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浸潤性膀胱がんの予後改善をめざした集学的治療の研究

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Ⅰ．総括研究報告書

厚生労働科学研究費補助金（がん臨床研究事業）
総括研究報告書

浸潤性膀胱がんの予後改善をめざした集学的治療の研究

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研究要旨

浸潤性膀胱癌に対する術前化学療法（MVAC 療法）の生存率向上への寄与を確立したエビデンスとする目的で、本研究班 22 施設および研究協力施設 15 施設の計 37 施設を組織し、術前 MVAC 療法＋根治的膀胱摘除（リンパ節郭清も含む）と根治的膀胱摘除のみの２つの治療群を設定した臨床試験に着手している。この臨床試験開始後、MVAC 療法の保険適用が認められたため（2004 年 1 月）、それに即したプロトコールの部分的な改訂も行った。さらに、実際にプロトコール治療を行うにあたって、症例適格規準の一部が臨床の状況にそぐわない点が出てきたため、その部分の改訂を行った。これらの改定は、JCOG 効果・安全性評価委員会での審議の後、承認された（2004 年 2 月 23 日）。このプロトコール改定により、症例の組み入れがより容易になった。現在まで、28 例に症例登録があった（2005 年 3 月 31 日現在）。　MVAC 療法を施行の副作用の検討では、血液毒性を中心とした有害事象がこれまでの報告と同様に認められたが、術前化学療法として 2 コース施行する上では比較的安全に施行できると考えられた。浸潤性膀胱癌の手術後の局所再発が症例の QOL を損ねる点では遠隔転移の出現に勝るとも劣らないことがこれまでの経験で判明していたが、局所再発に影響する臨床病理学敵的な因子が特定されていなかった。そこで、この因子の特定を行うことを試みて、膀胱癌組織の扁平上皮癌の混在がその大きな要因であることを突き止めた。

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A. 研究目的

浸潤性膀胱癌対しては、現在の標準治療では、その効果が十分ではないことが明らかになってきた。そのため治療成績の向上を期待し、術前あるいは術後の化学療法を補助療法として追加することが試みられ

てきた。しかし、補助化学療法の内容およびその時期（術前あるいは術後）に関してはいまだに確立されてはおらず、標準治療の補助療法としての役割も明確にはなってはいない。にもかかわらず、実際の臨床では補助化学療法がルーチンに行われており、補助化学療法で利益を得ない症例に対するいわば無駄な治療が結果的に行われている。このことは、医療経済の面でも明らかに問題がある。特に、2004 年 1 月に MVAC 療法の保険適用が承認されたことから、早急に解決すべき臨床的、医療経済的な問題となる。また、最近、欧米のみならず本邦でも手術の quality が問題にされている。浸潤性膀胱癌の手術に関していえば、それぞれの施設における手術症例数、あるいは手術に際してのリンパ節郭清の範囲、程度などが問題となる。特に、リンパ節郭清に関しては郭清の範囲を拡大することで予後の改善が期待できるという報告もある。このような新しい問題に対しても本試験は一定の示唆を与えることが予想される。

上記の背景に基づき、本研究では、前年度に引き続き、浸潤性膀胱癌の標準治療である根治的膀胱摘除＋リンパ節郭清の補助療法としての術前化学療法（MVAC 療法）の臨床的な位置づけを確立するための臨床研究を遂行する。さらに、術前化学療法、根治的膀胱摘除にともなう QOL の変化の調査および本疾患の臨床経過を予測しうるような指標の特定を行うことを目的とした。

B. 研究方法

上記の研究目的のために以下の臨床試験のプロトコールを作成した。MVAC 療法は Day 1: MTX 30mg/m^2 、Day 2:VBL 3mg/m^2、ADM 30mg/m^2、CDDP: 70mg/m^2、Day 15、22: MTX 30mg/m^2、VBL 3mg/m^2 のスケジュールで施行する。

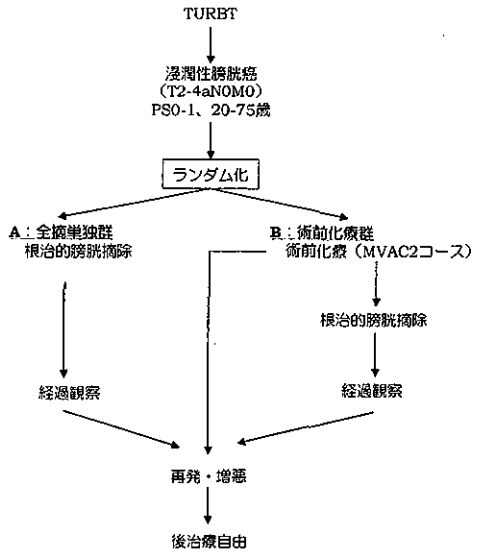

図１　臨床試験プロトコールの概略

上記の臨床試験の適格条件を満たし、本人の文書による同意が得られた症例を無作為に割り付ける（JCOG データーセンター）。これは本研究の班員が属する 22 施設と研究協力施設 15 施設が共同して行った。同時に、根治的膀胱摘除あるいは術前化学療法による QOL の調査も定期的に合わせて行った。さらに各班員の施設では術前化学療法が奏功する症例、膀胱温存が可能な症例あるいは臨床経過が良好・不良な症例の臨床・病理学的因子の検索を行った。なお、本試験への参加を促すため、適格症例に対して本試験の意義、治療内容などを用容易に理解してもらうため、参加施設医師に対する同意取得の研修などを計画した。

術前あるいは術後化学療法の有用性および MVAC 療法の副作用をこれまで各施設で経験した症例を分析した。

〈倫理面への配慮〉

本臨床試験では以下のような倫理面への配慮を行っている。

1) 本試験に参加可能な症例の各種条件（年齢、臨床病期、各種臓器機能など）を設定し、臨床試験プロトコールに明示している。
2) 本試験はヘルシンキ宣言を遵守し、試験参加の利益、不利益を「説明文書」に記載することで、参加者が容易に理

解可能となるようにしている。

3) 本参加はあくまでも本人の自由意志であることを明示し、文書で参加の意思を確認するようにしている。
4) 本臨床試験での治療費は通常の保険診療で行われることを明示している。
5) 本臨床試験に参加する施設での倫理委員会あるいはそれに準ずる委員会の承認を求めている。
6) 既にJCOG臨床試験員会あるいは各施設の倫理員会で承認された臨床試験であることを明示している。

C. 研究結果

1) 浸潤性膀胱癌に対する術前化学療法（MVAC療法）の生存率向上への寄与を確立したエビデンスとする目的で、本研究班22施設および研究協力施設15施設の計37施設を組織し、術前MVAC療法＋根治的膀胱摘除（リンパ節郭清も含む）と根治的膀胱摘除のみの２つの治療群を設定した臨床試験に着手している。この臨床試験開始後、MVAC療法の保険適用が認められたため（2004年1月）、それに即したプロトコールの部分的な改訂も行った。さらに、実際にプロトコール治療を行うにあたって、症例適格規準の一部が臨床の状況にそぐわない点が出てきたため、その部分の改訂を行った。すなわち、当初の症例選択規準では、「画像診断で浸潤性膀胱癌が疑われた症例」という項目があったが、実際には画像診断では疑われずに経尿道的切除標本で浸潤癌と診断される症例が多く、このような症例は本試験への参加の有無にかかわらず原則的には根治的膀胱摘除および術前・術後の化学療法の適応になることから、上記の規準を撤廃しても倫理的には問題がないと判断した。これらの改定は、JCOG効果・安全性評価委員会での審議の後、承認された。このプロトコール改定により、症例の組み入れがより容易になった。現在まで、28例（2005年3月31日現在）の症例登録があった。これまでのところ、プロトコール治療による重篤な有害事象あるいは未知の有害事象は発生していない。

2) また、昨年度末に報告された班員各施設での浸潤性膀胱癌症例をさらに分析して、術前あるいは術後化学療法の有用性を検討した。その結果、臨床病期T2N0M0では術前化学療法群の5年生存率は72%、術前化学療法未施行群のそれは66%と前者にやや良好な傾向があった。臨床病期T3N0M0でもそれぞれ61%、47%と術前化学療法群が良好であった。一方、術後化学療法を行った場合にはT3+4pN0の症例において術後化学療法群の5年生存率が64%であるのに対し化学療法未施行群は39%と前者に良好な傾向があった。術後化学療法が明らかに有効と思われたのは、pN+群に対する術後化学療法で、術後化学療法群の5年生存率は43%、術後化学療法未施行群のそれは17%と有意差(p=0.03)を認めた。一方、術前、術後あるいは転移巣に対するMVAC療法施行例59例における副作用の分析では、grade 3以上の副作用は好中球減少：75%、発熱性好中球減少：6.8%、敗血症：3.4%、血小板減少：19%に認められた。遠隔転移のある症例において好中球減少をともなった敗血症による死亡例を1例認めた（MVCA療法1コース目）。しかし、術前あるいは術後のMVAC療法では死亡例はなかった。なお、それぞれのコースにおける15日目、22日目の化学療法の施行可能割合は、1コース目： 44%、2コース目：49%とそれぞれ約半数であった。

3) 浸潤性膀胱癌の手術後の局所再発が症例のQOLを損ねる点では遠隔転移の出現に勝るとも劣らないことがこれまでの経験で判明していたが、局所再発に影響する臨床病理学敵的な因子が特定されていなかった。そこで、この因子の特定を行うことを試みた(Honma et al, Urology, 2004;64:744)。浸潤性膀胱

癌に対し根治手術が可能であった145例を分析の対象とした。局所再発は27例(18.6%)に認められた。このうち、局所再発のみを認めた症例は8例(5.5%)、局所再発と遠隔転移をほぼ同時に認めた症例が19例(13.1%)であった。局所再発および遠隔転移の両者の出現のリスク要因は病理学的病期と骨盤リンパ節転移であった。しかし、局所再発のみのリスク要因は原発巣における扁平上皮癌(squamous differentiation)のみであった。したがって、膀胱癌組織の扁平上皮癌の混在がその大きな要因であることを突き止めた。臨床経過の予後予測因子として、matrix metallo-proteinase 2 による gelatinolytic activity が表在性および浸潤性膀胱癌の予後と相関することを明らかにした (Kawamura et al, J Urol, 2004;172: 1480)。

D. 考案

MVACの保険適応承認、それによるプロトコールの改訂などもあり、本試験の実施が以前より容易になってきてはいるが、さらに症例集積に向けた努力を行う必要がある。そのため昨年度は同意取得などにかんする講習会を開催して本試験の質の向上を図っている。

現在行っている臨床研究では補助化学療法としての術前化学療法（MVAC療法）による治療効果の改善が主な目的である。補助療法としての化学療法はこれまでも術前あるいは術後に種々の化学療法を用いた検討がなされてきた。術前化学療法と術後化学療法のいずれかがより有用なのかという点に関しても確立してはいない。本研究によりこの点が明らかなることが期待されている。

昨年度の研究では、本研究参加施設における浸潤性膀胱癌の5年および10年生存率を多数例で明らかにした。今年度はさらに結果の分析をすすめ、浸潤性膀胱癌に対する根治的膀胱摘除（＋骨盤リンパ節郭清）に術前あるいは術後化学療法を追加することで、比較的良好な臨床経過が得られる症例がいることが判明した。しかし、今回の検討結果はあくまでも後ろ向き研究の結果であることか、術前あるいは術後化学療法の有用性をエビデンスとして示すまでにはいたっていないことは明らかである。その意味でも現在施行中の本試験の検討結果が待たれるところである。本試験におけるこれまでの状況では術前化学療法による重篤な有害事象はない。これまで行ってきたMVAC療法の有害事象を明らかにするために、術前あるいは術後、および遠隔転移巣に対してMVAC療法を行った59例おける血液毒性を中心とした有害事象について検討した。今回の血液毒性の割合、程度はこれまでに報告されているものと大きな差はなく、またこれまでに報告されていない未知の有害事象はなかった。これまでの報告でも、好中球、血小板を中心とした有害事象が多かったが、今回の結果も同様であった。今回の検討では、各コースともgrade 3以上の好中球減少が60-70%に認められたが、これによると思われる発熱のエピソードは1コース目で6.8%、2コース目で3.8%と試行回数の増加による発熱出現の増加はなかった。また、好中球減少が原因となり敗血症をきたした症例を2例経験したが、複数の遠隔転移巣を認め全身状態が良好でなかった1例に敗血症が原因と考えられる経過があった。しかし、この1例以外に結果的に重篤な有害事象が認められなかったことから、術前2コースのMVAC療法は安全に施行可能と考えられた。一方、MVAC療法における15日目、22日目の薬剤投与は、半数の症例でのみ可能という結果であった。これまでも、MVAC療法における15日目、22日目の薬剤投与は実際には50-60%の症例でしか可能ではないと報告されており、今回も同様の結果であった。好中球数および血小板数がnadirとなる時期が通常MVAC投与12-16日目であるため、これが両日の化学療法の未施行に結びつく原因であることは明らかである。しかし、この両日の化学療法の未施行が術前化学療法の効果にどの程度影響を与えるのかは判明していない。

根治的膀胱摘除後の局所再発は、CTがルーチンに利用できるようになる前は臨床的にはほとんど検出されず、局所再発が発見された際には治療法がきわめて限られていた。その後、CTが臨床的に利用可能になった1990年以降には、根治的膀胱摘除後の局所再発に関しては検討が多くはなかった。これまでの報告では、局所再発の頻度は遠隔転移を伴った例も含め15-20%と報告されている。今回のわれわれの検討での頻度は18.6%であり、これまでの報告と同様の結果であった。一方、局所再発のみに限定してみるとその頻度は10%前後と推測され、今回の頻度の5.5%と大きな差はなかった。一方、局所再発のリスク要因に関しては病理学的病期、摘除リンパ節数などが報告されている。われわれの検討では、原発巣の尿路上皮癌に混在している扁平上皮癌(squamous differentiation)の存在が、局所再発のみのリスク要因であった。膀胱癌におけるこの扁平上皮癌の混在の意義に関しては、われわれの以前の報告(Urology, 1992;40;477)も含め、高井、垣添らの報告（日泌尿会誌、1988;79:1837）がある。これらの報告では、grade 3 膀胱癌（尿路上皮癌あるいは移行上皮癌）の中には扁平上皮関連抗原を発現している例があること、また、扁平上皮癌が混在しているような膀胱癌は局所進展度が高く、癌死の頻度も高いことが示されている。したがって、今回の結果で認められた局所再発に関するリスク要因としての扁平上皮癌の存在は、臨床的にも十分根拠のあること考えられる。今後は、扁平上皮癌の混在とその分子生物学的分析が必要となろう。

E. 結論

1) 浸潤性膀胱癌に対する術前化学療法（MVAC療法）の生存率向上への寄与を確立したエビデンスとする目的で、本研究班22施設および研究協力施設15施設の計37施設を組織し、術前MVAC療法＋根治的膀胱摘除（リンパ節郭清も含む）と根治的膀胱摘除のみの2つの治療群を設定した臨床試験に着手している。この臨床試験開始後、MVAC療法の保険適用が認められたため（2004年1月）、それに即したプロトコールの部分的な改訂も行った。さらに、実際にプロトコール治療を行うにあたって、症例適格規準の一部が臨床の状況にそぐわない点が出てきたため、その部分の改訂を行った。このプロトコール改定により、症例の組み入れがより容易になった。現在まで、28例に症例登録があった（2005年3月31日現在）。
2) MVAC療法を施行した59例の副作用の検討では、血液毒性を中心とした有害事象がこれまでの報告と同様に認められたが、術前化学療法として2コース施行する上では比較的安全に施行できると考えられた。
3) 浸潤性膀胱癌の手術後の局所再発が症例のQOLを損ねる点では遠隔転移の出現に勝るとも劣らないことがこれまでの経験で判明していたが、局所再発に影響する臨床病理学敵的な因子が特定されていなかった。そこで、この因子の特定を行うことを試みて、膀胱癌組織の扁平上皮癌の混在がその大きな要因であることを突き止めた。

F. 健康危険情報

特になし。

G. 研究発表

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H. 知的財産の出願・登録状況

1. 特許取得
   特になし

2. 実用新案登録
   特になし

3. その他
   特になし

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書 籍

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Tsukamoto T, Takahashi A, et al.	Treatment of invasive bladder cancer: Lessons from the past and perspective for the future	Jpn. J. Clinical Oncology	34	295-306	2004
Honma I, Takahashi A, Tsukamoto T, et al.	Local recurrence after radical cystectomy for invasive bladder cancer: An analysis of predictive factors	Urology	64	744-748	2004.
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Ⅲ. 研究成果の刊行物・別刷

Jpn J Clin Oncol 2004;34(6)295–306

Review Article

Treatment of Invasive Bladder Cancer: Lessons from the Past and Perspective for the Future

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Radical cystectomy with lymphadenectomy is the gold standard for treatment of invasive bladder cancer. However, the treatment alone does not always provide a satisfactory result for the disease extending outside the bladder. In this review we discuss several clinical issues in the diagnosis and treatment of this invasive disease. Although the quality of diagnostic imaging modalities has improved, they are still not sensitive enough for the staging of the disease, especially for early invasive disease. In addition, lack of serum markers hinders appropriate monitoring of patients with the disease. Regarding the surgical aspect of lymphadenectomy, the area of its dissection, the standard number of nodes retrieved and the method of pathological examination should be established so that the clinical benefits of surgery can be more clearly defined. Neoadjuvant chemotherapy for invasive disease is promising for improvement of survival of patients. A chemotherapy regimen as effective as, but less toxic than, MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) has been reported and several phase III clinical trials have been launched to determine the benefits of adjuvant or neoadjuvant chemotherapy with newly developed agents. However, we still lack a chemotherapy regimen more effective than MVAC, which is the most crucial issue in the treatment of this invasive disease. An alternative option for such disease may be bladder preservation with transurethral resection of tumor followed by chemoradiotherapy. However, patients who are indicated for this treatment may be limited to those with early invasive disease having certain favorable clinical and pathological features.

Key words: bladder cancer – invasive – surgery – chemotherapy – radiation

INTRODUCTION

Bladder cancer is the second most common genitourinary cancer. In Japan, 12 000 patients are newly diagnosed as having this disease and 5000 patients die of it per year (1). It is usually divided into superficial and invasive diseases. The former is defined as that confined to the mucosal or submucosal layer of the bladder. In the latter, cancer cells invade the muscle layer or extend beyond it. The superficial disease found in two-thirds of patients with bladder cancer is basically managed by the transurethral resection of the bladder tumor (TUR-Bt), with or without adjuvant intravesical treatment with chemotherapy or bacille Calmette-Guerin, and thus the bladder can be preserved. The clinical course of the superficial disease is favorable with 5-year cause-specific survival higher than 95%. However, the invasive disease found in one-third of patients with bladder cancer usually has an unfavorable clinical course with a 5-year survival of 50–60%. Thus, treatment of the invasive disease remains a challenge for us (2).

The standard treatment for invasive bladder cancer is radical cystectomy with lymphadenectomy. This treatment is indicated for patients who have a clinically invasive disease but not pelvic lymph node or distant metastases. However, there are several pitfalls in this standard management of the disease. First, not all patients are indicated for radical cystectomy with lymphadenectomy followed by urinary diversion or reconstruction because of the invasive nature of surgery. Surgery is generally contraindicated for some patients with medical complications such as cardiovascular disease. More importantly, there is a group of patients who do not achieve full benefit from surgery alone. Many studies have been performed to decide whether treatments in addition to surgery alone provide a better

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clinical course or survival for such patients. Unfortunately, there is still little clinical evidence that clearly demonstrates clinical benefit of treatments added to surgery, since either the numbers of patients in past studies were small or the studies were retrospective. Recently, however, the efficacy of neoadjuvant chemotherapy prior to radical cystectomy was demonstrated by both an excellent clinical randomized study that recruited many participants and a meta-analysis (3,4). Many more clinical trials are now under way which will evaluate the efficacy of current modalities of treatment.

We overview in this review what we have learned from past and present studies on this invasive disease and consider the future of its treatment.

The grading and staging system of the disease in this article is based on the General Rules for Clinical and Pathological Studies on Bladder Cancer based on the TNM Classification of Malignant Tumours (Fifth edition) (5), unless otherwise indicated.

DILEMMA IN CLINICAL STAGING AND LACK OF SERUM MARKERS IN INVASIVE BLADDER CANCER

TUR-Bt is the standard procedure to detect invasion of cancer cells into the muscle layer of the bladder. Invasive bladder cancer can be verified by TUR-Bt only when its specimens contain the bladder muscle tissue. Thus, resection must be deep enough to obtain muscle tissue, otherwise, the extent of bladder cancer cannot be accurately known. In addition, even when the specimens contain bladder muscle tissue, damage caused by the resection itself does not always allow surgical pathologists to stage them accurately. Indeed, understaging of TUR specimens can often occur in patients with clinically non-muscle invasive disease who undergo radical cystectomy (6). This is particularly common in T1 G3 disease (7). Deep resection of all visible tumors in the bladder is a cornerstone for diagnosis and treatment of invasive bladder cancer.

Computed tomography (CT) and/or magnetic resonance imaging (MRI) are widely used modalities for staging of invasive bladder cancer. However, they do not necessarily allow us to achieve accurate staging of the disease. In particular, an early muscle-invasive disease cannot be distinguished from a superficial one by CT or MRI (8). For this purpose, TUR-Bt is still the most reliable method for staging. When patients have a tumor large enough to be detected by CT or MRI, however, staging of the disease becomes more reliable. Barentsz et al. (9) showed that the accuracy of CT ranged from 40 to 92% (mean, 74%) and that MRI accuracy was 10–30% higher than CT. In terms of imaging diagnosis of lymph node metastasis, both imaging modalities achieve similar accuracy. However, minimal disease of the node, which is found in 10–30% of invasive disease depending on the extent of the primary lesion, cannot be accurately detected by CT or MRI, because their false negative rates are as high as 40% (10). Even positron emission tomography achieves only a 67% detection rate of node disease (10). Thus, at this time, urologists should integrate all information available from clinical and TUR-Bt-findings, and those obtained from imaging diagnosis, to determine the clinical stage of patients with the disease.

It is unfortunate that bladder cancer does not have a 'serum marker' that can reflect the clinical course of patients and monitor the response to treatment, like prostate-specific antigen for prostate cancer. Efforts so far have been mainly towards developing methods for detecting new lesions in the bladder rather than monitoring the response to treatment or the clinical course. We now have various methods that can be used for screening high-risk patients with superficial disease or for detecting early recurrence of the disease in the bladder. Indeed, markers for urine protein and chromosomal or gene alterations have become available (8,11). In addition, various oncogenes, tumor-suppressor genes, microvessel density and angiogenic inhibitors are available as tissue markers (12). Although these markers potentially allow us to retrospectively stratify patients with invasive disease who are likely to respond to a specific treatment such as chemotherapy, they cannot be used as convenient serum markers reflecting disease status at a given time. Thus, what we really need in the treatment of invasive bladder cancer is a serum marker on which we can rely for determining the treatment policy.

RADICAL CYSTECTOMY WITH LYMPHADENECTOMY AS THE GOLD STANDARD FOR TREATMENT OF INVASIVE BLADDER CANCER

Radical Cystectomy With or Without Urethrectomy

Radical cystectomy is the gold standard for treatment of invasive bladder cancer. This procedure includes bilateral pelvic lymphadenectomy in addition to removal of the bladder, seminal vesicles and prostate with perivesical fat in male patients. In female patients, the bladder with perivesical fat, urethra, anterior wall of the vagina, uterus and ovary are removed together with lymphadenectomy. Many studies have reported that favorable long-term survival is achieved for patients with pathologically organ-confined disease (13–18). Five-year overall survival rates by pathologic stage after radical cystectomy are summarized in Table 1. Although the rate for patients with organ-confined disease (pT2N0) is higher than 60%, it decreases to 30–50% in those with locally advanced diseases (pT3N0 and pT4N0) or lymph node involvement. Thus, the curability of bladder cancer by radical cystectomy primarily depends on the pathologic stage of the primary tumor and pathological status of the lymph nodes. Indeed, Dalbagni et al. (14) reported that only the pT stage and previous chemotherapy were significant factors for disease-specific survival in Cox's proportional hazards analysis, and the survival prognosis for non-organ-confined disease was significantly worse than that for organ-confined disease. Involvement of the prostatic stroma has a significant effect on survival, but prostatic ductal or urethral involvement does not (19,20). Esrig et al. (20) reported that 5-year overall survival rates of patients with

Table 1. Five-year overall survival rates of patients with invasive bladder cancer following radical cystectomy according to pathologic stage

Authors	Year	No. of patients	pT2N0	pT3N0	pT4N0	N (+)
Bassi et al. (13)	1999	369	63/53*	33	28	15
Dalbagni et al. (14)	2001	300	64	31	30	–
Stein et al. (15)	2001	1054	77/64†	49	44	31
Madersbacher et al. (16)	2003	507	62‡	40‡	49‡	26
Nishiyama et al. (17)	2004	1113	84/69§	59	43	35
Takahashi et al. (18)	2004	466¶	74	47	38	30

*pT2N0/pT3aN0 in TNM classification, 1978 Edn.
†pT2N0/pT3aN0 in TNM classification, 1987 Edn.
‡Data suggested by figure.
§pT2a/2b.
¶48% of patients received neo- and/or postadjuvant chemotherapy.

urethral tumors, ductal involvement and stromal invasion were 74%, 67% and 36%, respectively.

When radical cystectomy is attempted, urethrectomy is indicated only for male patients with urethral involvement of the disease. Thus, recurrence of the disease in the urethra is always considered whenever the urethra is left intact. The incidence of recurrence in the retained male urethra ranges from 4 to 14% (21,22). Urethral washing cytology has been recommended for early detection of recurrence in the urethra. Indeed, the procedure has high sensitivity and specificity in detecting early disease (23). However, a recent study raised a question about the procedure as a routine test, since early detection of the urethral disease may not guarantee patients a favorable survival outcome (24). The aggressive biological nature of bladder cancer generally affects survival more strongly than urethral recurrence. This issue should be confirmed by studying a larger number of patients.

Interestingly, the rate of urethral recurrence in patients who underwent orthotopic neobladder construction was reported to range between 2 and 6% (22,25,26), which was lower than the rate for those with cutaneous urinary diversion (27). In other words, urine flow potentially contributes to prevention of recurrence in the urethra. However, diffuse carcinoma in situ (CIS) extending to the prostatic urethra is a sign of high risk for synchronous anterior urethral involvement (28). Therefore, prophylactic urethrectomy is recommended for patients with this risk factor, and an orthotopic neobladder is basically contraindicated for such patients.

In female patients, radical cystourethrectomy has been the standard procedure. Coloby et al. (29) reported that 6% of female patients who underwent radical cystourethrectomy had urethral involvement. All of them had grade 3 disease with adjacent CIS, located in the bladder neck. In a study by Stenzl et al. (30), urethral involvement was found in 2% of female patients with bladder cancer (including superficial disease), and a risk factor for the involvement was simultaneous disease in the bladder neck. Thus, they recommended that most of the urethra should be left intact for orthotopic urinary diversion when patients did not have any cancerous changes or atypia in the bladder neck in transurethral biopsy before cystectomy or frozen sections of the distal end of the urethra at cystectomy. To date, however, there has been no report of urethral recurrence after orthotopic neobladder construction in women (31).

Radical cystectomy with lymphadenectomy is indicated for patients with clinical stages T2-4N0M0. When patients clinically have node metastasis in the pelvis or distant metastasis, they are believed not to benefit from this treatment alone. However, symptoms caused by locally advanced disease such as gross hematuria, difficulty on urination, urgency and pain on urination often cause conspicuous deterioration of the quality of life (QOL) of patients. Palliative cystectomy is an optional treatment for a relief of those symptoms, since palliative urinary diversion alone does not always improve patients' QOL (32,33). Indeed, even in our small series of such patients, some had the chance to benefit from cystectomy in terms of maintenance of their QOL and survival, although the selection of candidates for the treatment was biased (34).

Pelvic Lymphadenectomy

Pelvic lymphadenectomy is an integral part of treatment for patients with invasive bladder cancer. It provides accurate extension and staging of the disease, information that is valuable for prediction of the clinical course. Indeed, as shown in Table 1, the disease status of pelvic lymph nodes is surely one of the critical determinants for survival. Lymphadenectomy is believed to have a therapeutic role as well for a very limited burden of node metastasis in some patients, depending on the extent of node dissection. This issue will be discussed later.

Before reviewing staging and the therapeutic role of lymphadenectomy, we will discuss how extensive lymphadenectomy should be. Unfortunately, there is no consensus on the extent of lymphadenectomy. Limited pelvic lymphadenectomy consists of node dissection in the areas of the external iliac artery and vein, the internal iliac artery and vein and the obturator nerve on both sides (Fig. 1). It removes all lymph nodes that are regarded as the 'regional lymph nodes' of bladder cancer defined by the TNM classification. The conventional or

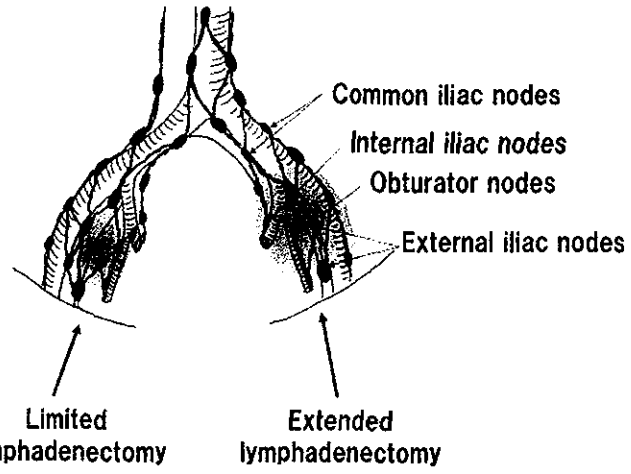

Figure 1. Areas of the extended and limited pelvic lymphadenectomies.

extended type is defined as that removing the bilateral common iliac lymph nodes as well as regional lymph nodes. There are some differences in the dissection areas for conventional or extended lymphadenectomy according to the studies (35–37). For example, Bochner et al. (35) defined conventional (or standard) lymphadenectomy as removal of the distal common iliac (or the mid-common iliac) nodes together with the regional lymph nodes. Poulsen et al. (36) regarded lymphadenectomy as the 'extended type', when they removed the common iliac lymph nodes together with the regional lymph nodes. However, in another study, removal of lymph nodes above the level of the aortic bifurcation and those located in the presacral area together with the regional lymph nodes was included in 'extended lymphadenectomy' (37). Thus, we should be careful in interpreting results for extended lymphadenectomy when this may represent a different area of dissection in each study.

Although lymphadenectomy is included in the surgical procedure for radical cystectomy, there is some controversy over whether limited or extended lymphadenectomy should be performed. The guidelines on bladder cancer of the European Association of Urology recommend limited lymphadenectomy, although they refer to recent studies that show the benefit of the extended type (38). This is partly because lymph node metastases are found more frequently in the regional lymph nodes than in the common iliac or presacral ones, and also metastasis beyond the regional lymph nodes is regarded as disseminated disease. The lack of an established adjuvant chemotherapy for patients who are node positive is another explanation for the limited type to be recommended.

As for staging and prognostic indicators, extensive lymphadenectomy retrieving 16 lymph nodes or more was reported to detect a higher proportion of pathologically proven node metastases in those with pT3 and pT4 cancer, although this was not the case in those with pT2 or less (39). Poulsen et al. (36) compared the incidence of lymph node metastasis in limited lymphadenectomy with that in the extended type. They found that the incidence was higher in patients with the extended type, although it was more prominent when the disease was pathologically confined to the bladder or was less extensive. How many lymph nodes should be retrieved by lymphadenectomy for accurate diagnosis of node metastasis? In the study by Poulsen et al. (36), extended lymphadenectomy retrieved a larger number of lymph nodes than the limited type. The extended lymphadenectomy recovered 23–25 nodes, ranging from 9 to 67, and the limited type recovered 5–14, with a range of 5–30. A postmortem study suggested that removal of approximately 20 nodes may be the reference number of nodes for retrieval by limited pelvic lymphadenectomy (40). It can be expected that node metastasis will be found more frequently with an increase in the number of nodes retrieved. According to the study of Leissner et al. (39), 60% of node-positive patients had, at most, 15 nodes retrieved. To detect more than 80% of patients who are node positive, at most 23 nodes should be removed (39). A similar number of nodes, around 20, was also reported to detect 80% of node-positive patients (41).

It is well known that the number of positive nodes strongly affects the survival of patients with invasive disease who undergo radical cystectomy with pelvic lymphadenectomy. Indeed, two recent large series clearly confirmed this (42,43). Stein et al. (42) showed that patients with eight positive nodes or less had a clearly better prognosis than those with more than eight. Frank et al. (43) also reported that the number of positive nodes was a significant prognostic parameter. In their study, patients with more than five positive nodes had a significantly worse prognosis than those with five or less. Since the number of positive nodes may depend on the number of lymph nodes removed by lymphadenectomy, the absolute number does not necessarily indicate an accurate prognosis. Thus, the concept of the ratio of positive nodes per total number of nodes removed or the positive-lymph node density was introduced and this ratio has been reported to be more predictive of the prognosis of patients in two studies (41,42). These studies demonstrated that patients with a ratio of 20% or greater definitely had a lower survival rate than those with ratios less than 20%. While the ratio of 20% remains to be confirmed by future studies, it can be applicable in the clinical setting, in particular in the case of limited lymphadenectomy, which recovers a smaller number of nodes than the extended type.

Finally, there is still the question of whether the number of lymph nodes retrieved affects the prognosis of the patient. In other words, does retrieval of a greater number of lymph nodes achieve a more favorable clinical outcome?

There are few studies that compare survival of patients who received extended lymphadenectomy with that of those who received regional or limited lymphadenectomy. The study of Poulsen et al. (36) showed that patients with disease confined to the bladder wall and negative nodes achieved a higher survival rate when the limit of lymphadenectomy was extended (Table 2). Unfortunately, it was not a randomized study, and it used historical controls, so it may not be possible to extrapolate their conclusion. However, several recent studies have emphasized the survival benefit of extended lymphadenectomy. Leissner et al. (39) reported that patients who had 16 or

Table 2. Impact of the extent of lymphadenectomy and number of lymph nodes retrieved on survival

Study	Pathological stage	End-point	Comments
Poulsen et al. (36)	≤T2	RFS	Extended LAD is higher than limited LAD.
	≤T2N0	RFS	Extended LAD is higher than limited LAD.
Leissner et al. (39)	all stages	DSS	16 L/N retrieved or more is higher than 15 or less.
		DFS	16 L/N retrieved or more is higher than 15 or less.
	≤T2N0	DFS	16 L/N retrieved or more is higher than 15 or less.
	T3N0	DFS	No difference between 16 L/N retrieved or more and 15 or less.
	N+ (1–5 positive L/N)	DFS	16 L/N retrieved or more is higher than 15 or less.
Herr (44)	T2-4N0	DSS	8 L/N or more retrieved is higher than 7 or less.
	T2-4N+	DSS	11 L/N retrieved or more is higher than 10 or less.

RFS, recurrence-free survival; LAD, lymphadenectomy; DSS, disease-specific survival; DFS, disease-free survival; L/N, lymph nodes.

more lymph nodes removed by extended lymphadenectomy achieved cancer-specific and disease-free survivals significantly higher than those who had 15 or less removed. Even when patients were subcategorized according to several pathological stages, significantly higher disease-free survival was confirmed. Similar results were reported in other studies, all of which suggested that the number of lymph nodes recovered by lymphadenectomy and thorough pathological study of them affected the outcomes of patients (44,45). Interestingly, using the Cox proportional hazards model, Herr (46) indicated that the number of lymph nodes examined was one of the significant risk factors for both survival and local recurrence in node-negative patients. Even in node-positive patients, the number of lymph nodes retrieved similarly affected these outcomes. Finally, based on personal and others' experience, Herr (47) suggested that complete lymphadenectomy along with securing a wider margin around the bladder and more thorough examination of surgical specimens by pathologists contributed to improvement of outcomes in patients with invasive bladder cancer.

Although recent studies have suggested that extended lymphadenectomy may be more beneficial than the limited type for staging accuracy and survival benefit, as indicated earlier, this issue remains to be determined in a prospective, randomized study.

Local Recurrence

Local recurrence of cancer in the pelvis after definitive surgical treatment for patients with invasive disease is a greatly frustrating problem both for patients and physicians. Its development potentially compromises not only survival but also the QOL of patients. Local recurrence may not produce any symptomatic findings in the early stage but eventually causes bowel obstruction and pain due to involvement of various nerves, both of which strongly affect the QOL of patients. For physicians, that there is no effective treatment for such lesions is a devastating problem. Before the era of modern imaging diagnosis, many small lesions recurring in the pelvis were not precisely detected if they did not produce specific signs and symptoms. However, the current use of CT allows us to more frequently detect even small lesions of recurrence in the pelvis. Accurate diagnosis and specific treatment of such lesions is a matter for debate in daily practice, in particular when they are not associated with distant metastasis.

A recent study indicated that local recurrence was much more frequent than previously believed (48). Recurrence with or without concurrent distant metastasis was found in 5–20% of patients who received radical surgery, depending on their clinical and pathological features (49). In patients with pT3 or pT4 disease, the rate of local recurrence or systemic recurrence was reported to be around 30% (50). Although pathological stage and lymph node status were suggested to be risk factors for local recurrence, recent studies indicate that it may be avoided by meticulous radical cystectomy and extended lymphadenectomy (44,51).

Once local recurrence develops, its clinical course is generally pessimistic. Westney et al. (52) reported that the survival interval from diagnosis of local recurrence was less than one year with treatments currently available. Unfortunately, there have been no studies suggesting any specific treatments that can clearly reduce the rate of local recurrence after cystectomy. Whether or not neoadjuvant and adjuvant chemotherapy regimens currently available and newly developing are effective for reduction of the rate remains to be determined.

BENEFITS AND PITFALLS OF CHEMOTHERAPY ADJUNCTIVE TO RADICAL CYSTECTOMY FOR INVASIVE BLADDER CANCER

Adjuvant and Neoadjuvant Chemotherapy

As indicated earlier, radical cystectomy with lymphadenectomy alone cannot achieve satisfactory survival for patients with pT3, pT4 and node-positive disease. Patients with such diseases need additional treatments for improvement of their survival. Preoperative irradiation, which was tried in the early

Table 3. Current clinical trials for adjuvant chemotherapy for invasive bladder cancer (60)

Title of ongoing clinical trials	Status of trial	Protocol ID
Phase II study of adjuvant gemcitabine, cisplatin, and amifostine in patients with completely resected locally advanced bladder cancer	Active	UCCRC-9193
Phase II study of adjuvant paclitaxel, ifosfamide, carboplatin and gemcitabinein patients with high-risk transitional cell carcinoma of the urothelium	Active	TULCC-RM-002
Phase III randomized study of adjuvant cisplatin and gemcitabine versus observation in patients with transitional cell cancer of the bladder at high risk after radical cystectomy	Active	ITNRC-CU02.00447ST/97
Phase III randomized study of *immediate versus* deferred adjuvant chemotherapy after radical cystectomy in patients with stage III or IV transitional cell carcinoma of the urothelium	Active	EORTC-30994

Table 4. Randomized phase III trials of neoadjuvant chemotherapy

Authors	Year	No. of patients	Chemotherapy	Survival benefit
Martinez-Pineiro et al. (61)	1995	122	Cisplatin versus control	No significant difference
Malmström et al. (62)	1996	325	Cisplatin + doxorubicin versus control	Chemotherapy > control (in patients with T3-4)
Bassi et al. (63)	1998	206	MVAC versus control	No significant difference
MRCA-Advanced Bladder Cancer Working Party (64)	1999	976	CMV versus control	No significant difference
Sherif et al. (65)	2002	317	Cisplatin + methotrexate versus control	No significant difference
Grossman et al. (3)	2003	317	MVAC versus control	MVAC > control

MRCA, Medical Research Council; MVAC, methotrexate + vinblastine + doxorubicin + cisplatin; CMV, cisplatin + methotrexate + vinblastine.

1980s, finally turned out not to have advantage for survival in a randomized study conducted by the Southwest Oncology Group (SWOG) (53,54). Since then, along with progress in clinical efficacy of cisplatin-based combination chemotherapy for metastatic bladder cancer, many chemotherapeutic regimens have been studied for this purpose. Unfortunately, until very recently, only non-conclusive results were reported. In addition, the timing of chemotherapy adjunctive to cystectomy, neoadjuvant or adjuvant, has not been established.

Adjuvant and neoadjuvant chemotherapies have their own advantages and disadvantages (55). The advantages of adjuvant chemotherapy consist of accurate stage diagnosis, more appropriate selection of patients based on pathologically identified risk factors for recurrence, and no delays in performing cystectomy. On the other hand, its disadvantages include the lack of a marker lesion for assessment of the response to chemotherapy, no chance to preserve the bladder, relative delay for treatment of micrometastases and difficulties in giving chemotherapy with a planned dose intensity and treatment cycle. In the daily clinical setting, many patients seem to receive adjuvant chemotherapy when the disease pathologically extends beyond the bladder or have margin-positive status of the cystectomy specimen. However, no published studies have proved any definite benefit of adjuvant chemotherapy for long-term disease-free and overall survivals, although several investigators have conducted randomized trials (56–59). Currently, the adjuvant phase II and III protocols using newly developed drugs and their combinations are under investigation (Table 3) (60).

Advantages of neoadjuvant chemotherapy include information about the response to chemotherapy that may predict future clinical course, possible treatment of micrometastases without delay and potential preservation of the bladder if the disease responds well to chemotherapy (55). Another advantage is that patients may better tolerate chemotherapy in a neoadjuvant setting than in an adjuvant one.

Disadvantages of neoadjuvant chemotherapy are the negative sides of each advantage of adjuvant chemotherapy, which include less accurate staging of the primary tumor, no identifiable pathological risk factors and unavoidable chemotherapy not beneficial for patients with a low risk for recurrence.

As with adjuvant chemotherapy, many randomized trials of neoadjuvant chemotherapy have been conducted over the last 10 years to determine whether the chemotherapy improved survival (3,61–65). Unfortunately, there have been no reports that clearly demonstrate any survival benefit of chemotherapy in the neoadjuvant setting before the study conducted by the SWOG (Table 4). The group reported in 2003 that three cycles of MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) neoadjuvant chemotherapy followed by radical cystectomy provided patients with invasive disease a median interval of survival longer than that with cystectomy alone (3). Even when patients were stratified according to age and stage, the survival benefit was predominant in those who received neoadjuvant chemotherapy. The study concluded that neoadjuvant chemotherapy can be offered to patients with invasive disease who need radical cystectomy. Hopefully, there will be additional successful trails that support the results of the SWOG.

Table 5. Phase II and III studies of chemotherapy using paclitaxel and/or gemcitabine (55,60,80)

Phase	Title of trial	Protocol ID
II	RS of induction paclitaxel, cisplatin and XRT versus fluorouracil, cisplatin and radiotherapy followed by consolidation chemoradiotherapy or radical Cx and adjuvant gemcitabine, paclitaxel and cisplatin in patients with operable stage II or III bladder cancer	RTOG-0233
II	Study of adjuvant gemcitabine, cisplatin and amifostine in patients with completely resected locally advanced bladder cancer	UCCRC-9193
II	Study of adjuvant paclitaxel, ifosphamide, carboplatin and gemcitabine in patients with high-risk transitional cell carcinoma of the urothelium	TULCC-RM-002
II	Study of cisplatin, ifosphamide and paclitaxel in patients with unresectable or metastatic urothelial tumors	MSKCC-95031
II	Study of gemcitabine and paclitaxel in patients with advanced or recurrent urothelial cancer	SWOG-S0028
II	Study of neoadjuvant carboplatin, paclitaxel and gemcitabine followed by concurrent cisplatin and XRT in patients with locally advanced or recurrent carcinoma of the urothelium	SWOG-S0121
II	Study of neoadjuvant gemcitabine, paclitaxel, carboplatin followed by observation or immediate Cx in patients with stage II or III transitional cell cancer of the urothelium	SWOG-S0219
II/III	RS of gemcitabine and carboplatin versus methotrexate, carboplatin and vinblastine in previously untreated patients with transitional cell cancer of the urothelium who are ineligible for cisplatin-based chemotherapy	EORTC-GU-30986
III	RS of adjuvant cisplatin and gemcitabine versus observation in patients with transitional cell cancer of the bladder at high risk after radical Cx	ITNRC-CU02.00447ST/97
III	RS of cisplatin and gemcitabine with or without paclitaxel in patients with stage IV transitional cell carcinoma of the urothelium	EORTC-30987

RS, randomized study; XRT, radiation; Cx, cystectomy.

The predominant benefit of neoadjuvant chemotherapy before radical cystectomy is supported by a recent meta-analysis summing up 11 randomized, potentially eligible studies of neoadjuvant chemotherapy (4). This analysis, including survival data for a total of 2492 patients, showed a 9% relative reduction in the risk of death with neoadjuvant chemotherapy. Furthermore, the platinum-based chemotherapy in the neoadjuvant setting achieved significantly improved overall survival that was characterized by a 13% relative reduction in risk of death, 5% absolute benefit at 5 years and improvement of overall survival from 45% to 50%. The author concluded that the platinum-based combination chemotherapy showed a significant survival benefit although platinum alone did not contribute to improved survival of patients. In Japan, a randomized phase III study of two cycles of MVAC neoadjuvant chemotherapy followed by radical cystectomy, compared with cystectomy alone for T2-T4aN0M0 bladder cancer is being conducted by the Japan Clinical Oncology Group.

Currently, the SWOG is conducting a phase II study of neoadjuvant chemotherapy consisting of gemcitabine, paclitaxel and carboplatin followed by observation or immediate cystectomy in patients with stage II or III transitional cell cancer of the urothelium (SWOG-S0219) (60). The aim of this study is to evaluate the effectiveness of the new combination chemotherapy.

More Effective Regimens of Chemotherapy in Adjuvant and Neoadjuvant Settings

At this moment, there are no adjuvant and neoadjuvant chemotherapy regimens more effective than MVAC, although several clinical trials with new agents are being carried out. Even for patients with advanced or metastatic disease, MVAC is still the standard regimen. Indeed, among many combination chemotherapy regimens that were studied, MVAC (66) and CMV (cisplatin, methotrexate and vinblastine) (67) achieved the highest overall response and CR rates. Randomized trials for metastatic urothelial cancer showed that MVAC was superior to the single agent cisplatin (68,69) and CISCA (cisplatin, cyclophosphamide and doxorubicin) (70). There is no randomized trial comparing MVAC with CMV. Although MVAC is one of the most effective chemotherapy regimens for advanced or metastatic diseases, it is associated with substantial toxicity, including leucopenia, culture-negative fever at the time of granulocytopenia, mucositis and renal failure (54). Furthermore, an escalated dosage of MVAC was associated with significant toxicity but had no apparent benefit over standard MVAC with regard to the complete response rate and survival (71). Interestingly, a combination of methotrexate, epirubicin and cisplatin was reported to achieve a response rate comparable to MVAC in patients with metastatic urothelial cancer but had milder intensity and less frequent toxicity (72). Unfortunately, the survival benefit was not reported.

New regimens using new chemotherapeutic agents have recently been studied for locally advanced or metastatic disease. Bellmunt et al. (73) demonstrated that a combination of cisplatin, paclitaxel and gemcitabine achieved 28% complete and 50% partial response rates for patients with previously untreated, locally advanced or metastatic urothelial cancer. In this phase II trial, the main nonhematologic toxicity was grade 2 and grade 3 asthenia, found in 37% and 8% of patients, respectively. Grade 3/4 neutropenia was found in 55% of patients and thrombocytopenia with the same grades occurred