abiraterone

Enzalutamide

Sipuleucel-T

Enzalutamide

Abiraterone

Radium-223

ADT (Androgen Deprivation Therapy)

Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases

ULRIKE SCHICK[1], SANDRA JORCANO[2], PHILIPPE NOUET[1], MICHEL ROUZAUD[1], HANSJOERG VEES[1], THOMAS ZILLI[1], OSMAN RATIB[3], DAMIEN C.WEBER[1] & RAYMOND MIRALBELL[1,2]

In summary, prostate cancer patients presenting with ≤4 metastases at diagnosis or after failure following curative treatment of the local tumour may be successfully treated with limited AD and high-dose focused irradiation to the metastatic lesions. Such a treatment strategy may hypothetically succeed to prolong the failure free interval between two consecutive AD courses when patients are on intermittent AD salvage and deserves to be further tested in controlled randomised trials. The administered dose for the OM(s) was an independent favourable prognostic factor for bRFS.

Acta Oncologica, 2013; 52: 1622–1628

Surgery-based Multimodal Management of High-risk Prostate Cancer Patients: What Is the Functional Price To Pay for Optimal Disease Control?

Thomas Seisen, Firas Abdollah *

In summary, the authors provide innovative information with regard to the impact of multimodal treatment on functional and quality-of-life outcomes among patients undergoing radical prostatectomy for high-risk prostate cancer. It is noteworthy that the incidence of such aggressive disease is likely to increase given the recent US Preventive Services Task Force recommendations against prostate-specific antigen screening [15,16]. Thus, care providers should be aware of the consequences associated with cumulative use of surgery, radiotherapy, and/or androgen deprivation therapy so that they can provide adequate counseling to prostate cancer patients, and notably advise selective use of adjuvant radiotherapy only for men with very high-risk disease at radical prostatectomy.

EUROPEAN UROLOGY 71 (2017) 337–339

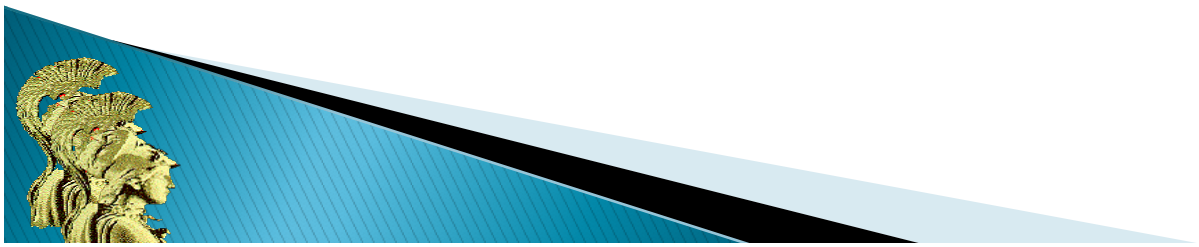
- De novo M1 PCa
- High volume disease (e.g. visceral)
- Anaplastic/neuroendocrine/small cell differentiation

- AR independent clones (e.g. AR-V7)

- PSA response (decline >50% /y . >30% /m)
- Primary resistance, rapid progression
- PSA -> radiological -> symptomatic

- Sequencing (e.g. CARD study)
- Toxicities, duration, cost, preference, QoL

- Biomarkers, genomic alterations



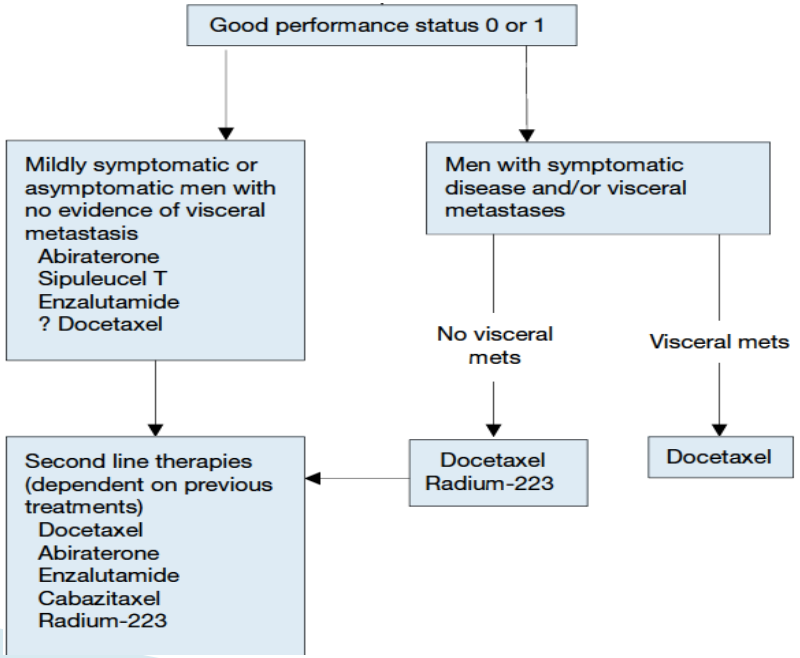
EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer

Table 3 – Guidelines for hormonal treatment of metastatic prostate cancer

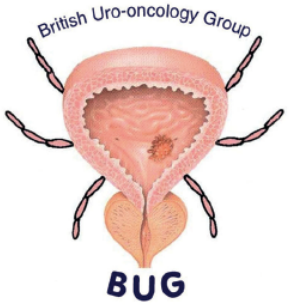
Recommendation	LE	GR
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.	1a	A

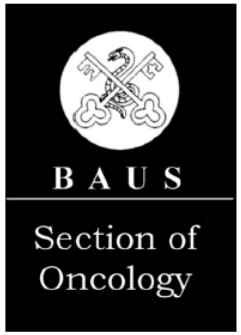
Table 5 – Guidelines for management of castration-resistant prostate cancer

Recommendation	LE	GR
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, and extent of disease (alphabetical order: abiraterone, cabazitaxel docetaxel, enzalutamide, Ra 223, sipuleucel-T).	1b	A
Base second-line treatment decisions of mCRPC on pretreatment performance status, comorbidities, and extent of disease.		B
Counsel, manage, and treat patients with mCRPC in a multidisciplinary team.	3	A



Multi-disciplinary Team (MDT) Guidance for Managing Prostate Cancer





Produced by:

- **British Uro-oncology Group (BUG)**

British Association of Urological Surgeons (BAUS) Section of Oncology

Table 1 Table presenting emergent themes (Left column) from free-text responses to the question, "How does attending the MDT meeting save time later?"

Theme	Explanation
Treatment plan	Plans for treatment can be formulated and clarified at MDT meeting
Investigations	Investigations (e.g. radiological investigations) can be collated and reviewed
Patient consultation	Being familiar with the clinical history, results of investigations and proposed treatment facilitates consultation with patients
Improving pathway	The passage of patients from one clinician to another is quicker and more direct
Facilitate discussion	Face to face discussion allows questions to be asked and answered directly
Referrals	Inappropriate referrals can be avoided and appropriate referrals made directly in person
Record keeping	A single record of results and multidisciplinary discussion can be created
Admin	Patient follow-up is streamlined and patients are not lost
Non-clinical	Improved relationships between team members

Explanations for the displayed themes are presented in the right column.

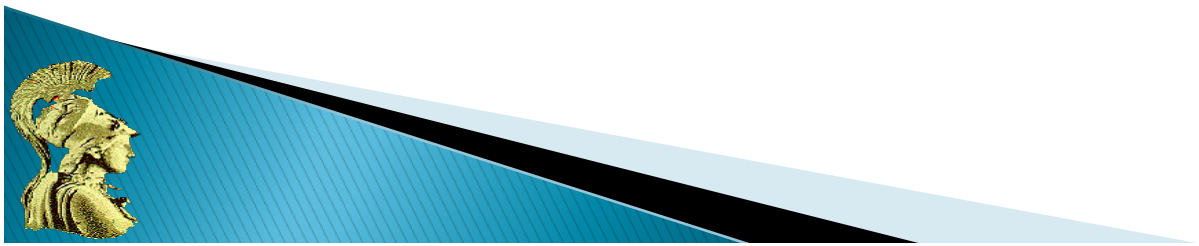


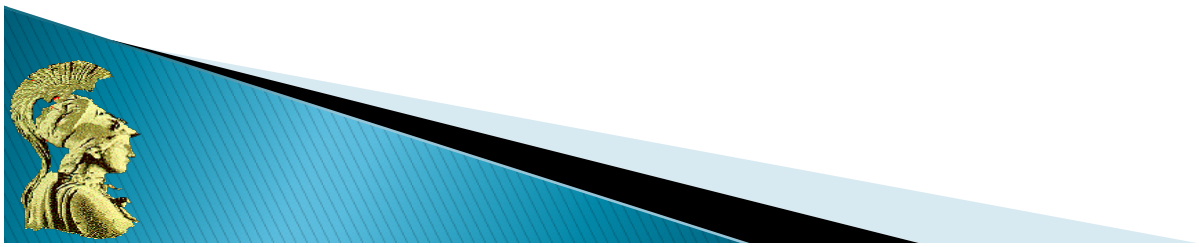
Table 1: The make-up of the MDT in the prostate cancer setting

• Urological surgeons	• Oncology and urology nurse specialists
• Clinical and medical oncologists	• Palliative care specialist
• MDT co-ordinator and secretarial support	• Histopathologists
• Radiologists	

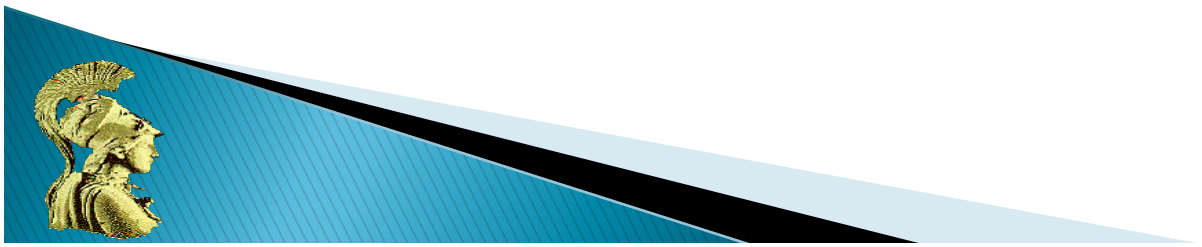
Η ελληνική νομοθεσία (νόμος 4052/2012, άρθρο 135)

Στα ογκολογικά νοσοκομεία (Ε.Σ.Υ. ή ιδιωτικά), καθώς και στα νοσοκομεία που λειτουργούν παθολογικές- ογκολογικές κλινικές και ακτινοθεραπευτικές μονάδες, καθιερώνεται η:

- διατομεακή αντιμετώπιση του ασθενούς που πάσχει (ή υπάρχουν υπόνοιες ότι πάσχει) από κακοήθη νεοπλάσματα.



Όρχεις



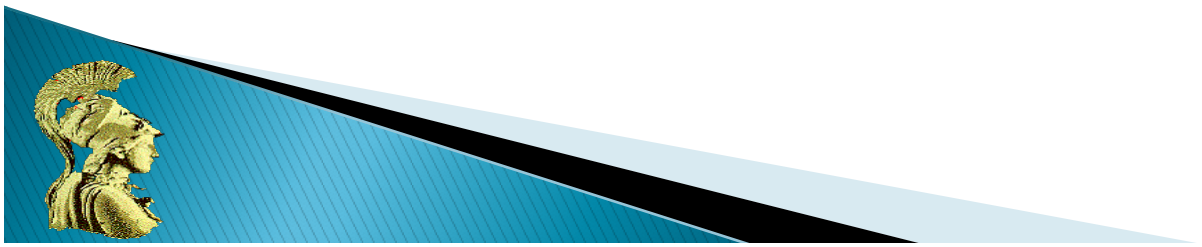
Importance of Continuous Sequential Chemotherapy and Multimodal Treatment for Advanced Testicular Cancer

A High-Volume Japanese Center Experience

Terukazu Nakamura, MD, PhD, Takashi Ueda, MD, PhD, Masakatsu Oishi, MD, PhD,

In conclusion, this is the first report of multimodal and chemotherapeutic sequences for patients with advanced GCT. Sequential treatment for advanced GCTs, especially ''difficult-to-treat'' GCTs, is very important to improve outcomes. Very high cure rates were achieved in patients who completed chemotherapy up to third-line therapies. In addition, even in heavily treated patients who had fifth or sixth-line therapy, continuous treatment might save their lives if accompanied by additional modalities. More systematic trials that include third-line or fourth-line treatment are needed.

Νεφρά



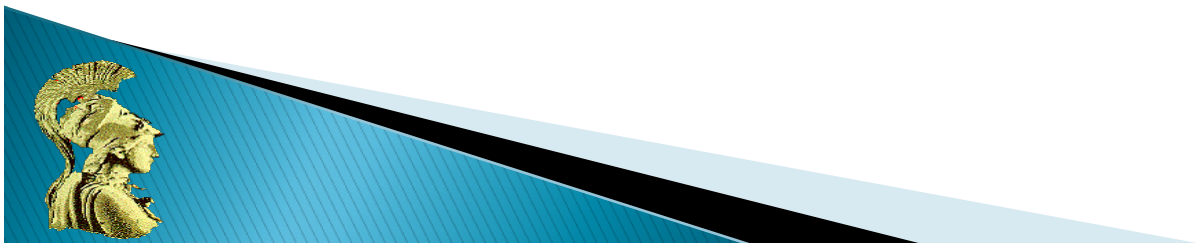
Multimodal treatment of advanced renal cancer in 2017

Alessia Mennitto, Elena Verzoni, Paolo Grassi, Raffaele Ratta, Giovanni Fucà & Giuseppe Procopio

Expert commentary: in early disease, radical or partial nephrectomy remains the standard of care, but innovative ablation techniques, including radiofrequency ablation, microwave ablation, cryoablation and so on, may represent an alternative option of treatment for small renal lesions in unfit patients who cannot undergo surgery. In metastatic setting, it is imperative a multidisciplinary team approach to select patients for a cytoreductive nephrectomy, metastasectomy, and/or systemic treatment, aiming to the optimization of the treatment strategy.

Expert Review of Clinical Pharmacology

Πέος

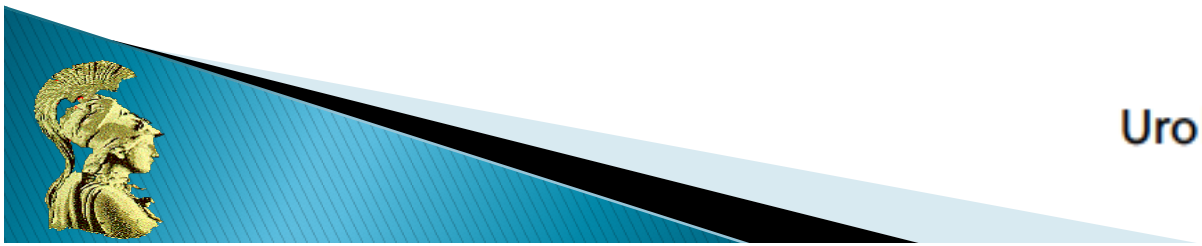


Multimodal Therapy in the Management of Advanced Penile Cancer

Praful Ravi, MBBChir[a], Lance C. Pagliaro, MD[b,*]

KEY POINTS

- A multimodal approach to therapy is increasingly used in treating men with advanced penile cancer.
- Adjuvant chemotherapy is associated with improved outcomes in chemotherapy-naïve men with node-positive penile cancer.
- Neoadjuvant systemic chemotherapy may downstage regional lymph node metastases sufficiently to permit surgery while imparting a potential improvement in long-term disease-free survival.
- International collaboration in clinical trials is required to optimize treatment and improve survival in men with advanced penile cancer.



Urol Clin N Am 43 (2016) 469–479

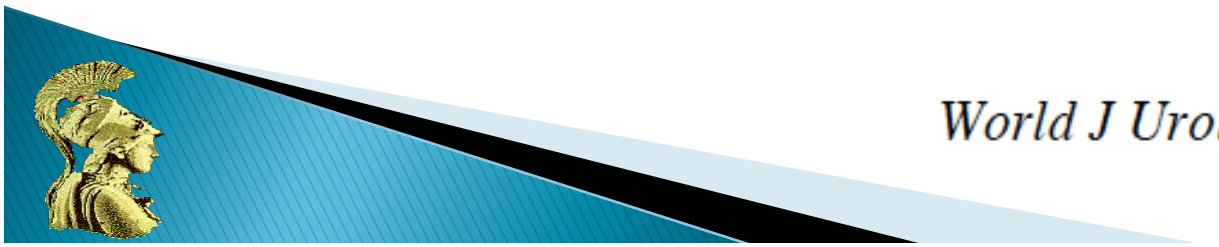
Multimodality therapy in penile cancer: when and which treatments?

Lance C. Pagliaro and

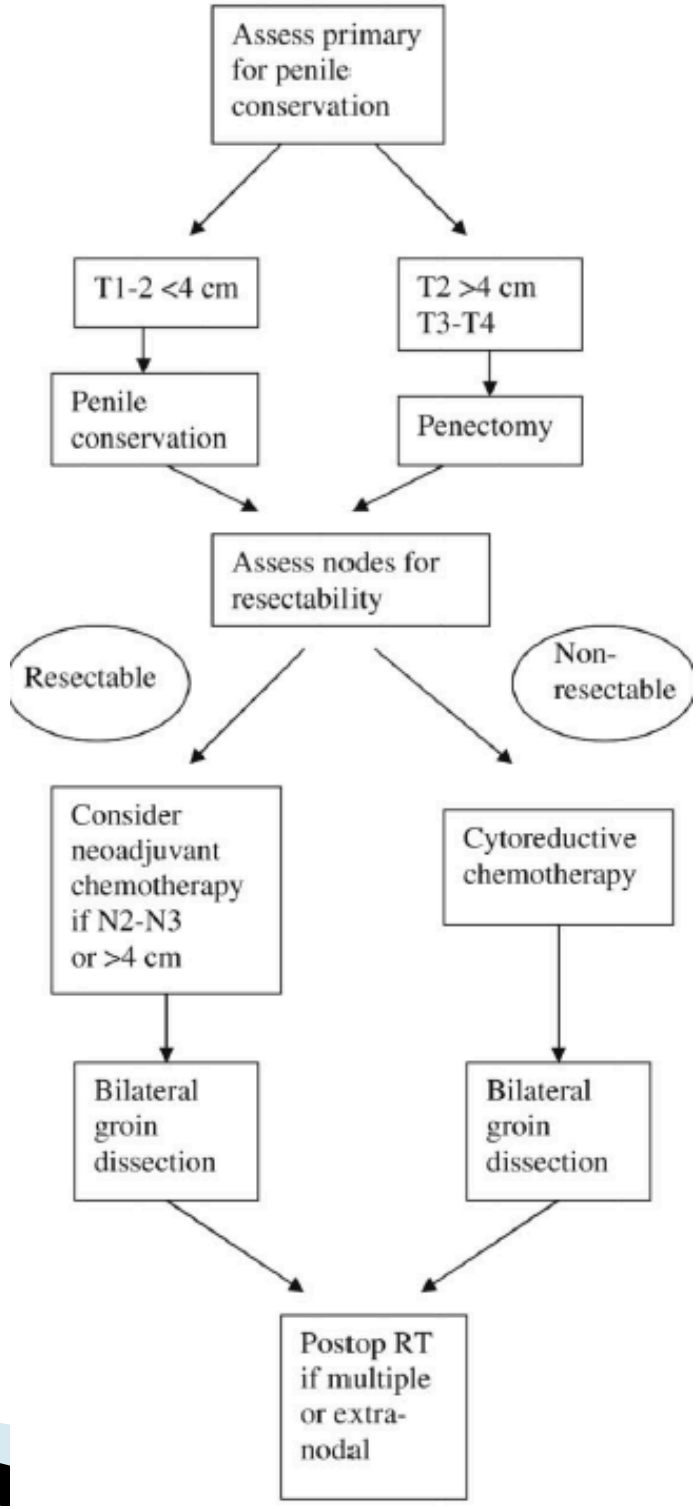
Conclusions—In patients with lymph node metastases, the benefit of ilioinguinal lymphadenectomy may be extended by the addition of neoadjuvant chemotherapy. Postoperative radiotherapy can be offered depending on the amount of residual disease after chemotherapy. Chemo-radiotherapy has been successful in squamous cell cancers from other sites (vulva and anal canal) and may be considered for unresectable penile cancer.

A neoadjuvant chemotherapy regimen (TIP)

	Dose	Schedule
Paclitaxel[a]	175 mg/m^2	Day 1 over 3 h
Ifosfamide[b]	1200 mg/m^2	Days 1–3
Cisplatin[c]	25 mg/m^2	Days 1–3

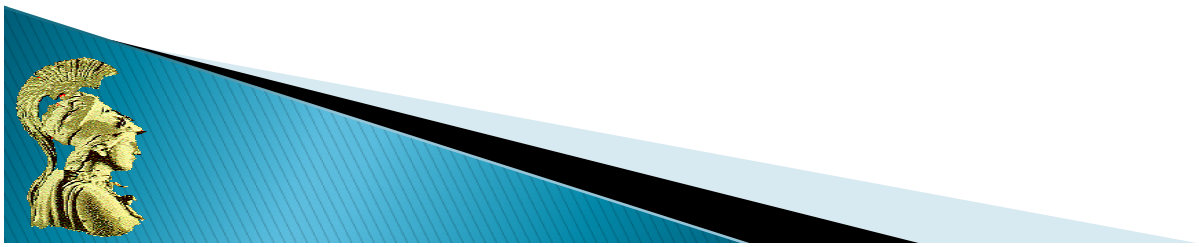


World J Urol. 2009 April ; 27(2): 221–225.


Assess primary for penile conservation
T1-2 <4 cm
T2 >4 cm T3-T4
Penile conservation
Penectomy
Assess nodes for resectability
Resectable
Non-resectable
Consider neoadjuvant chemotherapy if N2-N3 or >4 cm
Cytoreductive chemotherapy
Bilateral groin dissection
Bilateral groin dissection
Postop RT if multiple or extra-nodal

Προβληματισμοί

- Σειρά θεραπευτικών επιλογών (sequencing)
- Αποτελεσματικότητα
- Προγνωστικοί παράγοντες ανταπόκρισης
- Τοξικότητα



Σας ευχαριστώ πολύ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