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Current Perspective

# Current perspectives in muscle invasive bladder cancer

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**Abstract**

Muscle-infiltrating bladder cancer should be dealt with in a multimodality approch with collaboration between the urologist, medical oncologist and radiotherapist. Neo-adjuvant chemotherapy has not been proven to improve survival, but may be useful in programs of bladder preservation. Response to M-VAC neo-adjuvant chemotherapy is an important prognostic factor, but may represent patient selection factors. It is not known whether it is better to administer chemotherapy in the neo-adjuvant or in the adjuvant setting, that may spare some patients unnecessary chemotherapy. The international adjuvant chemotherapy trial coordinated by the EORTC (protocol 30994) will hopefully clarify some of the unanswered questions concerning whether or not adjuvant chemotheraphy immediately following cystectomy improves survival. © 2002 Published by Elsevier Science Ltd.

## 1. Introduction

Radical cystectomy is the standard treatment for patients with muscle invasive bladder cancer. Five-year survival is dependent upon the pathological stage and nodal status. Five-year survival for patients with muscle invasive bladder cancer is approximately 50%, yet for patients at higher risk with pT3-pT4 and/or pN+ M0 bladder cancer, 5-year survival after radical cystectomy is only 25–35% [1–4] Failure is due to occult systemic disease.

## 2. Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy is given before cystectomy or in some instances before radiation therapy. There are two principal reasons to use neo-adjuvant chemotherapy: to improve survival in patients with micrometastatic disease, and secondly to preserve the bladder [1,5]. This approach has been useful in the treatment of several solid tumours.

Patients with operable stages T2 to T4a may be _candidates for neo-adjuvant chemotherapy. Although neo-adjuvant chemotherapy was devised to eliminate micrometastases present at diagnosis, it has also been used to determine response to chemotherapy. The bladder tumour may serve as an *in vivo* marker to evaluate response. In this way, treatment that is effective may be continued, and ineffective therapy may be discontinued. The reported toxicity associated with neo-adjuvant therapy has been much lower than the toxicity in patients with metastatic disease, since the patients generally have a better performance status and localised disease.

The major disadvantages of neo-adjuvant chemotherapy have to do with the difficulties in assessing response in the primary tumour, because clinical rather than pathological criteria are used. This means that one must base any early conclusions about the impact of neo-adjuvant chemotherapy upon results from the transurethral resection of the bladder (TURB), which can be misleading. A more important disadvantage is that definitive local therapy (cystectomy or radiotherapy) is delayed. In addition, any chemotherapy is associated with a certain degree of toxicity. In the European Organization for Research and Treatment of Cancer (EORTC)/Medical Research Council (MRC) International trial that used neo-adjuvant cisplatin, methotrexate and vinblastine (CMV) chemotherapy, there was a 1% mortality rate due to CMV chemotherapy [6].

Thus far, randomised trials in the literature have failed to definitively demonstrate an improvement in survival in patients treated with neo-adjuvant chemotherapy. Table 1 displays the results of randomised neo-adjuvant chemotherapy trials in the literature. Many trials have a

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similar design, the differences between trials are due to the use of different types of chemotherapy.

Some of the trials have used single agent cisplatin, and some have used combination therapy. Although the equivalence of radiotherapy, cystectomy or a combination of both has not been proved by a randomised trial, all of these are used as local definitive treatment for muscle-invasive bladder cancer in several countries. There is no reason to expect that a benefit from chemotherapy would differ greatly with different local treatments. It seems that most of these trials appear to show no difference, but they may not have enrolled sufficient numbers of patients to detect realistic differences in survival.

The International EORTC/MRC trial of CMV chemotherapy prior to cystectomy or radiotherapy versus cystectomy or radiotherapy is the largest trial of neo-adjuvant chemotherapy [6]. In almost 1000 patients randomised, it showed a small difference in survival, in favour of the chemotherapy group that was not statistically significant at conventional levels of significance. As the largest trial, representing approximately one-third of the patients in all neo-adjuvant trials, it is worth examining in more detail. The trial enrolled 976 patients from 106 institutions in 20 countries. Accrual was over $5\frac{1}{2}$ years.

In this trial, a 15% reduction in the risk of death, which translated into a 3-year survival difference of 5.5% (50% in the no chemotherapy arm and 55.5% in the chemotherapy arm) was observed. Looking at the Hazard Ratio (HR) of 0.85 (95% Confidence Interval (CI): 0.71–1.02) in Fig. 1, with a two-sided $P$ value of 0.075 this difference was not statistically significant. The median length of follow-up for alive patients was 4 years. These results are therefore still consistent with the possibility of no benefit for neo-adjuvant chemotherapy. The improvement in 3-year survival may be anywhere from 0 to 11% ranging from no benefit to a clinically important benefit in survival. To reliably confirm this benefit would require a trial of more than 3000 patients (power 90%, type 1 error 5%) [7].

The South West Oncology Group (SWOG) Intergroup trial randomised patients between three cycles of neo-adjuvant methotrexate, vinblastine, doxorubicin, cisplatin (M-VAC) chemotherapy prior to cystectomy versus cystectomy alone [8]. The aim of this trial was to detect an increase in survival with the use of neo-adjuvant M-VAC chemotherapy.

The investigators designed the trial with a one-sided $P$ value, despite the fact that most randomised trials undertake two-sided testing [9]. One needs to observe 30% more events for two-sided testing, compared with one-sided testing, so the design of a clinical trial is important in comparisons between trials.

It is useful to consider the size of the Intergroup study. A trial with adequate power for the detection of a 10% survival advantage of investigational chemotherapy over standard therapy (60% 3-year survival for patients receiving chemotherapy compared with 50% in those treated with local therapy alone) requires some 1000 patients to be randomised over a 3–4 year period with a further 1–2 years follow-up [10]. Approximately 400 deaths are required in order for the study to have a 90% chance of detecting this difference [7]. In a smaller study of 400 patients recruited over a period of 3–4 years, typically 170 deaths would be observed and based on a two-sided logrank test (alpha = 0.05, 85% power), one would be able to reliably detect differences of the order 15% (from 50 to 65%). The SWOG trial recruited 307 patients and because of the long accrual period, a total of 186 deaths were observed. Thus, this trial could only realistically detect large improvements in survival of the order of 15% in absolute terms.

Table 1
Randomised phase III trials of neo-adjuvant chemotherapy

| Study group [Ref.] | Neo-adjuvant arm | Standard arm | Patients | Results |
|---|---|---|---|---|
| Aust/UK [38] | DDP/RT | RT | 255 | No difference |
| Canada/NCI [39] | DDP/RT or preop RT + Cyst | RT or preop RT + Cyst | 99 | No difference |
| Spain (CUETO) [40] | DDP/Cyst | Cyst | 121 | No difference |
| Australia/UK [38] | DDP/RT | RT | 255 | No difference |
| EORTC/MRC [6] | CMV/RT or Cyst | RT or Cyst | 976 | No difference |
| SWOG Intergroup [8] | M-VAC/Cyst | Cyst | 307 | No difference |
| Italy (GUONE) [14] | M-VAC/Cyst | Cyst | 206 | No difference |
| Italy (GISTV) [15] | M-VEC/Cyst | Cyst | 171 | No difference |
| Genoa [41] | DDP/5-FU/RT/Cyst | Cyst | 104 | No difference |
| Nordic 1 [16] | ADM/DDP/RT /Cyst | RT/Cyst | 311 | No difference, 15% benefit with ADM/DDP in T3-T4a |
| Nordic 2 [17] | MTX/DDP/Cyst | Cyst | 317 | No difference |
| Abol-Enein [42] | CarboMV/Cyst | Cyst | 194 | Benefit with CarboMV |

DDP or C, cisplatin; MTX, methotrexate; ADM, doxorubicin; E, epirubicin; V, vinblastine; Carbo, carboplatin; Cyst, cystectomy; RT, radiation therapy; 5-FU, 5-fluorouracil; preop, preoperatively; M-VEC, methotrexate, vinblastine, epirubicin, cisplatin; M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; Aust/UK, Australia/United Kingdom; NCl, National Cancer Institute; EORTC/MRC, European Organization for Research and Treatment of Cancer/Medical Research Council; SWOG, South West Oncology Group.

Accrual to the SWOG study was over an 11-year period. Standards of diagnosis, patient care and surgery have changed over this period, and patient selection factors may be important in deciding entry into the trial. In fact, 40% in both arms of the trial had T2 disease, which meant an excellent prognosis, and may have been cured by cystectomy alone [11,12]. In addition, of the 'eligible' patients in both arms of the trial, only 80% of the planned cystectomies were performed.

It is interesting that the SWOG trial is approximately one-third the size of the EORTC/MRC trial, and yet the survival curves of the two trials are very similar. The two-sided $P$ value ($P=0.088$) for the survival curves is actually less significant than what was observed in the EORTC/MRC study ($P=0.075$), which has been interpreted as inconclusive on its own [9].

In addition, the difference in the medians can be misleading, because it does not represent the whole curve, just a single point on the curve. It is well known that it is not a good idea to just choose a point in time because the curves appear to be separated there [13]. The best estimate is the HR which summarises the data comparing the whole curves, over the entire period of follow-up. For the SWOG trial, the 95% CI for the HR crosses 1, the line of equivalence (HR = 0.78; 95% CI: 0.58–1.04). In addition, given the shape of the survival curves, there is a suggestion that the curves come together in the end, which means that even if there is evidence of early benefit, there is no clear evidence of long lasting benefit. Furthermore, it should be noted that the American trial did not present an 'intention to treat analysis' as not all randomised patients were included in the survival curves. The Intergroup trial represents only 10% of all patients randomised into trials of neo-adjuvant chemotherapy and must be considered in that context.

Another trial that is very similar to the SWOG trial, is the Italian Gruppo Uro-Oncologico del Nord Est (GUONE) trial, in which 206 patients were accrued over a $6\frac{1}{2}$ year period [14]. Patients were randomised between four cycles of M-VAC before cystectomy and cystectomy alone. The sample size was calculated to detect an improvement in 3-year overall survival of 15%, from 45 to 60%. Survival at 3 years was 62% for the M-VAC arm and 68% for the cystectomy alone arm. This is a small trial, like the SWOG trial in which no clear difference in survival was observed. Likewise, no evidence of a difference in survival was seen in another Italian trial of methotrexate, vinblastine, epirubicin, cisplatin (M-VEC) versus cystectomy, when epirubicin was substituted for doxorubicin [15].

The Nordic cystectomy I trial reported a small difference only in a subgroup analysis of patients with T3-T4 [16], but did not confirm these results in the subsequent Nordic cystectomy II trial in 317 patients with muscle-invasive disease, which employed methotrexate and cisplatin instead of the Nordic I regimen containing doxorubicin, cisplatin and radiation prior to cystectomy [17].

Information from all relevant randomised trials in the form of a meta-analysis was done to update the

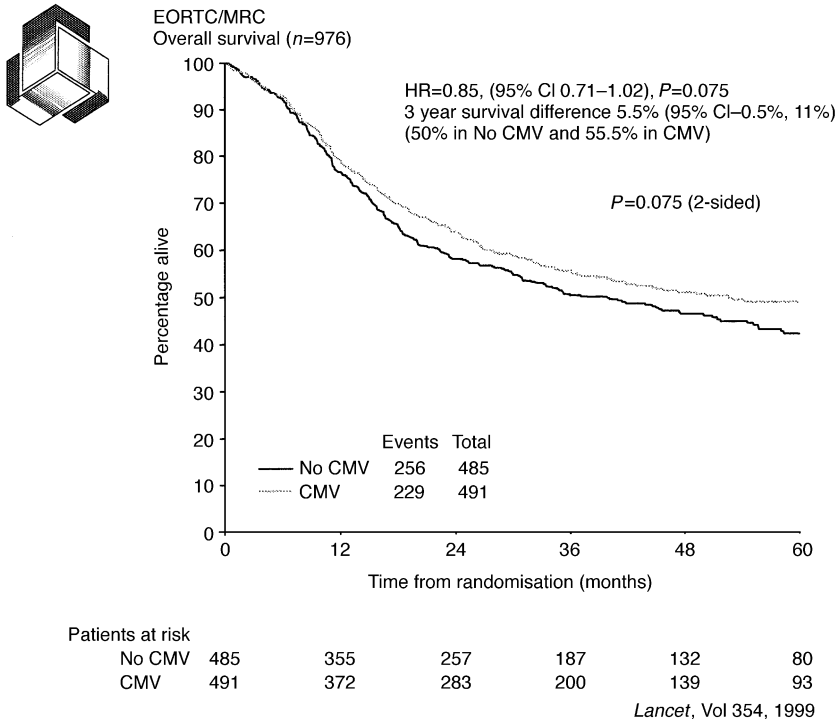


Fig. 1. Overall survival EORTC/MRC neo-adjuvant chemotherapy study. EORTC/MRC, European Organization for Research and Treatment of Cancer/Medical Research Council; CMV, cisplatin, methotrexate and vinblastine. Reprinted with permission [6].

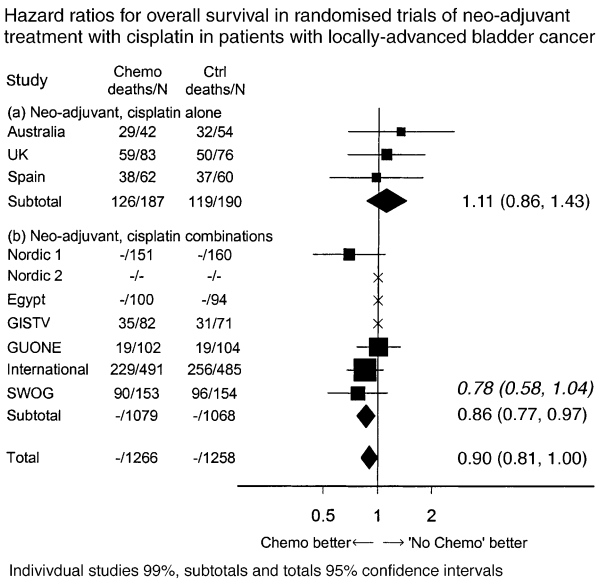


Fig. 2. The logrank "observed minus expected (O−E) statistic and its variance were calculated when possible. Analysis were stratified by trial and the logrank expected and observed numbers of deaths were used to calculate individual and overall pooled hazard ratio (HR). The time to death for individual patients was used to generate the HR which represents the overall relative risk of a patient dying on treatment compared with the control arm. A HR of 1 indicates no difference between the treatment and control groups. A HR of $<1$ favours the chemotherapy group, and a HR of $>1$ favours the no chemotherapy group. The logrank statistical analyses are then added together to provide an overall comparison of chemotherapy versus no chemotherapy. A black square indicates the ratio of the death rates, as calculated from the logrank statistics and the horizontal line gives the corresponding 99% CI. The area of the square is proportional to the amount of information it represents. The variance (V), represented by the size of the black square, represents the amount of information each trial represents. The total number of deaths in a trial is approximately 4 times the V, so the number of deaths also gives a measure of the amount of information. A study like the EORTC/ MRC International Intergroup trial with 485 deaths has almost 3 times the amount of information as the SWOG Intergroup trial. HR, Hazard Ration; Chemo, chemotherapy; Ctrl, control; CI, confidence interval; SWOG, South West Oncology Group; EORTIC/MRC. European Organisation for Research and Treatment of Cancer/Medical Research Council. Reprinted with permission from Sternberg and Parmar [9].

systematic review performed by Parmar and Burdett by incorporating what was available from the GUONE and SWOG trial results (Fig. 2) [9]. For every trial including the SWOG trial, the confidence intervals cross 1 (the equivalence line) and, therefore, no trial on its own is conclusive. For the overall combined value, the diamond gives the 95% CI. More favourable results appear to be seen for cisplatin combinations than for trials with single-agent cisplatin. The results are not clearly in favour of chemotherapy, and trials of combination chemotherapy just approach the vertical line of equivalence where the HR is 1, giving a very borderline result, in terms of conventional statistical significance. It is important to note that data from several trials, which could influence the results in either direction, are still missing. For this reason, the only way to come to a reliable conclusion is to have individual patient data from all of the relevant randomised trials. Such a meta-analysis is underway, and is being performed by the MRC.

## 3. Neo-adjuvant chemotherapy and bladder preservation

Since orthotopic bladder substitution has become available, many urologists prefer early definitive therapy with this ideal form of continent urinary diversion. However, if in selected cases, there is the possibility of bladder preservation this chance should not be dismissed. This approach has been used in the treatment of other solid tumours such as breast cancer, anal cancer, laryngeal carcinoma and osteosarcoma. Bladder preservation to the patient means less surgery, no need for a urinary diversion and a normal sexual life. These factors are clearly important in determining quality of life.

Following neo-adjuvant chemotherapy, bladder preservation may be possible in highly selected cases [18]. The pathological complete response rate in the cystectomy specimen (pT0) was 38% in M-VAC treated patients in the SWOG trial. Likewise, the pT0 rate in 417 patients in the EORTC/MRC trial who underwent surgery, was 33% for patients who had CMV chemotherapy, as compared with 12% for those who had TURB and cystectomy alone without chemotherapy.

Several investigators have shown that response to chemotherapy is an important prognostic factor [19–22]. However, this may represent patient selection factors, as it is always possible that patients who do well have characteristics that would make them survive longer whether or not they were treated with chemotherapy.

In our Italian neo-adjuvant M-VAC series, 5-year survival was 59% for patients with muscle invasive disease treated with neo-adjuvant M-VAC and either TURB, partial cystectomy or radical cystectomy [19,22]. These data compare favourably to the recently published data from the University of Southern California, in which 5-year survival after cystectomy in 633 patients with pT2, pT3a, pT3b and pT4 disease was 72%, 58%, 38% and 33%, respectively [3]. In 284 patients at the Memorial Sloan Kettering Cancer Center, 5-year survival with pT2 tumours was 59%, pT3 was 25%, and pT4 was 29% [4].

In addition, in series combining chemotherapy and radiation in an attempt to spare the bladder (Table 2), survival for patients with T2-T3 invasive bladder cancer is very similar to that observed in contemporary cystectomy series.

In the chemoradiation series from the Massachusetts General Hospital and from the Radiation Therapy Oncology Group, 5-year survivals were approximately 50% [23,24].

Table 2
Trials of combined chemotherapy and radiotherapy

| Series [Ref.] | Year | *n* | Chemotherapy | 5-year survival (%) | 5-year survival with intact bladder (%) |
|---|---|---|---|---|---|
| Radiation Therapy Oncology Group study 85-121 [23] | 1993 | 42 | DDP | 52 | 42 |
| Radiation Therapy Oncology Group study 88-02 [43] | 1996 | 91 | MCV + RT and DDP | 62[a] | 44 |
| Radiation Therapy Oncology Group study 89-03 [44] | 1998 | 123 | MCV + RT and DDP | 48 | 36 |
| Massachusetts General [24] | 1997 | 107 | MCV | 52 | 43 |
| University of Erlangen [45,46] | 2001 | 199 | DDP, or Carbo | 52 | 41 |
| University of Paris [47,48] | 2001 | 120 | DDP/5-FU | 63 | |

DDP, cisplatin; RT, radiation therapy; MCV, methotrexate, cisplatin, vinblastine; Carbo, carboplatin; 5-FU, 5-fluorouracil.
[a] Four-year survival data.

There is a similarity between contemporary cystectomy series and selected bladder preservation series, although the interpretation of results may be difficult due to the differences between clinical and pathological staging. Clinical staging is more likely to understage the extent of disease. Thus, if there is a favourable outcome, it is usually in favour of the pathologically staged patients.

Of course, there are differences between cystectomy series and studies that seek to conserve the bladder, complicating comparisons between the two. Cystectomy series do not report by 'intention to treat' and exclude those patients in whom cystectomy is inappropriate [25]. In addition, many patients in cystectomy series do not have preoperative proof of muscle invasion. Many cystectomy reports include 25–40% of the patients having $<$pT2 stage tumours.

Patients who elect to preserve the bladder must accept: frequent follow-up, multiple invasive procedures, the possibility that cystectomy may eventually become necessary and the uncertainty of tumour relapse. Patients who respond to chemotherapy are good candidates for bladder preservation protocols, and bladder preservation is a good alternative for patients who are not candidates for radical cystectomy. New strategies for bladder preservation should be the focus of clinical research. Bladder sparing in selected patients on the basis of response to neo-adjuvant chemotherapy is a feasible approach which must be confirmed in prospective randomised trials.

## 4. Adjuvant chemotherapy

Radical cystectomy is the standard treatment for patients with muscle invasive bladder cancer. Adjuvant chemotherapy is given after cystectomy to patients at high risk of relapse [1,5]. Adjuvant chemotherapy is widely used in patients with pT3-pT4a and/or pN+ M0 disease in an effort to delay recurrence and prolong survival. This approach of giving chemotherapy after local treatment has led to increases in survival in patients with several solid tumours.

The rationale for giving adjuvant (rather than neo-adjuvant) chemotherapy is that the local definitive treatment is performed immediately. There is no delay in surgery and no time is wasted especially for those patients who do not respond to chemotherapy. Treatment decisions are based on pathological criteria, after careful examination of the cystectomy specimen. Micrometastases are treated when really at a low volume. Orthotopic bladder substitutions and the decreased morbidity of cystectomy are reasons to perform cystectomy and adjuvant chemotherapy.

The major disadvantage of treatment with adjuvant chemotherapy is the delay in giving systemic therapy for occult metastases while treating the primary tumour. Response cannot be easily evaluated, and the only clinical endpoint that can be assessed is time to recurrence. An additional disadvantage may be that it is more difficult to administer chemotherapy following cystectomy. There have been very few randomised trials evaluating adjuvant chemotherapy (Table 3).

Two studies in the literature have received considerable attention. The most quoted is the Skinner study [26]. This was the first phase III prospective trial that showed a significant increase in time to progression and survival in patients who were randomised to receive chemotherapy following cystectomy.

This has been interpreted as a positive study. Median survival time for patients in the chemotherapy group was 4.3 years compared with 2.4 years in the observation group. The number of involved lymph nodes was the single most important variable. This study has been highly criticised by medical oncologists for its retrospective use of subgroup analyses and its statistical methodology. Use of the Wilcoxon test may have provided artificial results in the context of the survival curves which crossed over with follow-up. While chemotherapy appeared to prolong the median time to recurrence by 14 months, there was no residual advantage at 2 years.

Table 3
Trials of adjuvant chemotherapy following cystectomy

| Investigator [Ref.] | Year | Chemo | Chemo | No chemo | Randomised | Results |
|---|---|---|---|---|---|---|
| Logothetis [49] | 1988 | CISCA | 62 | 71 | No | Benefit, but not randomised |
| Skinner [26] | 1991 | CAP | 47 | 44 | Yes | Benefit, but too few patients received therapy |
| Stockle [27] | 1992 | M-VAC/ M-VEC | 23 | 26 | Yes | Benefit, small patient numbers, premature closure, no treatment at relapse |
| Studer [50] | 1994 | DDP | 40 | 37 | Yes | No benefit, single agent therapy probably inadequate |
| Bono [51] | 1995 | CM | 48 | 35 | Yes | No benefit for N0M0 |
| Freiha [52] | 1996 | CMV | 25 | 25 | Yes | Benefit in relapse-free survival |
| Otto [29] | 2001 | M-VEC | 55 | 53 | Yes | No benefit |

Chemo, chemotherapy; M, methotrexate; C, cisplatin; V, vinblastine; DDP, cisplatin; M-VEC, methotrexate, vinblastine, epirubicin, cisplatin; M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin. From Sternberg and Calabrò [1] with permission.

The Mainz group published the other adjuvant study that has received much attention [27,28]. Patients were randomised to either cystectomy or cystectomy followed by M-VAC or M-VEC. The population had poor risk factors. 60% had positive nodes and most were stage T4.

The study was closed prematurely with only a small number of patients entered, after an interim analysis revealed a benefit for those randomised to the chemotherapy arm with 27% progression in the treated versus 82% progression in the control, untreated arm. Survival was markedly different between the two arms, as the authors did not treat the patients who relapsed in the observation arm. In an intent to treat analysis, 5-year progression-free survival was 59% after the recommendation to receive chemotherapy versus 13% after a recommendation of cystectomy alone [28]. It is of interest that in a more recent German series comparing M-VEC with observation after cystectomy, no difference in survival was confirmed [29].

As the interpretation of these adjuvant chemotherapy trials proved difficult, a systematic review of published randomised trials of adjuvant cisplatin-containing combination chemotherapy in locally advanced bladder cancer was undertaken [30]. Although these trials appear to show a significant difference in favour of adjuvant chemotherapy, serious methodological flaws were found. Major deficiencies were found in sample size, early stopping of patient entry, statistical analyses, reporting of results and in the conclusions drawn.

These trials provided insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice due to small sample sizes, confusing analyses and terminology, and the reporting of questionable conclusions. Analyses of the duration of survival were either not done or were inconclusive, and quality of life was not considered.

Based on the desire to only treat patients who are really at high risk, the EORTC together with many other international groups throughout the world have now begun a new very large trial that will enlist 1344 patients worldwide, in the adjuvant setting, after cystectomy. This is a study evaluating four cycles of immediate chemotherapy versus therapy at the time of relapse in high-risk patients with pT3-pT4 or node-positive disease. Three different chemotherapy regimens are permitted: M-VAC, high-dose M-VAC (HD) M-VAC), and gemcitabine/cisplatin (GC) [31–33].

Another multicentre adjuvant trial seeks to evaluate patients with low stage T1-T2 tumours, who are randomised after surgery to M-VAC versus observation based on their *TP53* status. Following radical cystectomy, eligible patients are those with pT1-T2 disease, or those who have had T1-T2 on the TURB and are pT0 at the cystectomy. These patients are then evaluated for their *TP53* status. Patients with wild-type *TP53* are entered on the study and observed, and those with mutant *TP53* are randomised between three cycles of M-VAC and observation.

This study is based upon the University of Southern California (USC) experience that tumours expressing alterations in pRb and p53 had significantly increased rates of recurrence ($P < 0.0001$) and decreased survival ($P < 0.0001$) compared with patients without alterations in pRb and p53 [34,35]. They have also found that patients with altered p53 are more likely to benefit from chemotherapy. Although the USC results may be questioned [36,37], this is an important study in that it seeks to use molecular markers to determine the outcome of patients with locally advanced bladder cancer.

## 5. Optimal chemotherapy

The EORTC has compared HD M-VAC plus granulocyte-colony stimulating factor (G-CSF) with M-VAC in a phase III randomised trial in patients with metastatic bladder cancer. This trial suggested an improvement in 2-year survival with HD M-VAC, but more importantly, less toxicity and the ability to administer chemotherapy in one-half of the time. HD M-VAC was better in terms of

progression-free survival ($P = 0.037$; HR = 0.75; 95% CI: 0.58–0.98), although not for overall survival as planned by the study ($P = 0.122$; HR = 0.80 95% CI: 0.60–1.06). Patients who received HD M-VAC had a higher response rate ($P = 0.06$) and complete response (CR) rate ($P = 0.009$) and a 25% less chance of recurring or dying than patients on M-VAC (HR = 0.75; 95% CI: 0.58–0.98) [32].

Another large randomised trial in patients with metastatic disease revealed that the combination of gemcitabine and cisplatin was less toxic than M-VAC, with similar survival outcomes ($P = 0.75$; HR = 1.04; 95% CI: 0.82–1.32) [33].

For these reasons, M-VAC, HD M-VAC and gemcitabine–cisplatin are all considered to be acceptable alternatives for the treatment of bladder cancer. Physicians appear to be selecting the one with which they feel the most comfortable.

## 6. Conclusions

Physicians treating muscle-invasive bladder cancer face many challenges. This is a chemoresponsive disease and should be dealt with in a multimodality approach with collaboration between the urologist, medical oncologist and radiotherapist. Neo-adjuvant chemotherapy has not been proven to improve survival, but may be useful in programmes of bladder preservation. Response to M-VAC neo-adjuvant chemotherapy is an important prognostic factor, but this too may represent patient selection factors. It is not known whether it is better to administer chemotherapy in the neo-adjuvant or in the adjuvant setting, which may spare some patients unnecessary chemotherapy. The international adjuvant chemotherapy trial coordinated by the EORTC will hopefully clarify some of the unanswered questions concerning whether or not adjuvant chemotherapy immediately following cystectomy is necessary.

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