PELVIC LYMPHADENECTOMY IN PROSTATE CANCER TREATMENT

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SUMMARY – Despite the increasing number of patients being detected with a clinically localized (T1,2) prostate cancer, pelvic lymphadenectomy remains a standard in determining the exact histological staging as a reliable prognostic parameter. Extended lymphadenectomy is superior to limited lymphadenectomy, and with the use of appropriate surgical technique does not contribute significantly to the operative morbidity while providing an evidence based indication for additional treatment modalities. Lymphadenectomy may not be indicated in patients at a low risk of regional lymphatic metastasis (impalpable T1 carcinoma, PSA less than 10 and Gleason score less than 6), depending on the preferences of the surgeon and the patient. In all other patients, it is reasonable to perform lymphadenectomy, at least a limited one, however, extennded lymphadenectomy is being increasingly recommended. Good cooperation with clinical pathologist is of great importance. Pelvic lymphadenectomy is most probably without an oncologic therapeutic effect in highly selected patients with favorable prognostic factors. Although data concerning therapeutic effect of extended lymphadenectomy are few and contradictory, there are convincing indications of the possible therapeutic effect of such an approach, in particular for patients with micrometastases.

Key words: *Prostatectomy – methods; Prostatic neoplasms – surgery; Prostatic neoplasms – pathology; Lymph node excision – methods*

Introduction

With the development of modern screening and early diagnosis of prostate cancer, radical surgical treatment of the disease has become a therapeutic option. Dissection of lymph nodes (lymphadenectomy) is a generally accepted principle in oncologic surgery performed to assess exactly the degree of regional expansion of the disease (exact histopathologic staging). Another goal of lymphadenectomy is to achieve an oncologic therapeutic effect, i.e. to lower specific mortality and to prolong disease free survival.

Early diagnosis with the introduction of prostate specific antigen (PSA) and systematic prostate biopsy has resulted in an ever increasing proportion of patients diagnosed with prostatic cancer in a potentially surgically curable stage, i.e. clinically localized carcinoma (T1 and T2 stage). Therefore, the incidence of regional lymphatic matastases has decreased; analysis of the last ten years shows it to have occurred in less than 10% of patients with clinically localized carcinoma[1]. Due to these results and the opinion that lymphadenectomy has only a prognostic value, in some centers this surgical procedure has been abandoned or indicated on the basis of certain nomograms predicting a multifactorial risk of lymphatic progression[2-4].

Other authors continue to perform pelvic lymphadenectomy prior to radical prostatectomy, but reducing it to 'minimal' or 'limited pelvic lymphadenectomy'. More recent results of European authors, based on the analysis of 'extended pelvic lymphadenectomy', argue that such a procedure is necessary to perform in every patient due to low positive predictive value and sensitivity of the nomograms as well as anatomically un-

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grounded basis of minimal and limited lymphadenectomy[1,5,6].

Limited or Extended Staging Lymphadenectomy?

Minimal pelvic lymphadenectomy consists of removal of the lymph node chain next to obturator nerve, while limited expands dissection to the area of external iliac vessels. Extended dissection additionally removes nodes around internal iliac artery, common iliac artery proximal to the ureter and presacral nodes[5,7,8].

Nine years ago, Gil-Vernet showed that anatomically there were three prostate lymphatic drainage pathways. The cranial part of the prostate drains into outer and common iliac lymph nodes, lateral segments into hypogastric lymph nodes, and posterior segments into presacral lymph nodes[9]. At the same time, Weingartner *et al.* published a study claiming that adequate pelvic lymphadenectomy should contain an average of 20 lymph nodes in order to receive proper histopathologic staging[10]. Later studies of surgical material have shown that limited lymphadenectomy removes approximately 10-11 lymph nodes, while extended lymphadenectomy removes 24 nodes on an average. Similar results have been published by other authors, showing that extended lymphadenectomy removes twice the number of nodes, while detecting two or three times more regional micrometastases, even in patients with clinically localized disease, in approximately 20%-25% of cases, the primary surgical interest being internal iliac artery and presacral lymph nodes[1,6,8].

If we try to remove as many lymph nodes as possible, it is of great importance to have adequate cooperation with clinical pathologist who can evaluate all of the nodes. Otherwise, some regional lymphatic metastases may go unnoticed. Algaba *et al.* state that it is necessary to review all of the removed lymph nodes *ex tempore* in case of high biopsy Gleason score, informing the pathologist prior to the operation. The authors generally consider that histologic *ex tempore* analysis is no longer warranted routinely in prostate cancer[11]. The ratio between the number of positive and removed lymph nodes is called 'lymph node density' and this parameter has been shown to be of great prognostic importance in prostate and bladder cancer. In prostate cancer, it is prognostically favorable if the lymph node density is 15% or less. The value of lymph node density is based on the total number of nodes removed and this number should not be less than 20 analyzed nodes, which implies extended lymphadenectomy[8,12]. Such an approach, on the other hand, implies a potentially higher operative morbidity, higher workload for the pathologist as well as higher cost, and therefore it is not necessary in everyday surgical practice as long as further studies definitely prove its value in the prognostic and therapeutic effect in particular[13].

Is Lymphadenectomy Always Necessary?

After the emergence of nomograms proposed by Partin *et al.*, Crawford *et al.*, Narayan *et al.* and others, most authors believe that lymphadenectomy is not necessary to perform with favorable prognostic parameters (PSA less than 10, Gleason score less than 7, clinical stage T2a or lower) due to less than 5% incidence of lymphatic metastases[2,3,14]. The latest works of DiMarco *et al.*[15] and Weckermann *et al.*[16] consider lymphadenectomy to be unnecessary in a prognostically favorable group since the frequency of lymphatic metastases does not reach more than 10%. Likewise, Montinori *et al.* consider intraoperative histologic analysis unwarranted, citing the adequate predictive value of the nomograms[17]. On the other hand, studies by Heidenreich *et al.* and Bader *et al.* show that on using extended lymphadenectomy for clinically localized carcinoma, even with PSA levels less than 10, the frequency of histologically positive lymph nodes on an average reaches more than 20%, and in poorly differentiated tumors (Gleason score 8-10) even more than 50%[1,5,6]. Heidenreich *et al.* point to significant disparity between the frequency of positive lymphatic metastases based on nomograms and those observed using extended lymphadenectomy. Based on these observations, the authors consider it necessary to perform extended lymphadenectomy in all patients who do not belong to a group with favorable prognostic parameters[1,5,13]. Nomograms have been constructed on the basis of data from surgically limited lymphadenectomy, which probably explains the observations of these authors.

The opponents of extended lymphadenectomy often cite a higher frequency of complications compared to limited lymphadenectomy, as seen in earlier studies. Recently, the rate of complications in extended lymphadenectomy is under 10%, most often in the form of symptomatic lymphocele. Using a precise operative technique, maintaining lymphatic ducts laterally to external iliac artery and adequate drainage, and with the use of low molecular heparin, only 3% of operated patients require rehospitalization due to complications that can be attributed to expanded lymphadenectomy[18].

New technological options of radioisotope marking of sentinel nodes, by intraprostatic application of technetium-99 under the control of transrectal ultrasound, and intraoperative identification of marked nodes using a gamma camera show promising first results[19]. Similar technology using immunoscintigraphy with indium-111 displays a certain advantage compared to nomogram prediction, but further studies are warranted to determine the value of these methods in pragmatic usage[20].

Therapeutic Possibilities of Extended Lymphadenectomy

Biochemical relapse, i.e. postoperative rise in serum PSA value, is considered a sign of recurrent disease. According to the study by Fergany *et al.* in a group of patients with favorable prognosis (PSA less than 10, Gleason score less than 6, stage T1), there is no significant difference whether or not pelvic lymphadenectomy is performed. Four-year survival data showed no significant differences between these groups of patients[21]. Similar findings have been published by Meng and Carroll[22]. DiMarco *et al.* also report that the extent of lymphadenectomy and the number of lymph nodes removed does not influence the rate of biochemical relapse, systemic progression of the disease, or specific mortality in patients without lymphatic metastases, even with unfavorable prognostic parameters. If limited lymphadenectomy is performed leaving a few micrometastases, it has no impact on oncologic outcome[15].

However, Bader *et al*. state that extended lymphadenectomy may have an impact on disease progression and long term disease free survival, in particular in patients with a minimal number of positive lymph nodes[6]. First results comparing the rates of biochemical relapse in 3 years between the groups of patients with limited or extended lymphadenectomy show significant differences[1,5].

Allaf *et al*. found no significant disease free survival difference comparing data of radical prostatectomy alone or combined with limited lymphadenectomy in a group of patients with clinically localized prostate cancer. There was a significant difference when the results of limited and extended lymphadenectomy were compared, especially in patients whose lymph node density was less than 15%[8]. Schumacher *et al.*[13] claim that extended lymphadenectomy is required in all patients because studies increasingly show that dissection of all positive lymph nodes, in particular those with micrometastases, can have a beneficial effect on specific patient survival and lower rate of relapses.

Conclusion

Ever more patients are presented with a clinically localized prostate cancer (T1/2), but the role of pelvic lymphadenectomy remains undoubtful as a tool of determining histological staging as a reliable prognostic parameter. In this sense, extended lymphadenectomy is superior to limited procedure and with proper surgical technique it does not contribute significantly to operative morbidity, while providing evidence based indication for further treatment.

Lymphadenectomy as part of radical prostatectomy may be omitted only in patients with a very low risk of regional metastases (impalpable T1 carcinoma, PSA less than 10, Gleason score less than 6), depending on the preferences of the surgeon and the patient. Performing lymphadenectomy is warranted in all patients, at least a limited one, while it is widely considered that extended lymphadenectomy is necessary. Close cooperation with clinical pathologist is of great importance.

Pelvic lymphadenectomy is most likely without an oncologic therapeutic effect in a highly selected group of patients with favorable prognostic parameters. Although data on the therapeutic effect of extended lymphadenectomy are few and contradictory, there are plausible indications that such an approach may have a therapeutic effect especially in patients with micrometastases.

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Sažetak

ZDJELIČNA LIMFADENEKTOMIJA U LIJEČENJU RAKA PROSTATE

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Unatoč ranom otkrivanju sve većeg broja bolesnika s klinički lokaliziranim (T1/2) rakom prostate uloga zdjelične limfadenektomije ostaje neprijeporna u smislu točnog utvrđivanja histološkog stupnjevanja kao pouzdanog prognostičkog pokazatelja. S tim ciljem proširena limfadenektomija nadmašuje ograničenu limfadenektomiju te uz dobru kiruršku tehniku ne doprinosi značajno operacijskom pobolu, dok istodobno omogućava utemeljeno indiciranje dodatnog liječenja. Samo se u bolesnika s vrlo niskim rizikom od regionalnih limfnih metastaza (nepalpabilni T1 karcinom, PSA <10 i Gleasonov zbir <6) limfadenektomija može izostaviti kao sastavni dio radikalne prostatektomije, što ovisi o mišljenju operatera i bolesnika. U svih ostalih bolesnika opravdano je učiniti limfadenektomiju, makar i u ograničenim okvirima, a sve se više zastupa mišljenje o nužnosti proširene zdjelične limfadenektomije. Osobito se naglašava potreba uske suradnje s kliničkim patologom. U onkološkom smislu zdjelična limfadenektomija je najvjerojatnije bez terapijskog učinka u visoko selekcioniranih bolesnika s povoljnim prognostičkim pokazateljima. Iako su podaci o terapijskom učinku proširene limfadenektomije malobrojni i proturječni, postoje uvjerljive indicije o mogućem terapijskom učinku takvog pristupa osobito u bolesnika s mikrometastazama.

Ključne riječi: *Prostatektomija – metode; Neoplazme prostate – kirurgija; Neoplazme prostate – patologija; Izrezivanje limfnih čvorova – metode*