TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Fluorouracil

INDICATION: Bladder cancer, in combination with cisplatin and radiotherapy

COMPENDIA TRANSPARENCY REQUIREMENTS	
1	Provide criteria used to evaluate/prioritize the request (therapy)
2	Disclose evidentiary materials reviewed or considered
3	Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest
4	Provide meeting minutes and records of votes for disposition of the request (therapy)

EVALUATION/PRIORITIZATION CRITERIA: **A, C, S**
*to meet requirement 1

CODE	EVALUATION/PRIORITIZATION CRITERIA
A	Treatment represents an established standard of care or significant **advance** over current therapies
C	**Cancer** or cancer-related condition
E	Quantity and robustness of **evidence** for use support consideration
L	**Limited** alternative therapies exist for condition of interest
P	**Pediatric** condition
R	**Rare** disease
S	**Serious**, life-threatening condition

Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]

TRUVEN HEALTH ANALYTICS

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Weiss,C., et al: Radiochemotherapy with cisplatin and 5-fluorouracil after transurethral surgery in patients with bladder cancer. International Journal of Radiation Oncology Biology Physics Jul 15, 2007; Vol 68, Issue 4; pp. 1072-1080.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. All subjects were included in the analyses. The results should be interpreted with caution due to the absence of a control group.	S
Chen,W.C., Liaw,C.C., Chuang,C.K., et al: Concurrent cisplatin, 5-fluorouracil, leucovorin, and radiotherapy for invasive bladder cancer. Int J Radiat Oncol Biol Phys Jul 01, 2003; Vol 56, Issue 3; pp. 726-733.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. The results should be interpreted with caution due to the absence of a control group.	S
Zietman,A.L., et al: A phase I/II trial of transurethral surgery combined with concurrent cisplatin, 5-fluorouracil and twice daily radiation followed by selective bladder preservation in operable patients with muscle invading bladder cancer. Journal of Urology Nov 1998; Vol 160, Issue 5; pp. 1673-1677.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. The results should be interpreted with caution due to the absence of a control group.	S
Kaufman,D.S., Winter,K.A., Shipley,W.U., et al: The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist 2000; Vol 5, Issue 6; pp. 471-476.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. The results should be interpreted with caution due to the absence of a control group.	S

Danesi,D.T., Arcangeli,G., Cruciani,E., et al: Conservative treatment of invasive bladder carcinoma by transurethral resection, protracted intravenous infusion chemotherapy, and hyperfractionated radiotherapy - Long-term results. Cancer Dec 01, 2004; Vol 101, Issue 11; pp. 2540-2548.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Analyses looked at complete response rate by prognostic factors. The subjects lost to follow up were unlikely to introduce bias. The results should be interpreted with caution due to the absence of a control group.	1
Chretien,Y., Mejean,A., Durdux,C., et al: Invasive bladder cancer: Is radiochemotherapy an alternative to cystectomy?. Journal D Urologie 1996; Vol 102, Issue 1; pp. 3-8.		1
Akcetin,Z., Todorov,J., Tuzel,E., et al: Radiochemotherapy after transurethral resection is an effective treatment method in T1G3 bladder cancer. Anticancer Research May 2005; Vol 25, Issue 3A; pp. 1623-1628.		3
Hussain,M.H., Glass,T.R., Forman,J., et al: Combination cisplatin, 5-fluorouracil and radiation therapy for locally advanced unresectable or medically unfit bladder cancer cases: a Southwest Oncology Group Study. Journal of Urology Jan 2001; Vol 165, Issue 1; pp. 56-60.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. The subjects lost to follow up were unlikely to introduce bias. However, response could not be determined in 18 of the 53 patients because of early death of 3 and incomplete assessment of or refusal of therapy before scheduled assessment by 15. These 18 patients are assumed to be nonresponders for the purpose of response rate estimation. The results should be interpreted with caution due to the absence of a control group.	3
Housset,M., Maulard,C., Chretien,Y., et al: Combined Radiation and Chemotherapy for Invasive Transitional-Cell Carcinoma of the Bladder - A Prospective-Study. Journal of Clinical Oncology Nov 1993; Vol 11, Issue 11; pp. 2150-2157.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. All subjects were included in the analyses. The results should be interpreted with caution due to the absence of a control group.	1

Saracino,B., et al: Combined hyperfractionated radiotherapy and protracted infusion chemotherapy in bladder cancer for organ preservation. Clin Ter. May 1998; Vol 149, Issue 3; pp. 183-189.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. All subjects were included in the analyses. The results should be interpreted with caution due to the absence of a control group.	1
Lagrange,J.L., et al: Quality of Life Assessment After Concurrent Chemoradiation for Invasive Bladder Cancer: Results of A Multicenter Prospective Study (Getug 97-015). International Journal of Radiation Oncology Biology Physics Jan 01, 2011; Vol 79, Issue 1; pp. 172-178.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. The results should be interpreted with caution due to the absence of a control group.	1
Rodel,C., et al: Organ preservation in patients with invasive bladder cancer: Initial results of an intensified protocol of transurethral surgery and radiation therapy plus concurrent cisplatin and 5-fluorouracil. International Journal of Radiation Oncology Biology Physics Apr 01, 2002; Vol 52, Issue 5; pp. 1303-1309.		2
Hussain,S.A., Stocken,D.D., Peake,D.R., et al: Long-term results of a phase II study of synchronous chemoradiotherapy in advanced muscle invasive bladder cancer. British Journal of Cancer Jun 01, 2004; Vol 90, Issue 11; pp. 2106-2111.	Study methodology comments: This was an open-label, single-arm trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. The results should be interpreted with caution due to the absence of a control group.	1

Edland,R.W., Wear,J.B.,Jr., and Ansfield,F.J.: Advanced cancer of the urinary bladder. An analysis of the results of radiotherapy alone vs. radiotherapy and concomitant 5-fluorouracil; a prospective randomized study of 36 cases. Am J Roentgenol Radium Ther Nucl Med Jan 1970; Vol 108, Issue 1; pp. 124-129.		1
Lin,C.C., et al: Induction Cisplatin and Fluorouracil-Based Chemotherapy Followed by Concurrent Chemoradiation for Muscle-Invasive Bladder Cancer. International Journal of Radiation Oncology Biology Physics Oct 01, 2009; Vol 75, Issue 2; pp. 442-448.		1
Poortmans,P.M., Richaud,P., Collette,L., et al: Results of the phase II EORTC 22971 trial evaluating combined accelerated external radiation and chemotherapy with 5FU and cisplatin in patients with muscle invasive transitional cell carcinoma of the bladder. Acta Oncol 2008; Vol 47, Issue 5; pp. 937-940.		3
Russell,K.J., et al: Transitional cell carcinoma of the urinary bladder: histologic clearance with combined 5-FU chemotherapy and radiation therapy. Preliminary results of a bladder-preservation study. Radiology Jun 1988; Vol 167, Issue 3; pp. 845-848.		1

Sherwood,B.T., Jones,G.D.D., Mellon,J.K., et al: Concomitant chemoradiotherapy for muscle-invasive bladder cancer: The way forward for bladder preservation?. Clinical Oncology May 2005; Vol 17, Issue 3; pp. 160-166.		4
Shipley,W.U.: Thoughtful, practical and timely radiation therapy guidelines for patients with muscle-invasive bladder cancer. Journal of Medical Imaging and Radiation Oncology 2012; Vol 56, Issue 1; p. 4.		4
Valduga,F., Caffo,O., Fellin,G., et al: 5-Fluorouracil continuous infustion (5FUci) plus concurrent radiotherapy (XRT) as conservative treatment for frail patients with localized bladder cancer (LBC). Annals of Oncology 2004; Vol 15, pp. 119-119.		4

Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)

TRUVEN HEALTH ANALYTICS

CONTRIBUTORS:

*to meet requirement 3

PACKET PREPARATION	DISCLOSURES	EXPERT REVIEW	DISCLOSURES
Margi Schiefelbein, PA	None	Edward P. Balaban, DO	None
Stacy LaClaire, PharmD	None	Jeffrey A. Bubis, DO	Other payments: Dendreon
Felicia Gelsey, MS	None	Keith A. Thompson, MD	None
		James E. Liebmann, MD	None
		John M. Valgus, PharmD	None

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---	---		B
Edward P. Balaban, DO	Evidence favors efficacy	Class IIb - Recommended, In Some Cases	It would appear that chemoradiation for bladder ca would be an alternative in patients unfit for radical cystectomy or are seeking to preserve their bladder - however it does have considerable physiologic cost and subsequently those who receive this approach have to be chosen very carefully	N/A
Jeffrey A. Bubis, DO	Evidence favors efficacy	Class IIa - Recommended, In Most Cases	Data is from non-randomized trials, but favors a benefit. Despite this, a lack of other phase III data would imply this can be a standard of care. Manageable toxicity in selected patients with significant outcomes benefit.	N/A
Keith A. Thompson, MD	Evidence is inconclusive	Class III - Not Recommended	No clear data to guide decisions.	N/A

James E. Liebmann, MD	Evidence favors efficacy	Class IIb - Recommended, In Some Cases	In the last 15 years there has been increasing acceptance of radiation + chemotherapy for bladder cancer. However, studies of this approach have used a variety of chemotherapy regimens and radiation techniques. Thus, it is difficult to say that there is a "standard" regimen for this disease. However, a randomized trial from Britain showed that concurrent chemotherapy with mitomycin C and 5-FU with radiation resulted in better outcomes compared with radiation alone. Most other trials (typically single treatment ARM) used cisplatin-based regimens, the addition of 5-FU to cisplatin seems to result in rates of survival and disease-free survival comparable to what is seen with MMC + F-FU. While cystectomy still is the standard of care for this disease, 5-FU + radiation + cisplatin (or MMC) is an alternative for patients unable to have surgery.	N/A
John M. Valgus, PharmD	Evidence is inconclusive	Class IIb - Recommended, In Some Cases	None of these studies demonstrate the importance of 5-FU in this combination regimen. Although the response rates and survival are impressive, these are all single arm, non-comparative studies. The contribution of 5-FU to his regimen remains unknown.	N/A