ANNALI ITALIANI DI CHIRURGIA
Edizione Digitale
ISSN 2239-253X
Direttore Nicola Picardi

The surgical treatment of a melanoma patient with macroscopic metastasis in peri and retrocaval lymph nodes and with a positive sentinel lymph node in the groin

Ann. Ital. Chir.
Published online (EP) 4 February 2016
pii: S2239253X16024762
www.annitalchir.com

Giuseppe Giudice*, Fabio Robusto**, Eleonora Nacchiero*

**Department of Emergency and Organ Transplantation, Complex Operating Unit of Plastic, Aesthetic and Reconstructive Surgery, Aldo Moro University, Bari, Italy.*
***Mario Negris Sud Institute, Santa Maria Imbaro, Chieti, Italy*

The surgical treatment of a melanoma patient with macroscopic metastasis in peri and retrocaval lymph nodes and with a positive sentinel lymph node in the groin

BACKGROUND: *The extension of iliac-obturator dissection in melanoma patient with metastatic sentinel node of the groin is very debated. More recent studies - in accord with guidelines for urogenital cancers - suggest the extension to pelvic lymph nodes. At present, however, anatomical limits and indications to pelvic dissection are not defined in melanoma patients with metastatic lymph nodes of groin.*
CASE REPORT: *A 46-year-old man affected by nodular cutaneous melanoma (Breslow-thickness 10 mm, Clark-level V) on the anterior-medial surface of the right leg underwent sentinel node biopsy of groin. Three macro-metastatic sentinel lymph nodes were removed in right inguinal field and, after 2 weeks, an ipsi-lateral inguinal lymphadenectomy with an extended pelvic dissection was performed. During the surgery, we reported the presence of macrometastases also in retro/peri caval lymph nodes. As a result of these findings, we decided to perform the super-extended pelvic lymphadenectomy. Overall we removed 56 lymph nodes with 9 peri-caval and 2 retro-caval macro metastatic lymph nodes. After a period of 49 months, the patients came to our attention with multiple scrotal metastases. The imagining restaging of the patient was already negative for other melanoma localizations.*
DISCUSSION: *Currently there are no guidelines about indications and anatomical limits of iliac-obturator extension in melanoma patients. The extended pelvic dissection is the gold-standard procedure used in urogenital carcinomas. In case of finding of macro-metastases during the surgical procedure, the approach to follow is even more uncertain. We perform a super-extended pelvic dissection with a good prognosis for the patient.*

KEY WORDS: Caval-metastasis, Extended-pelvic-lymphadenectomy, Metastatic-melanoma

Background

During metastatic progression, melanoma develops a rich vascular network, developing capacity to disseminate to the lymphatic pathway [1]. Sentinel node (SN) biopsy is a consolidated procedure to assess the lymphatic involvement in melanoma patients and lymphadenectomy is recommended in case of tumor-positive SN. Although the lymphadenectomy of metastatic lymph nodes has demonstrated an improvement on prognosis in patients with tumor-positive SNB [2] – the surgical procedure and the extension of lymph node dissection is already debated. Recently many studies have suggested that the number of excised lymph nodes is associated with survival[3] and with quality of lymphadenectomy [4] in melanoma patient with lymph node metastasis, testifying the importance of complete dissection in the surgical management of metastatic lymphatic basin. The groin is the anatomical region in which the surgical procedure for lymphatic dis-

Pervenuto in Redzione Settembre 2015. Accettato per la pubblicazione Novembre 2015
Correspondence to: Eleonora Nacchiero, Department of Emergency and Organ Transplantation, Complex Operating Unit of Plastic Aesthetic and Reconstructive Surgery, Aldo Moro University, P.zza Giulio Cesare, 11, 70124 Bari, Italy (e-mail: eleonora.nacchiero@uniba.it / eleonora.nacchiero@yahoo.it)

section is more controversial and recent studies disagree on the indications to iliac-obturator extension [5-8]. Even in the case of execution of inguinal-iliac-obturator dissection, the anatomical limits of the extension to pelvic region are not well established in melanoma patients. In fact, although the extended radical pelvic lymphadenectomy is the gold-standard procedure in patients with urogenital carcinomas [9-11], currently there are no guidelines about definition of the limits of iliac-obturator extension in melanoma patient with metastatic lymph nodes of the groin.

Case Report

A 46-year-old man presented in our clinic showing a painless, pigmented, ulcerate, and exophytic skin lesion with irregular margins on the anterior-medial surface of the right leg. The patient referred several traumas of the area and he reported a change in the shape of the lesion and an increase in its size in the last year.

On clinical examination we testified an exophytic, roundish skin lesion with a diameter of about 3 cm with irregular margins with two little cutaneous satellitosis. The familiar and pathological anamneses were negative, and physical examination did not show any other disorders for lymphatic masses in the popliteal and inguinal regions.

We removed the lesion with a direct wound closure and an anatomo-pathological analysis was performed. The relative pattern was "nodular exophytic cutaneous melanoma, infiltrating adipose tissue with a neoplastic endo-lymphatic permeation. The neoplasia presented satellitosis on the lateral and deeper resection margins". The Breslow thickness was 10 mm and a V Clark level invasion. CT scan of the whole body with contrast revealed no images referable to metastases.

Then we performed a wide excision of skin of the previous skin scare down to the muscle fascia, using a contralateral thigh skin graft to cover the cutaneous defect. Contextually, a sentinel lymph node dissection was performed and three sentinel lymph nodes were removed in right inguinal field. The histological examination revealed the absence of neoplasm in cutaneous excision, while all the three lymph nodes were positive for macrometastases. After 2 weeks, we performed a complete superficial and deep inguinal lymphadenectomy with the addition of iliac-obturator lymph node laparotomy dissection (Fig. 1). During the surgery, we reported the presence of several macrometastases in internal iliac, external iliac, common iliac, obturator, and also retro/peri caval lymph nodes (Fig. 2). According to the lymphatic treatment of urogenital carcinomas, in this case we decided to perform the super-extended[12] pelvic lymphadenectomy, removing also retro/peri caval lymph

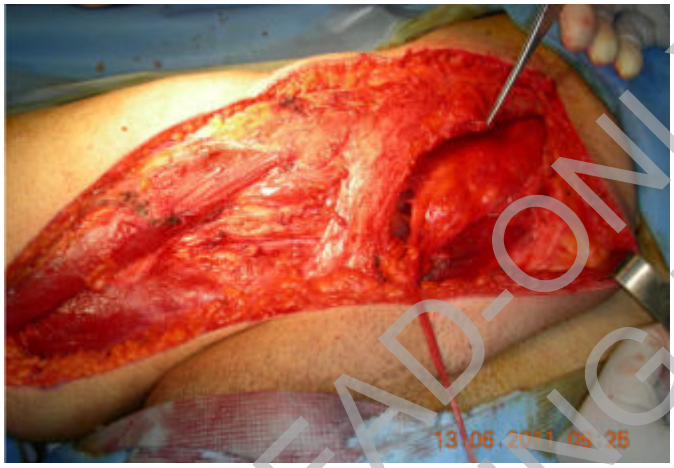

Fig. 1.

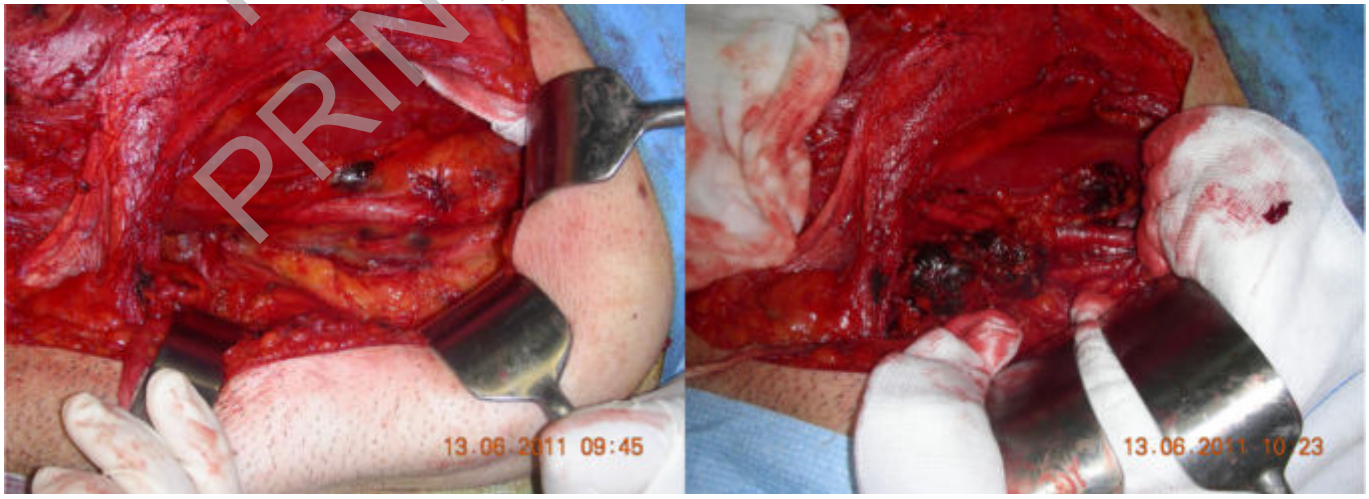

Fig. 2.

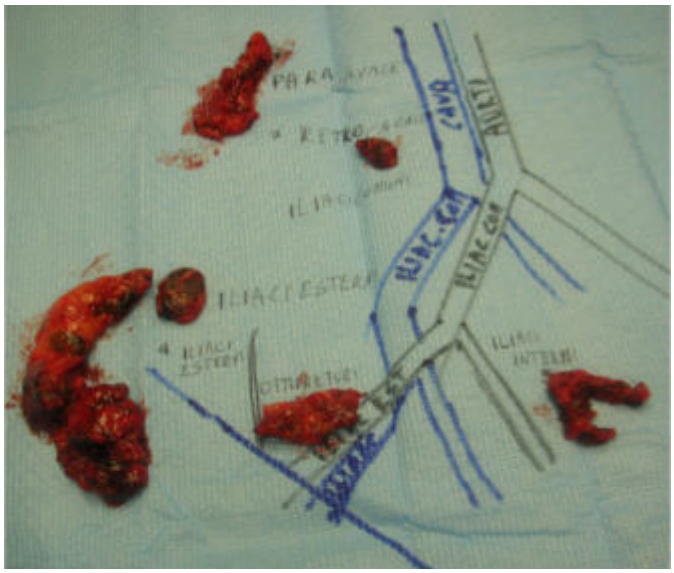

Fig. 3.

nodes. Histologically, overall 56 lymph nodes (21 external iliac, 4 internal iliac, 10 common iliac, 10 obturator, 9 peri-caval, and 2 retro-caval) were removed and 54 were macrometastatic (20 external iliac, 4 internal iliac, 9 common iliac, 10 obturator, 9 peri-caval, and 2 retro-caval) (Fig. 3).
The patient was included into a phase III randomized clinical trial (DERMA study) in which recMAGE-A3+As15 (ASCI) was confronted in double-blind versus placebo. According with the protocol of this trial, the patient underwent a clinical and imagining follow-up with CT every 3 months. This protocol terminated after 2 years without any clinical or instrumental demonstration of progression of melanoma.
After a period of 49 months from the first diagnosis of melanoma, the patients came to our attention with multiple swollen lesions in bilateral scrotal region. We removed one of them that resulted as a multi-nodular dermic and sub-cutaneous melanoma metastasis with endolymphatic and microvenular neoplastic permeation at the anatomo-phatological analysis. The imagining restaging of the patient was already negative for other melanoma localizations.
Genetic-molecular analysis testified BRAF mutation and NRAS wild-type; so the patient began immunoteraphy with ipilimumab.

Discussion

Dissection of the lymphatic basin is even recommended and improvement of prognosis in patients with tumor-positive SN biopsy who underwent lymphadenectomy is testified [13]. Recent studies have shown the importance of the complete dissection of metastatic lymphatic basins and the number of excised lymph nodes is used as indicator of quality and completeness of the lymphadenectomy[4]. For this reason, the extension of lymphadenectomy to iliac-obturator lymph nodes appears reasonable in all the patients with tumor-positive SNs of the groin. This topic is controversial in literature: some authors reported that the addition of an iliac-obturator lymph node dissection did not improve nodal recurrence or survival in melanoma [14], but more larger studies showed contradictory results [15]. Moreover the demonstration of a relationship between improvement of prognosis in patients with a tumor-positive SN biopsy and a greater numbers of excised lymph nodes [3] seems to definitively prove the usefulness of the extension of lymphadenectomy to iliac-obturator lymph nodes.
Currently there are not guidelines about the anatomical limits of the addition of iliac-obturator dissection in melanoma patients. The extension of iliac-obturator dissection is well studied in urogenital oncology; in fact, three different surgical procedures are described:
– **limited lymphadenectomy** [16]: in this procedure only the lymph nodes placed along the external iliac vein and the obturator fossa are removed;
– **extended lymphadenectomy** [17], in which cranial border of the lymphadenectomy was the aortic bifurcation, lateral border was the genitofemoral nerve and caudal border was the pelvic floor;
– **super-extended lymphadenectomy** [18] extends above the aortic bifurcation, until the inferior mesenteric artery, including the pre-sacral lymph and the retro/peri caval nodes.
Although most of the lymphatic drainage primary is localized below the iliac bifurcation [19] (10), more than 25% with SN+ have disease in common iliac and/or sacral lymph nodes [18], while >28% with SN+ has metastases in para-caval or para-aortic regions [20]. These findings recommend the extension of the iliac-obturator dissection over the external iliac vein and the obturator fossa. In fact, the extended lymphadenectomy is associated with a lower rate of positive margins, a lower rate of local recurrence [21]. The incidence of metastatic lymph node outside the standard template is 41% [22-23]. Moreover, the extended lymphadenectomy improves survival for patients with urogenital cancers [24-25]. The improvement of survival and recurrence outcome of the super-extended lymphadenectomy are similar to those of a meticulous extended lymph node dissection up to the mid-upper third of the common iliac vessels, but with a greater incidence of complications [26].
We report the case of a patient with SN+ of groin who underwent a inguinal lymphadenectomy with an extended dissection of iliac-obturator lymph nodes. Macrometastatic retro/peri caval lymph nodes were reported during this surgical procedure; for this reason, we decided to remove also these macroscopically pathologic lymph nodes through a super extended pelvic dissection. Although there are not guidelines about the management

of iliac-obturator nodes in melanoma patients and the recommended extension of pelvic lymph node dissection in urogenital cancers is the extended lymphadenectomy (in which the cranial border of the lymphadenectomy was the aortic bifurcation), we extended the lymphadenectomy to peri/retro caval region, identifying 9 peri-caval and 2 retro-caval metastatic lymph nodes. The presence of metastatic lymph nodes along the cava vein and the good prognosis of this patient (with a local metastasis after a period of 49 months) seems justifies our surgical approach.

Conclusion

This case report underlies the necessity to accurately investigate the possible macro metastatic involvement of peri/retro caval lymph nodes during the iliac-obturator lymph nodes dissection. Moreover, the frequency of metastases in peri/retro caval lymph nodes should be evaluated in melanoma patients. In fact, the current management and the anatomical limits of pelvic lymph nodes dissection in melanoma derived on studies on urogenital cancers. Therefore, specific studies on the surgical management of inguinal metastases are indispensable in a cancer such as melanoma that has characteristics and behaviours very different from that of the urogenital tract carcinomas.

Riassunto

INTRODUZIONE: L'estensione della linfadenectomia in pazienti affetti da melanoma con linfonodo sentinella inguinale metastatico è molto dibattuta. Gli studi più recenti – in accordo con le linee guida per il trattamento chirurgico di carcinomi del tratto uro-genitale – suggeriscono l'estensione della dissezione chirurgica ai linfonodi iliaco-otturatori. Attualmente, però, i limiti anatomici e l'indicazione all'allargamento pelvico della linfadenectomia inguinale non sono ancora definiti.
CASE REPORT: Un uomo di 46 anni con un melanoma nodulare cutaneo sulla faccia antero-mediale della gamba destra è stato sottoposto a biopsia del linfonodo sentinella dell'inguine, risultato positiva per macrometastasi. Dopo 2 settimane è stata eseguita la linfadenectomia inguinale con completamento con dissezione pelvica estesa; ma durante l'intervento è stata notata la presenza di metastasi macroscopicamente visibili anche in sede peri e retro cavale. Si è optato pertanto per passare alla linfadenectomia pelvica super-estesa, rimuovendo anche questi linfonodi. In totale sono stati rimossi 56 linfonodi, 54 sono risultati macrometastatici e di questi ultimi 9 erano peri-cavali e 2 retro-cavali. Dopo 49 mesi il paziente è giunto alla nostra attenzione per metastasi scrotali multiple, in assenza di ulteriori localizzazioni secondarie.
DISCUSSIONE: Attualmente non ci sono linee guida per i pazienti affetti da melanoma a riguardo di indicazioni e limiti anatomici dell'estensione iliaco-otturatoria. La dissezione pelvica estesa è la procedura chirurgica di elezione nei pazienti affetti da carcinoma uro-genitali. In caso di riscontro intraoperatorio di macrometastasi in regione peri/retro cavale, l'approccio da seguire risulta ancora più incerto. Noi abbiamo eseguito una dissezione super-estesa pelvica con una buona prognosi per il paziente.
CONCLUSIONI: Questo case-report testimonia la necessità di analizzare accuratamente l'eventuale presenza di metastasi linfatiche macroscopicamente visibili in regione peri/retro cavale, mettendo in evidenza la necessità di ulteriori studi per valutare la frequenza di metastasi in tale localizzazione nonché di sviluppare linee guida specifiche su indicazione ed estensione della dissezione pelvica nei pazienti affetti da melanoma con metastasi linfonodali inguinali.

References

1. Ribatti D, Vacca A, Palma W, Lospalluti M, Dammacco F: *Angiogenesis during tumor progression in human malignant melanoma.* EXS,1992; 6:415-20.

2. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Glass EC, Wang HJ. MSLT Group: *Sentinel-node biopsy or nodal observation in melanoma.* N Engl J Med, 2006; 32:1307-17.

3. Rossi CR, Mozzillo N, Maurichi A, Pasquali S, Quaglino P, Borgognoni L, Solari N, Piazzalunga D, Mascheroni L, Giudice G, Mocellin S, Patuzzo R, Caracò C, Ribero S, Marone U, Santinami M: *The number of excised lymph nodes is associated with survival of melanoma patients with lymph node metastasis.* Ann Oncol, 2014; 25(1):240-46.

4. Rossi CR, Mozzillo N, Maurichi A, Pasquali S, Macripò G, Borgognoni L, Solari N, Piazzalunga D, Mascheroni L, Giudice G, Mocellin S, Patuzzo R, Caracò C, Ribero S, Marone U, Santinami M: *Number of excised lymph nodes as a quality assurance measure for lymphadenectomy in melanoma.* JAMA Surg, 2014; 149(7):700-6.

5. Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH, Gore ME, Lorigan P, Mackie R, Nathan P, Peach H, Powell B, Walker C: *British Association of Dermatologists (BAD) Clinical Standards Unit. Revised UK guidelines for the management of cutaneous melanoma 2010.* 2010; 63(9):1401-19.

6. Koh YX, Chok AY, Zheng H, Xu S, Teo MC: *Cloquet's node trumps imaging modalities in the prediction of pelvic nodal involvement in patients with lower limb melanomas in Asian patients with palpable groin nodes.* Eur J Surg Oncol, 2014; 40(10):1263-20.

7. Essner R, Scheri R, Kavanagh M, et al.: *Surgical management of the groin lymph nodes in melanoma in the era of sentinel lymph node dissection.* Arch Surg, 2006; 141(9):877-84.

8. Mozzillo N, Pasquali S, Santinami M, Testori A, Di Marzo M, Crispo A, Patuzzo R, Verrecchia F, Botti G, Montella M, Rossi

CR, Caracò C: *Factors predictive of pelvic lymph involvement and outcomes in melanoma patients with metastatic sentinel lymph node of the groin: Multicentre study*. Eur J Surg Oncol, 2015; 41(7):823-29.

9. Leissner J, Ghoneim MA, Abol-Enein H, Thuroff JW, Franzaring L, Fisch M, Schulze H, Managadze G, Allhoff EP, el-Baz MA, Kastendieck H, Buhtz P, Kropf S, Hohenfellner R, Wolf HK: *Extended radical lymphadenectomy in patients with urothelial bladder cancer: Results of a prospective multicenter study*. J Urol, 2004; 171(1):139-44.

10. Matin SF, Sfakianos JP, Espiritu PN, Coleman JA, Spiess PE: *Patterns of lymphatic metastases in upper tract urothelial carcinoma proposed dissection templates.* J Urol, 2015.

11. Roscigno M, Brausi M, Heidenreich A, Lotan Y, Margulis V, Shariat SF, Van Poppel H, Zigeuner R: *Lymphadenectomy at the time of nephroureterectomy for upper tract urothelial cancer.* Eur Urol, 2011; 60(4):776-83.

12. Poulsen AL, Steven K: *Radical cystectomy: Extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall*. J Urol, 1998; 160(6Pt1):2015-19.

13. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Glass EC, Wang HJ: *MSLT Group. Sentinel-node biopsy or nodal observation in melanoma*. N Engl J Med, 2006; 32:1307-317.

14. Egger ME, Brown RE, Roach BA, Quillo AR, Martin RC, Scoggins CR, Stromberg AJ, McMasters KM: *Addition of an iliac/obturator lymph node dissection does not improve nodal recurrence or survival in melanoma*. J Am Coll Surg, 2014; 219(1):101-8.

15. Badgwell B, Xing Y, Gershenwald JE, Lee JE, Mansfield PF, Ross MI, Cormier JN: *Pelvic lymph node dissection is beneficial in subsets of patients with node-positive melanoma.* Ann Surg Oncol, 2007; 14(10):2867-75.

16. Link RE, Morton RA: *Indications for pelvic lymphadenectomy in prostate cancer.* Urol Clin North Am, 2001; 28(3):491-98.

17. Stein JP, Lieskovsky G, Cote R, et al.: *Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1054 patients*. J Clin Oncol, 2001; 19:666-75.

18. Leissner J, Ghoneim MA, Abol-Enein H, et al.: *Extended radical lymphadenectomy in patients with urothelial bladder cancer: Results of a prospective multicenter study*. J Urol, 2004; 171:139-44.

19. Roth B, Wissmeyer MP, Zehnder P, et al.: *A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder.* Eur Urol, 57:205.

20. Dorin RP, Eisenberg MS, Caj J, et al.: *Location of lymph node metastases in bladder cancer- a prospective study of 408 patients undergoing radical cystectomy with extended lymph node dissection*. J Urol suppl, 2010; 183:635.

21. Dangle PP, Gong MC, Bahnson RR, et al.: *How do commonly performed lymphadenectomy templates influence bladder cancer nodal stage?* J Urol, 2010; 183:499-503.

22. Stein JP, Penson DF, Cai J, et al.: *Radical cystectomy with extended lymphadenectomy: evaluating separate package versus en bloc submission for node positive bladder cancer.* J Urol, 2007; 177:876-81, discussion 881-82.

23. Bochner BH, Herr HW, Reuter VE: *Impact of separate versus en bloc pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens.* J Urol, 2001; 166:2295-96.

24. Poulsen AL, Horn T, Steven K: *Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall*. J Urol, 1998; 160:2015-19.

25. Heidenreich A, Varga Z, Von Knobloch R.: *Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: High incidence of lymph nodemetastasis.* J Urol. 2002; 167(4):1681-686.

26. Zehnder P, Studer UE, Dorin RP, Cai J, Roth B, Miranda G, Birkhauser F, Stein J, Burkhard FC, Daneshmand S, Thalmann GN, Gill IS, Skinner DG: *Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: A comparative study*. J Urol, 2011; 186(4):12612-68.