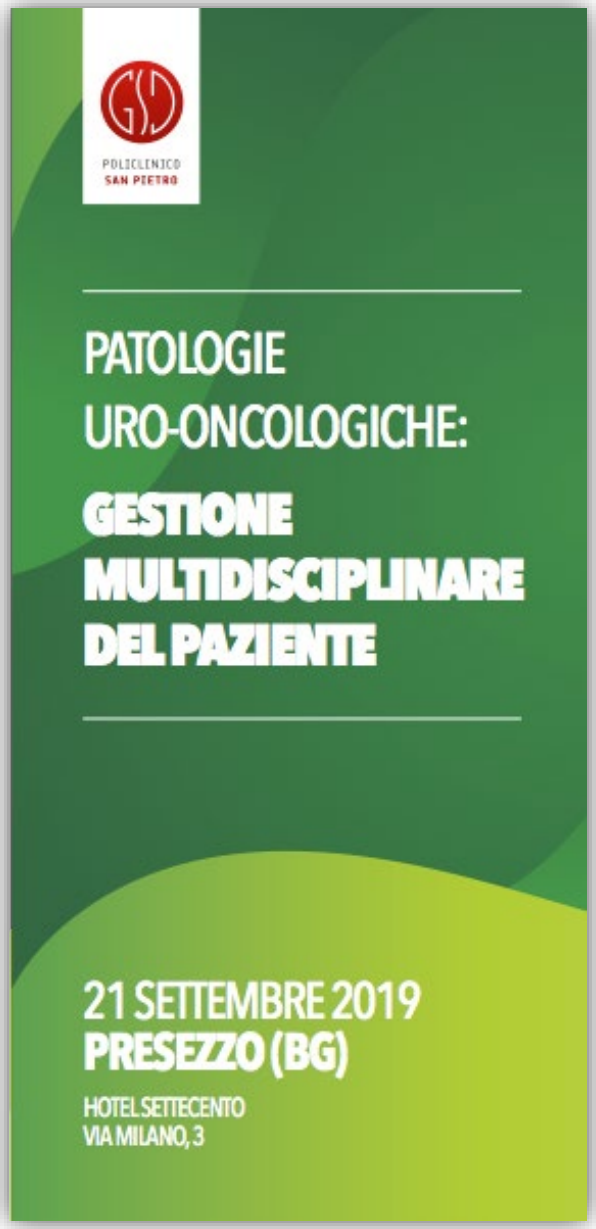
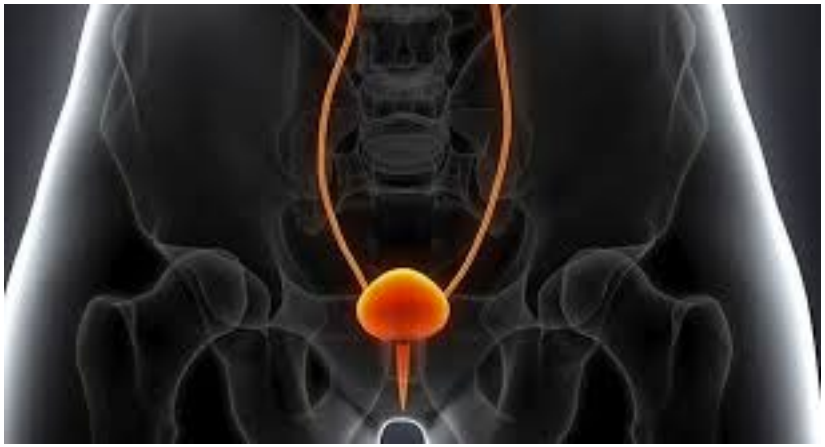


Radioterapia "bladder sparing"



Stefano Masciullo
Servizio di Radioterapia, Policlinico S. Pietro

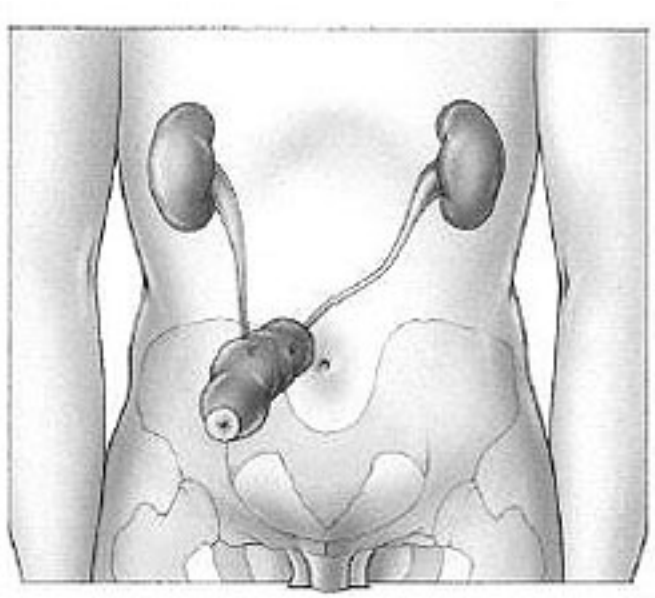
Malattia muscolo-invasiva non metastatica

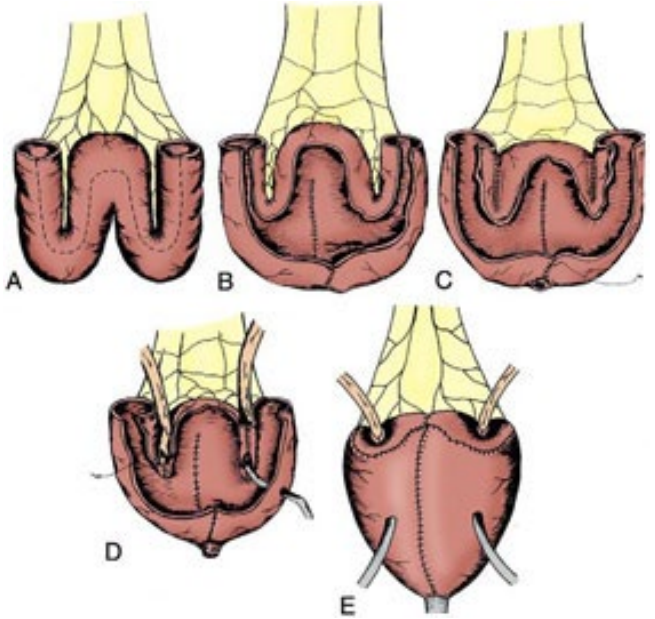
<u>TERAPIA STANDARD:</u>

CISTECTOMIA +/- CHEMIOTERAPIA

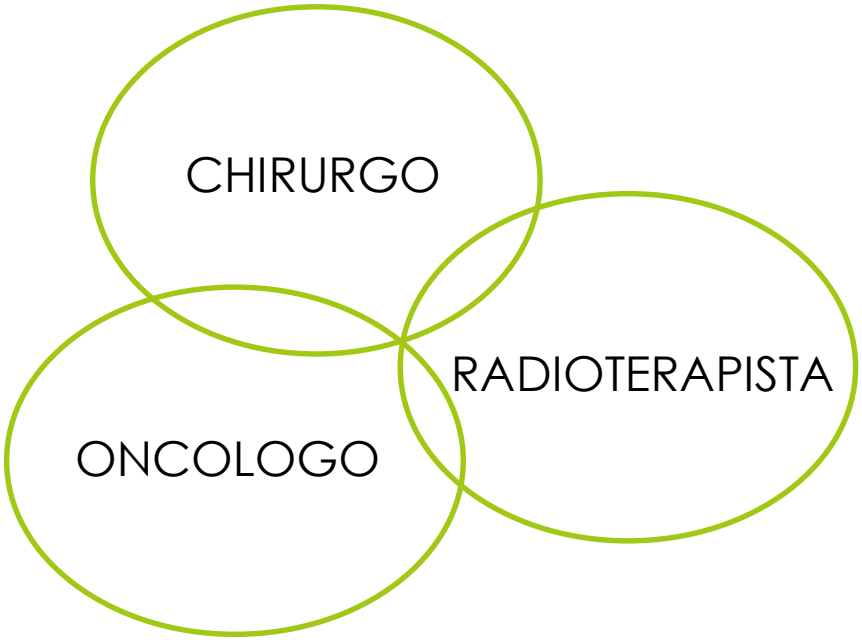
LA CISTECTOMIA INCLUDE LA RIMOZIONE DEGLI URETERI DISTALI E DEI LINFONODI, DELLA PROSTATA E VESCICOLE SEMINALI NEGLI UOMINI, DI URETRA, VAGINA ADIACENTE E UTERO NELLE DONNE.

PREVEDE UNA DERIVAZIONE URINARIA NON CONTINENTE O CONTINENTE (ILEOCUTANEOSTOMIA O NEOVESCICA ILEALE).





TERAPIA TRIMODALE



TURV

CHEMIORADIOTERAPIA CONCOMITANTE

TERAPIA TRIMODALE: razionale

- **Razionale:** correlazione diretta tra volume tumorale e dose di radiazioni necessaria per controllo tumorale → TURV. L'aggiunta della chemioterapia è finalizzata al potenziamento della RT.

- **Obiettivo:** preservare la vescica e massimizzare QoL, senza compremettere l'esito oncologico.

TERAPIA TRIMODALE: esecuzione

- Resezione endoscopica completa della neoplasia (**TURV "massimale"**).
- Schema di **radioterapia** più utilizzato in Europa: **30-33 sedute** giornaliere (totale 6-7 settimane). Possibili trattamenti più brevi, aumentando la dose per frazione (20 sedute).
- Chemioterapia con **cisplatino**; se controindicato, gemcitabina.

UGUALE SOPRAVVIVENZA

- Assenza di studi randomizzati, disponibili numerose serie retrospettive, prospettiche e revisioni sistematiche della letteratura
- Eterogeneità tra casistiche chirurgiche e radioterapiche, queste ultime spesso includenti pazienti più anziani e con minore accuratezza nella stadiazione

UGUALE SOPRAVVIVENZA

Crit Rev Oncol Hematol. 2015 Sep;95(3):387-96. doi: 10.1016/j.critrevonc.2015.04.006. Epub 2015 Apr 17.

Radical cystectomy versus organ-sparing trimodality treatment in muscle-invasive bladder cancer: A systematic review of clinical trials.

Arcangeli G[1], Strigari L[2], Arcangeli S[3].

Author information

Abstract

BACKGROUND: Radical cystectomy (RC) represents the mainstay of treatment in patients with muscle-invasive urinary bladder cancer but how it compares with the best organ preservation approach is not known.

MATERIALS AND METHODS: The objective of our review is to compare the 5-year overall survival (OS) rates from retrospective and prospective studies of RC and trimodality treatment (TMT), i.e. concurrent delivery of chemotherapy and radiotherapy after a transurethral resection of bladder tumor (TURBT), involving a total of 10,265 and 3131 patients, respectively. We used random-effect models to pool outcomes across studies and compared event rates of combined outcomes for TMT and RC using an interaction test.

RESULTS: The median 5-year OS rate was 57% in the TMT group, when compared with 52% (P=0.04), 51% (P=0.02) and 53% (P=0.38) in the whole group receiving RC or the group treated with RC alone or RC+chemotherapy, respectively. The hazard risk (HR) of mortality of patients treated with TMT or RC was 1.22 (95% CI=1.13-1.32) with an absolute benefit of 5% in favor of the former. The HR of mortality from TMT persisted significantly better not only versus the group treated with RC alone (HR=1.22; 95% CI=1.12-1.32), but also versus the group receiving RC+chemotherapy (HR=1.22; 95% CI=1.09-1.36). Multivariate analysis confirmed TMT as a significant prognostic variable for both RC alone and RC+chemotherapy.

CONCLUSION: Compared with RC, TMT seems to be associated with a better outcome for patients with muscle-invasive bladder cancer (MIBC). The addition of chemotherapy may improve the RC outcome in some subgroups of patients with a higher probability of micrometastases. Prospective randomized trials are urged to verify these findings and better define the role of organ preservation and radical treatment strategy in the management of patients with MIBC.

ALTI TASSI DI CONSERVAZIONE DELLA VESCICA

- In seguito a terapia trimodale alti tassi di risposta completa (70-90%)
- 10-30% dei pazienti presenta residuo tumorale
- 20-30% dei pazienti sviluppa una recidiva nella vescica

Arcangeli et al. Crit Rev Oncol Hematol 2015

TRATTAMENTO RECIDIVA VESCICALE

- Più della metà dei tumori recidivi sono superficiali (Ta/Tis/T1) → TURV +/- trattamento endovescicale
- Non vi sono differenze di sopravvivenza

Giacalone NJ et al, Eur Urol 2017
Weiss C et al, Int J Radiat Oncol Biol Phys 2008
Zietman AL et al, Urology 2001
Rodel C et al, J Clin Oncol 2002

CISTECTOMIA DI SALVATAGGIO

- Il tasso di cistectomie di salvataggio è compreso tra il 10 e il 30% (sopravvivenza cancro-specifica a 5 aa tra il 45 e il 50%, praticamente invariata)
- La cistectomia di salvataggio può essere eseguita senza ulteriori rischi di complicazioni rispetto all'intervento primario di cistectomia. Inoltre, la precedente RT pelvica non sembra precludere la possibilità di diversione urinaria continente

Giacalone NJ et al, Eur Urol 2017
Weiss C et al, Int J Radiat Oncol Biol Phys 2008
Zietman AL et al, Urology 2001
Rodel C et al, J Clin Oncol 2002

BASSA TOSSICITA'

- EFFETTI ACUTI: includono pollachiuria, nicturia, disuria, urgenza minzionale e occasionale incontinenza. I pazienti possono sviluppare nausea, vomito o diarrea. Questi sintomi sono usualmente lievi, sono controllabili con terapia medica sintomatica e si risolvono in poche settimane dopo la RT

- EFFETTI TARDIVI: includono ematuria e pollachiuria cronica. La tossicità di grado 3 è comunque molto contenuta (<5% a 5 aa)

- La tossicità locale non sembra incrementata significativamente con l'aggiunta della chemioterapia

Bouchner BH et al, J Urol 1998
Zietman Al et al, J Urol 2003
James ND et al, N Engl J Med 2012

BASSA TOSSICITA'

Nell'80% dei pazienti vescica normo-funzionante con normale capacità di flusso. Attività sessuale normalmente conservata in più della metà dei casi

J Urol. 2003 Nov;170(5):1772-6.

Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors.

Zietman AL[1], Sacco D, Skowronski U, Gomery P, Kaufman DS, Clark JA, Talcott JA, Shipley WU.

Author information

1 Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, 100 Blossom Street, Cox 302, Boston, MA 02114, USA. azietman@partners.org

Abstract

PURPOSE: Transurethral resection, chemotherapy and radiation with salvage cystectomy may be used as alternatives to immediate radical cystectomy in the management of invasive bladder cancer. Concern exists about the function of the retained bladder after such therapy.

MATERIALS AND METHODS: Of 221 patients with clinical T2-4a bladder cancer treated at Massachusetts General Hospital from 1986 to 2000 with trimodality therapy, 71 were alive with native bladders and disease-free in 2001. These patients were asked to undergo a urodynamic study and to complete a quality of life questionnaire. A total of 69% participated in some component of this study with a median time from trimodality therapy of 6.3 years (range 1.6 to 14.9).

RESULTS: Of 32 patients 24 had normally functioning bladders by urodynamic study. Decreased bladder compliance was seen in 7. Bladder hypersensitivity, involuntary detrusor contractions and incontinence were present in 2 women. The questionnaire showed that flow symptoms occurred in 6%, urgency in 15% and control problems in 19%. Of all women 11% wore pads. Distress from urinary symptoms was half as common as prevalence. Bowel symptoms occurred in 22% with 14% recording any level of distress. The majority of men retained sexual function. Global health related quality of life was high.

CONCLUSIONS: The majority of patients treated with trimodality therapy retain good bladder function. A fifth have evidence of bowel dysfunction.

BASSA TOSSICITA'

Fibrosi vescicale radio-indotta con compromissione funzionale molto rara. Necessità di cistectomia per contrazione della parete vescicale nell'1-2% dei pazienti

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

Nicholas D. James, M.B., B.S., Ph.D., Syed A. Hussain, M.B., B.S., M.D., Emma Hall, Ph.D., Peter Jenkins, M.B., B.S., Ph.D., Jean Tremlett, M.Sc., Christine Rawlings, M.Sc., Malcolm Crundwell, M.D., B.Chir., Bruce Sizer, M.B., B.S., Thiagarajan Sreenivasan, M.B., B.S., Carey Hendron, M.Sc., Rebecca Lewis, B.Sc., Rachel Waters, M.Sc., et al., for the BC2001 Investigators*

SECONDARY OUTCOMES

For the secondary outcomes, an exploratory analysis of invasive locoregional disease showed a 2-year relapse rate of 18% in the chemoradiotherapy group versus 32% in the radiotherapy group (hazard ratio, 0.57; 95% CI, 0.37 to 0.90; P=0.01) (Figure 2B). Chemoradiotherapy was associated with a trend toward a reduction in cystectomy, with a 2-year rate of 11.4% (95% CI, 7.1 to 18.0) in the chemoradiotherapy group versus 16.8% (95% CI, 11.6 to 23.9) in the radiotherapy group (P=0.07), although the comparison was underpowered. Of the 51 cystectomies that were performed, 41 (80.4%) were for recurrence (27 for invasive disease, 9 for non–muscle-invasive disease, and 5 for an unknown type of recurrence); 4 were performed for late effects of radiotherapy.

FOLLOW-UP

La terapia di conservazione d'organo effettuata al posto della cistectomia richiede uno **stretto follow-up** a lungo termine comprensivo di cistoscopia, esame citologico delle urine ed esami radiologici come la TAC.

PAZIENTI OPERABILI: CANDIDATI IDEALI A TRATTAMENTO TRIMODALE

- Assenza di CIS esteso o multifocale.
- Assenza di idronefrosi.
- Lesione unica con diametro < 5-6 cm.

Circa un quinto dei pazienti sottoposti a cistectomia

T2-T3a

TUTTI I CANDIDATI A TRATTAMENTO TRIMODALE

- Pazienti selezionati candidati a cistectomia.
- Pazienti che rifiutano la cistectomia.
- Pazienti non candidati a cistectomia, ma fit per chemioterapia e TURV, con buona funzionalità vescicale e senza CIS estesa.

TRATTAMENTO TRIMODALE
POTENZIALMENTE CURATIVO

LINEE GUIDA

- Le linee guida delle maggiori organizzazioni e società scientifiche includono ormai la preservazione della vescica come opzione per pazienti selezionati

SUO Society of Urologic Oncology, Inc.

ASTRO American Society for Radiation Oncology

American Urological Association

ESMO Good Science Better Medicine Best Practice
European Society for Medical Oncology

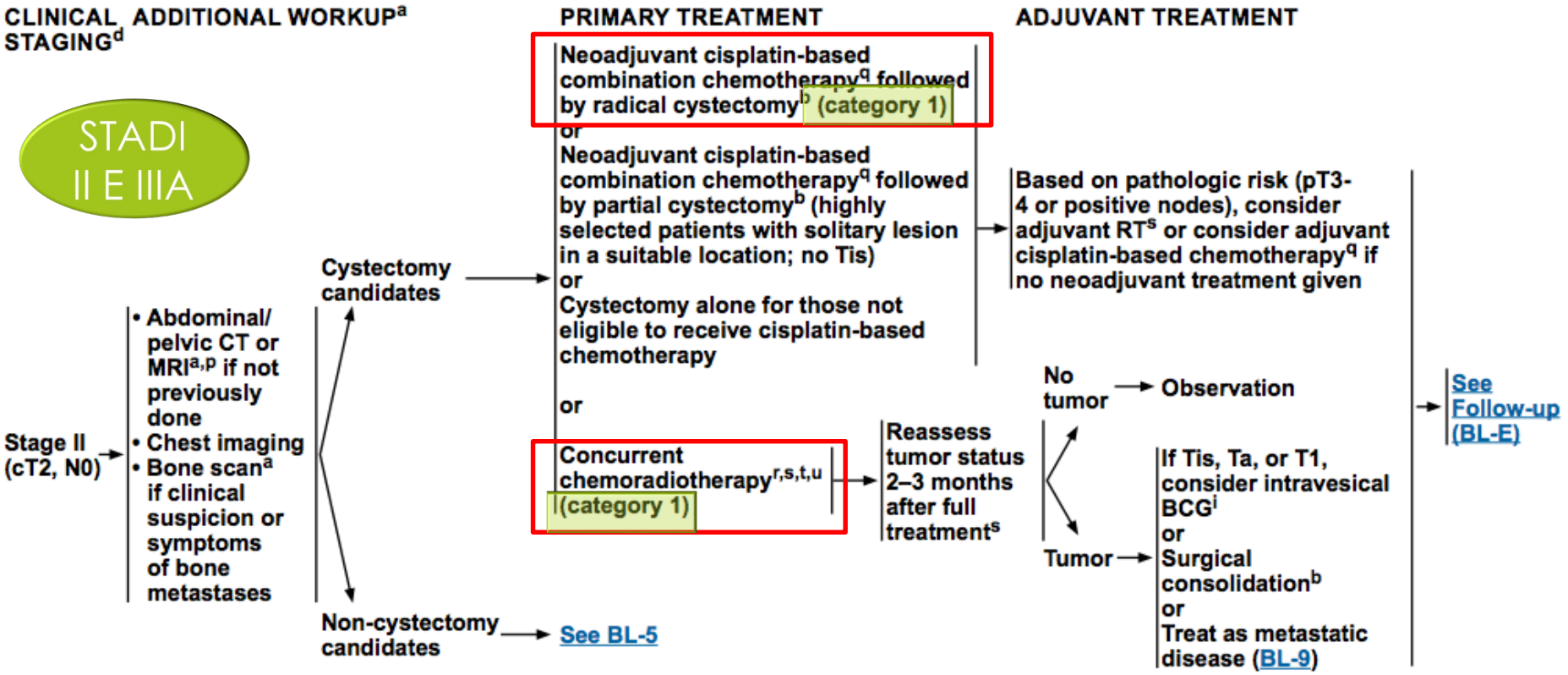
ASCO American Society of Clinical Oncology

NCCN National Comprehensive Cancer Network®

RAIO Associazione Italiana Radioterapia Oncologica

eau European Association of Urology

AIOM Associazione Italiana di Oncologia Medica



[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See Principles of Surgical Management (BL-B).
[d] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[i] See Principles of Intravesical Treatment (BL-F).
[p] Consider PET/CT scan (skull base to mid-thigh) (category 2B).
[q] See Principles of Systemic Therapy (BL-G 1 of 5).
[r] See Principles of Systemic Therapy (BL-G 4 of 5).
[s] See Principles of Radiation Management of Invasive Disease (BL-H).
[t] There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.
[u] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See Recurrent or Persistent Disease (BL-10)

TERAPIA TRIMODALE – FREQUENZA DI UTILIZZO

Nonostante l'efficacia e le potenzialità curative, in Europa e negli Stati Uniti soltanto una piccola parte dei pazienti potenzialmente curabili viene curata con trattamento trimodale.

Tumori. 2015 Mar-Apr;101(2):174-8. doi: 10.5301/tj.5000235. Epub 2015 Mar 5.

Urinary bladder preservation for muscle-invasive bladder cancer: a survey among radiation oncologists of Lombardy, Italy.

Jereczek-Fossa BA[1], Colombo R, Magnani T, Fodor C, Gerardi MA, Antognoni P, Barsacchi L, Bedini N, Bracelli S, Buffoli A, Cagna E, Catalano G, Gottardo S, Italia C, Ivaldi GB, Masciullo S, Merlotti A, Sarti E, Scorsetti M, Serafini F, Toninelli M, Vitali E, Valdagni R, Villa E, Zerini D, De Cobelli O, Orecchia R.

Author information

1 European Institute of Oncology, Milan - Italy.

Abstract

AIMS AND BACKGROUND: Bladder preservation is a treatment option in muscle-invasive bladder carcinoma. The most investigated approach is a trimodality schedule including maximum transurethral resection of bladder tumor (TURBT) followed by chemoradiotherapy. Our aim was to evaluate the use of bladder preservation by radiation oncologists of the Lombardy region in Italy.

METHODS AND STUDY DESIGN: A survey with 13 items regarding data of 2012 was sent to all 32 radiotherapy centers within the collaboration between the Lombardy Oncological Network and the Lombardy Section of the Italian Society of Oncological Radiotherapy.

RESULTS: Thirteen centers (41%) [illegible] patients were treated with external-beam ra[illegible]herapy as palliative treatment for T, N or M les[illegible]s to small volumes) and postoperatively, respectively. Bladder preservation was performed in 12 cases and included trimodality and other strategies (mainly TURBT followed by radiotherapy). A multidisciplinary urology tumor board met regularly in 5 of 11 centers. All responders declared their interest in the Lombardy multicenter collaboration on bladder preservation.

CONCLUSIONS: Our survey showed that bladder preservation is rarely used in Lombardy despite the availability of the latest radiotherapy technologies and the presence of an urology tumor board in half of the centers. The initiative of multicenter and multidisciplinary collaboration was undertaken to prepare the platform for bladder preservation as a treatment option in selected patients.

bladder preservation is rarely used in Lombardy

Versione 3 – 07/06/2018

Preservazione della vescica urinaria in Lombardia. Studio osservazionale nell'ambito delle Rete Oncologica Lombarda (ROL)

Codice dello studio : ROL BLADDER

RADIOTERAPIA IOB - NOSTRA ESPERIENZA

Numero pazienti	dal 2013 ad oggi 56 pazienti irradiati sulla vescica per npl vescicale confinata o metastatica. Tra questi 16 (28%) pazienti sono stati trattati con terapia trimodale.
Età	Mediana 80 anni (65-88 aa)
Stadio	T2 n=13, T3 n=2
Dose RT	vescica (60-66 Gy, mediana 60 Gy), linfonodi pelvici (46 Gy)
Chemioterapia	gemcitabina in 10 pazienti, nei restanti CBDCA o cisplatino
Operabilità	Operabili 6 e non operabili 10
Candidati ideali a TMT	4 pazienti
TURV	Resezione completa in 5 pazienti, incompleta nei restanti.

RADIOTERAPIA IOB - NOSTRA ESPERIENZA

Follow-up	mediana 16 mesi (6-69 mesi)
Controllo locale	4 pazienti con evidente tumore residuo dopo resezione parziale hanno avuto RP prolungata, tranne uno. I rimanenti NED a livello vescicale.
Controllo a distanza	1 paziente con recidiva ureterale, 2 pazienti con mts ossee
Cistectomia salvataggio	1 paziente
Tossicità acuta	tossicità GI e GU di grado <2, 1 paziente con tox GU di grado G3. Tossicità ematologica accettabile. No interruzioni del trattamento.
Tossicità tardiva	vescica con funzionalità normale,1 paziente con incontinenza urinaria permanente. 1 paziente con idronefrosi radio-indotta.

CONCLUSIONI

- La conservazione di vescica mediante terapia trimodale, capace di ridurre le complicazioni e la menomazione funzionale della chirurgia senza penalizzare l'efficacia del trattamento, rappresenta una **importante opzione terapeutica** sia in pazienti selezionati rispetto a RC sia in pazienti non candidati a RC.

"Better is possible. It does not take genius. It takes diligence. It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try."

Atul Gawande