

Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial

International collaboration of trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party, EORTC Genito-Urinary Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico (CUETO) group

Summary

Background Several non-randomised trials have shown that transitional-cell carcinoma of the bladder is a moderately chemosensitive tumour. We investigated whether the addition of neoadjuvant cisplatin-based chemotherapy to radical surgery or radiotherapy would improve survival.

Methods Patients with T2 G3, T3, T4a, N0-NX, or M0 transitional-cell carcinoma of the bladder undergoing curative cystectomy or full-dose external-beam radiotherapy were randomly assigned three cycles of neoadjuvant chemotherapy (cisplatin, methotrexate, and vinblastine, with folinic acid rescue, n=491) or no chemotherapy (n=485). When possible, clinical tumour response was assessed cytoscopically after completion of chemotherapy but before cystectomy or radiotherapy; histopathologically assessed response was on cystectomy samples. We recorded every 6 months locoregional persistence or relapse of tumour, appearance of distant metastases, survival, and cause of death.

Findings Median follow-up of patients still alive was 4.0 years. 485 patients died, and 78.6% of deaths were due to transitional-cell carcinoma. Chemotherapy mortality was 1% and operative (cystectomy) mortality was 3.7%. Kaplan-Meier curves compared by means of the log-rank test gave a calculated absolute difference between groups in 3-year survival of 5.5% (95% CI -0.5 to 11.0, p=0.075; 55.5% for chemotherapy, 50.0% for no chemotherapy). Median survival in the chemotherapy group was 44 months compared with 37.5 months for the no-chemotherapy group. 32.5% of cystectomy samples contained no tumour after neoadjuvant chemotherapy.

Interpretation Three cycles of neoadjuvant chemotherapy before cystectomy or radiotherapy did not give the 10% improvement in 3-year survival that was judged to be necessary for introduction into routine use. The chemotherapy regimen was associated with a higher pathological complete-response rate in primary tumours, but there was no clear evidence that it would increase survival.

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Introduction

Locally advanced bladder cancer is associated with a high risk of occult distant disease, shown by a high death rate from metastases after locally successful treatment with radical cystectomy or external-beam radiotherapy. The aim of neoadjuvant chemotherapy is to lower cancer mortality caused by occult metastatic disease that is present at the time of local radical treatment. Bladder cancers are moderately chemosensitive, and neoadjuvant chemotherapy given before cystectomy or radiotherapy may be useful in muscle-invasive cancers. Reduction of the size of the primary tumour may make local therapy more effective, occult metastatic disease can be treated as early as possible, and compliance with planned chemotherapy is more likely.

Cisplatin, methotrexate, vinblastine, and doxorubicin are all active against bladder cancer. Non-randomised studies of combinations that include cisplatin in patients with metastatic disease have yielded overall response rates of up to 70%.^{1,2} In a randomised trial, a regimen that included all four drugs led to significantly more complete responses and longer survival of patients with metastatic disease than cisplatin alone, and 5-year progression-free survival of 3.4%.³ In the randomised Medical Research Council BA07 trial,⁴ cisplatin, methotrexate, and vinblastine led to significantly longer survival than methotrexate and vinblastine, and the absolute improvement in 1-year survival was 13%. Studies of primary muscle-invasive bladder cancer as the indicator lesion have shown similarly encouraging response rates,^{5–7} with pathologically confirmed complete remissions (at cystectomy) in about 20% of tumours.^{5,7} Clinically complete remission for 3 years has been reported in 18% of patients with T2, T3, and T4a transitional-cell carcinoma treated by chemotherapy.⁸

In a meta-analysis of five trials,^{9–12} of which four used only cisplatin as adjuvant treatment for muscle-invasive bladder cancer, no improvement was seen in survival,¹³ although a small benefit could have been missed because of the small number of patients. Despite the lack of improvement with this single agent, combination adjuvant chemotherapy could be useful because of the superior activity seen for methotrexate, vinblastine, doxorubicin, and cisplatin compared with cisplatin alone. Three studies of adjuvant combination chemotherapy reported a delay in the development of metastases and increased survival after cystectomy.^{11–16} Limitations in the methods, including small numbers of patients,^{14–16}

premature closure,^{15,16} selection of patients,^{14,15} and statistical analysis,^{14,15} however, left the principal question about adjuvant therapy unanswered.

In November, 1989, the Medical Research Council Advanced Bladder Cancer Working Party and the Genito-Urinary Group of the European Organisation for Research and Treatment of Cancer (EORTC) started a prospective randomised trial of neoadjuvant cisplatin, methotrexate, and vinblastine in patients undergoing cystectomy or full-dose external-beam radiotherapy for muscle-invasive bladder cancer. Other national groups from Australia, Canada, Finland, France, Norway, and Spain contributed. The three-drug chemotherapy regimen was chosen because it was thought to have similar efficacy to methotrexate, vinblastine, doxorubicin, and cisplatin, but the four-drug regimen was expected to be more toxic in multicentre use. Also, we were concerned that inclusion of doxorubicin might lead to undesirable interaction with radiotherapy, which was expected to be the local radical treatment in about half of the patients. Although the equivalence of radiotherapy, cystectomy, or a combination of both has not been proved by randomised trial, these three approaches are used currently as local radical treatment for muscle-invasive bladder cancer in several countries. Furthermore, we had no reason to expect that any benefit of chemotherapy would differ greatly with different local treatments. We therefore did a multicentre randomised trial to compare local radical treatment alone (cystectomy, full-dose external-beam radiotherapy, or preoperative radiotherapy and cystectomy, according to the choice of the patient or physician) with local radical treatment preceded by three cycles of neoadjuvant chemotherapy.

Methods

Patients

We enrolled patients with transitional-cell carcinoma of the bladder, categories T2 G3, T3, or T4a,¹⁷ who were judged suitable for curative treatment. Patients who had tumours with mixed cell types comprising transitional-cell carcinoma and squamous or glandular metaplasia were also eligible. All patients were assessed by cystoscopy, transurethral-resection biopsy of the tumour, bimanual palpation under anaesthesia, chest radiography, measurement of renal function, full blood count, and liver function tests. Patients with tumours shown by bimanual palpation or imaging to be larger than 7 cm were ineligible. Computed tomography, magnetic resonance imaging, or ultrasonography of the pelvis and abdomen were recommended but were not mandatory. Patients with nodal metastases (confirmed if necessary with needle biopsy) were excluded; all other patients were classified as N0. If no imaging had been done, we classified patients as NX. Renal function (glomerular filtration rate) was calculated according to the Cockcroft and Gault formula.¹⁸ Initially, the inclusion threshold for glomerular filtration rate was 60 mL/min, but this was changed to 50 mL/min after 448 patients had been enrolled. Other inclusion criteria were total white cell count more than $3.5 \times 10^9/L$ and platelet count more than $100 \times 10^9/L$. There was no age limit; patients had to be fit to receive three cycles of chemotherapy, having received no previous systemic chemotherapy or radiation, or had any other previous cancer. We obtained informed consent from all patients who participated. Histological confirmation of muscle invasion by tumour was a prerequisite for randomisation. Participating centres were requested to submit duplicate histopathology sections from the transurethral-resection biopsy samples at entry for central review to confirm tumour type, histological grade, and the presence of detrusor muscle invasion.

	Chemotherapy (n=491)	No chemotherapy (n=485)
T category		
T2	169 (34%)	165 (34%)
T3	285 (58%)	282 (58%)
T4a	37 (8%)	38 (8%)
Histological grade (local pathologist)		
G1	6 (1%)	2 (0.4%)
G2	52 (11%)	61 (13%)
G3	433 (88%)	421 (87%)
Not known	0	1 (0.2%)
Nodal status		
N0	327 (67%)	307 (63%)
NX	164 (33%)	178 (37%)
Age (years)		
≤50	44 (9%)	55 (11%)
51–60	137 (28%)	115 (24%)
61–70	236 (48%)	224 (46%)
>70	74 (15%)	91 (19%)
Median	64	64
Sex		
Male	433 (88%)	430 (89%)
Female	58 (12%)	55 (11%)
WHO performance status		
0	340 (69%)	337 (69%)
1	130 (26%)	128 (26%)
2	20 (4%)	19 (4%)
3	1 (0.2%)	1 (0.2%)
Tumour size (cm)		
≤2.5	82 (17%)	93 (19%)
2.6–5.0	306 (62%)	315 (65%)
5.1–6.9	88 (18%)	63 (13%)
≥7.0	11 (2%)	8 (2%)
Missing	4 (0.8%)	6 (1%)
Median	4	4
Calculated glomerular filtration rate (mL/min)		
<50	5 (1%)	1 (0.2%)
50–59	33 (7%)	41 (8%)
60–69	120 (24%)	134 (28%)
≥70	331 (67%)	305 (63%)
Missing	2 (0.4%)	4 (0.8%)
Local radical treatment		
Radiotherapy	207 (42%)	208 (43%)
Cystectomy	246 (50%)	239 (49%)
Radiotherapy plus cystectomy	38 (8%)	38 (8%)

Table 1: Characteristics of patients and tumours

Randomisation and treatment

Patients were randomly assigned combined chemotherapy in addition to radiotherapy or surgery or no chemotherapy. The local radical treatment was chosen before randomisation for all patients.

Randomisation was done by telephone, facsimile, or Eurocode to the Medical Research Council Clinical Trials Unit, EORTC Data Center, National Cancer Institute of Canada Clinical Trials Group Central Office, or the Australian National Health and Medical Research Council Clinical Trials Centre. Minimisation was used and patients were stratified by institution, local radical treatment, and T category.

Chemotherapy was administered as: methotrexate 30 mg/m² and vinblastine 4 mg/m² intravenous bolus on day 1; on day 2, before hydration, cisplatin 100 mg/m² intravenous infusion, and after hydration, folic acid 15 mg (oral or intravenous) every 6 h (total four doses) started 24 h after methotrexate on day 1; on day 8, methotrexate 30 mg/m² and vinblastine 4 mg/m² intravenous bolus; and on day 9, folic acid 15 mg (oral) every 6 h (total four doses) started 24 h after methotrexate on day 8. This schedule was repeated every 21 days for three cycles. The protocol included detailed dose-reduction schedules.

If cystectomy was done, the protocol recommended that, in men, resection should include the peritoneum, fat, and lymph nodes of the deep pelvis, defined by the medial border of the psoas muscle and the midpoint of the common iliac artery. The bladder, seminal vesicles, prostate, and lower ends of the ureters were to be removed en bloc, together with the lymph nodes in the obturator space, along the obturator nerves and the

hypogastric vessels. The external iliac nodes were to be removed if involvement was suspected at the time of surgery. Simultaneous urethrectomy was optional. In women, the whole urethra, the anterior and lateral walls of the vagina, uterus, fallopian tubes, and ovaries were included in resection. The extent of lymphadenectomy and details of surgical technique were left to usual institutional practice.

For radiotherapy, the protocol permitted a range of radiation dose-schedules that were intended to be curative rather than specifying a single regimen. Computed tomography was essential for planning of radiotherapy fields. These were clearly defined and treated the whole bladder with a margin, but no attempt was made to treat the entire lymph-node drainage areas of the bladder. We used a box technique with anterior, posterior, and two lateral fields. The protocol recommended an intersection dose per fraction of 2 Gy per day on 5 days per week, to a dose of 60 Gy (biological equivalent dose 100 Gy) to 64 (biological equivalent dose 106.67 Gy). Any variations outside these limits were reviewed individually by the radiotherapy coordinator. All patients who received radiotherapy as local radical treatment were recommended by the trial protocol to undergo regular cystoscopic follow-up to facilitate salvage cystectomy at the earliest opportunity if cancer persisted or recurred in the bladder.

Radiotherapy before cystectomy consisted of two or three fields, including the pelvic lymph nodes, with a target dose of 4 Gy on 5 days in the week before cystectomy.

Statistical analysis

Overall survival was expected to be 50% at 2 years for patients in the no-chemotherapy group. To detect an absolute improvement of 10% (50% increased to 60%) we planned to recruit 915 patients (with power of about 90%, type I error 5%). In response to a questionnaire during the design of the trial, most prospective medical participants stated that they would recommend neoadjuvant chemotherapy in routine practice if the trial showed at least a 10% absolute improvement in survival at 2 years. As the trial proceeded, median survival seemed to be 3 years rather than 2 years for patients in the no-chemotherapy group. Therefore, to calculate the absolute difference in survival time and the other endpoints, we applied the hazard ratio to the 3-year rate in the no-chemotherapy group.¹⁹

We compared Kaplan-Meier curves of overall survival, metastasis-free survival, locoregional disease-free survival and

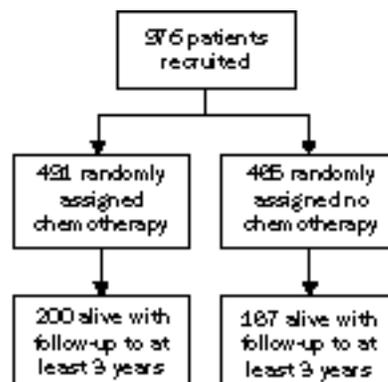


Figure 1: Trial profile

overall disease-free survival by the Mantel-Cox version of the log-rank test, which compares curves over the whole period and gives a hazard ratio that states differences only at particular time points for description purposes.¹⁹ All analyses were by intention to treat. To calculate the absolute difference in survival time and the other endpoints between the two groups at 3 years, we applied the hazard ratio to the 3-year rate for the no-chemotherapy group.¹⁹

We defined overall survival as the time from randomisation to death from any cause. Metastasis-free survival was defined as the time from randomisation to first recognition of metastases or death. Locoregional disease-free survival was defined as the time from randomisation to reappearance of locoregional disease (invasive tumour within the bladder or pelvis) or death. Disease-free survival was defined as the time from randomisation to reappearance of locoregional disease, metastases, or death. Patients who had not experienced the event being studied by the time of their last follow-up were censored at that time.

We planned exploratory subgroup analyses to assess whether chemotherapy or no chemotherapy was more or less effective (in terms of overall survival) in subgroups defined by all characteristics of patients recorded at randomisation and by local radical treatment. To test for consistencies in the size of any effect of chemotherapy, we used χ^2 test for interaction or, when appropriate, χ^2 test for trend.¹⁹

An independent data-monitoring committee was set up to review the progress of the trial annually and to recommend closure if unexpected toxic effects occurred or if interim analysis showed a clear outcome in favour of or against chemotherapy. No prospectively defined stopping rules were stated.

Results

Between November, 1989, and July, 1995, 976 patients were recruited from 106 institutions in 20 countries. The initial characteristics of patients and local radical treatment were similar in the two groups (table 1). Median length of follow-up for patients who were still alive was 4 years (IQR 2.5–5.5). Pretreatment biopsy samples were reviewed for 753 (77.2%) patients. Muscle invasion was not confirmed in 3.5% of samples, and another 8.4% were equivocal or not assessable (table 2).

Of 491 patients assigned chemotherapy (figure 1), 99 did not receive all three cycles of chemotherapy: 23 because of renal toxic effects or impaired renal function; 18 because of other toxic effects of chemotherapy; 14 because of disease progression or early death; 21 because of refusal to continue treatment; and 23 because of protocol errors or unspecified reasons. One patient received four cycles, 37 two cycles, 33 one cycle, and 28 no cycles. Total amounts of chemotherapy received, as percentages of the planned dose, are shown in figure 2.

	Chemotherapy (n=373)	No chemotherapy (n=380)
Tumour present		
Yes	370	378
No	3	2
Tumour type		
TCC alone	269	288
TCC+other cell types	57	59
Other*	44	31
No tumour present	3	2
Histological grade		
G1	1	2
G2	32	31
G3	335	344
GX	2	1
No tumour present	3	2
Muscle present		
Yes	361	364
No	6	10
Not assessable/equivocal	6	6
Muscle invaded		
Yes	332	332
No	11	15
Not assessable/equivocal	30	33

TCC=transitional-cell carcinoma.

*Includes adenocarcinoma, squamous, and mixed cell types.

Based on 753 patients for whom central review was done

Table 2: Histopathology (central review)

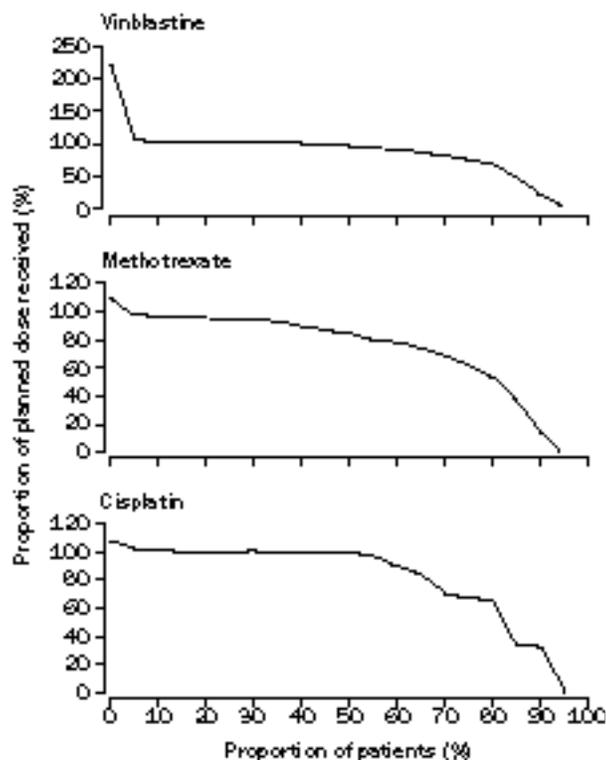
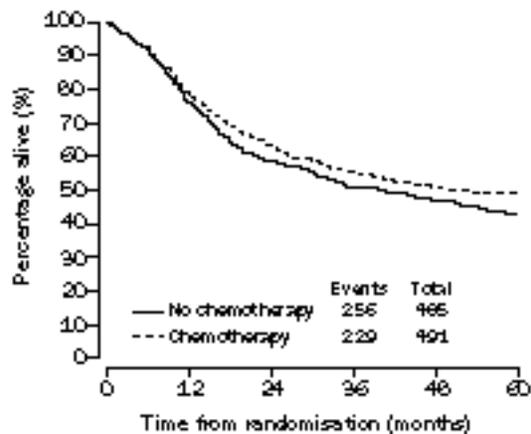


Figure 2: Proportion of planned treatment received
Curves represent cumulative percentage of patients (x axis) who received at least a given percentage of the planned dose (y axis).

Serious side-effects from chemotherapy were not common. Five patients assigned chemotherapy died from toxic effects during treatment (mortality 1%). Data on nausea and vomiting were not collected, but anecdotal reports suggest that they were common despite the recommended use of antiemetics according to institutional practice. WHO grades 3 and 4 leucopenia occurred in 16%, thrombocytopenia in 6.5%, and neutropenic fever in 10% of patients. No grade 3 or 4 renal toxic effects occurred, but 26% of patients required dose decreases or delay (according to protocol) because of impaired renal function.

422 patients underwent cystectomy alone and 66 underwent preoperative radiotherapy and cystectomy. Cystectomy was recorded as radical in 425 patients and total in 60 (missing information in three patients, two of whom had partial cystectomy). 76 of 561 patients did not receive their planned cystectomy, because of disease progression (35 patients), change of mind (15 patients), death (five patients), chemotherapy toxic effects (four patients), or other reasons (17 patients). 18 deaths in the two groups were attributable to cystectomy (operative mortality 3.7%), six in the chemotherapy group, 12 in the no-chemotherapy group. Postoperative wound infections were recorded in 10.5% of patients (20 in the chemotherapy group, 31 in the no-chemotherapy group), wound dehiscence in 4.9% (six and 18), and urinary or faecal fistulae in 4.5% (five and 17). There was no evidence that chemotherapy increased the rate of postoperative complications.

Of the 415 patients planned to receive radiotherapy, 95 (23%) did not receive the full dose as planned because of technical difficulties (28 patients), refusal (27), disease progression (14), toxic effects (six), or other reasons (20). One patient died after receiving radiotherapy because of



Patients at risk

No chemotherapy	466	355	257	187	132	60
Chemotherapy	491	372	283	200	139	93

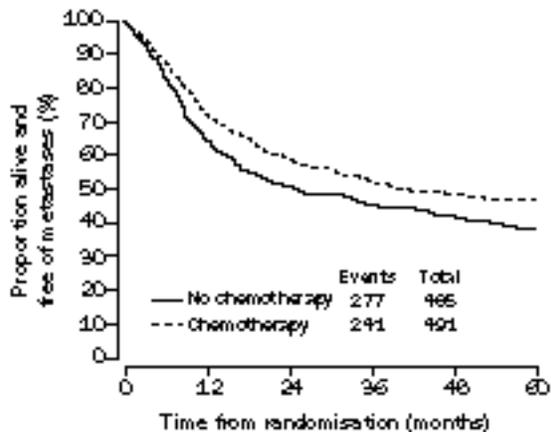
Figure 3: Overall survival

complications from a vesicovaginal fistula (without bladder-cancer recurrence). There was no evidence that morbidity during and immediately after radiotherapy was increased by chemotherapy.

Dysuria (worse or severe) was recorded in 37.3% of patients (53 of 171 in the chemotherapy group, 83 of 194 in the no-chemotherapy group) and grade 3 or 4 diarrhoea in 11.3% (23 of 181 and 20 of 198, respectively).

As an optional part of the trial, in patients assigned chemotherapy, we assessed response of the primary cancer by cystoscopy, bimanual palpation, and transurethral-resection biopsy (the latter method was used irrespective of the presence or absence of visible persistent tumour) after the three cycles of chemotherapy and before radiotherapy or cystectomy. 159 (32.4%) patients underwent cystoscopy after chemotherapy. Biopsy seemed to confirm endoscopic complete response in 71 (44.7%).

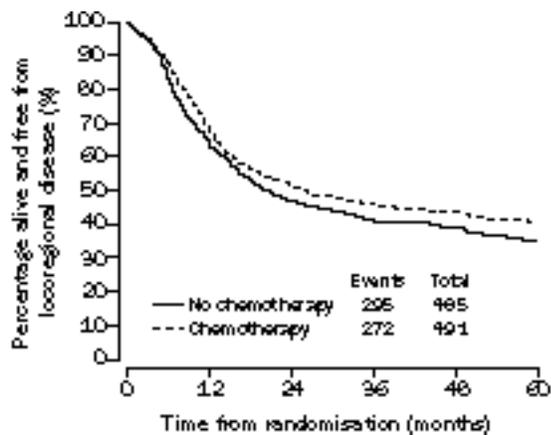
The presence or absence of any tumour was recorded at cystectomy for 417 patients who underwent cystectomy without preoperative radiotherapy. Of the 211 who received no chemotherapy, 26 (12.3%) had no residual cancer in the bladder on histological examination of the cystectomy sample. In the 206 patients who



Patients at risk

No chemotherapy	466	299	224	169	121	75
Chemotherapy	491	337	260	190	134	69

Figure 4: Metastasis-free survival



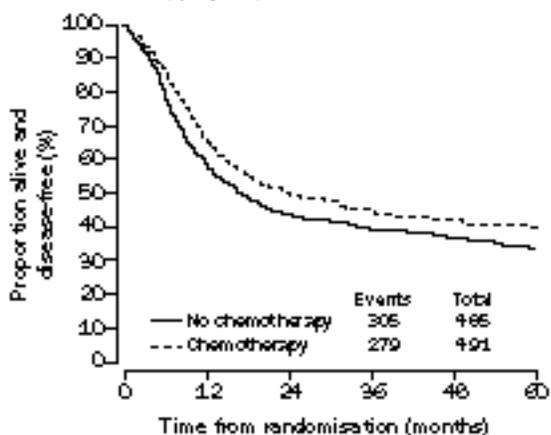
Patients at risk						
No chemotherapy	465	301	209	154	109	66
Chemotherapy	491	324	232	168	119	77

Figure 5: Locoregional disease-free survival

received chemotherapy, 67 (32.5%) had no cancer detectable in the cystectomy sample.

485 patients died; 381 (79%) deaths were related to transitional-cell carcinoma, 34 (7%) of which were cardiovascular and 24 (5%) treatment-related (18 after cystectomy, one after radiotherapy, and five after chemotherapy). Comparison of the survival in the two groups gave a hazard ratio of 0.85, [95% CI 0.71–1.02], $p=0.075$, which was a 15% decrease in risk of death after chemotherapy (figure 3). The absolute difference in 3-year survival was 5.5% (50.0% in the chemotherapy group, 55.5% in no-chemotherapy group [95% CI for difference -0.5 to 11.0]). The median survival for the chemotherapy group was 44 months and for the no-chemotherapy group was 37.5 months, a difference of 6.5 months (-0.5 to 15).

518 patients developed metastases or died. The hazard ratio was 0.79 (0.66–0.93, $p=0.007$; figure 4), which showed a 21% decrease in the risk of metastases or death with chemotherapy and an absolute difference in 3-year metastasis-free survival of 8% (2 to 14), 45% in the chemotherapy group and 53% in the no-chemotherapy group. Median metastasis-free survival was 32 months for the chemotherapy group and 25 months for the



Patients at risk						
No chemotherapy	465	271	192	145	102	63
Chemotherapy	491	308	222	163	116	75

Figure 6: Disease-free survival

	χ^2 value for interaction or trend (degrees of freedom)	p
Age (<55, 55–65, >65 years)	0.77 (1)	0.380
Sex (male, female)	0.75 (1)	0.387
T category (T2, T3, T4a)	0.88 (1)	0.348
Histological grade (G1/G2, G3)	8.58 (1)	0.003*
Local radical treatment (RT, cystectomy, RT and cystectomy)	0.01 (2)	0.908
WHO performance status (0, 1, 2/3)	0.006 (1)	0.939
Nodal status (NO, NX)	0.002 (1)	0.964
Tumour size (<2.5, 2.6–5.0, >5 cm)	3.54 (1)	0.060
Renal function (≤ 59 , 60–69, >69 [GFR])	5.10 (1)	0.024†

RT=radiotherapy; GFR=glomerular filtration rate. *In favour of G3 (ie, benefit of chemotherapy greater in G3 group than in G1/G2 group). †In favour of GFR >69 mL/min (ie, chemotherapy becomes more effective than no chemotherapy as GFR increases).

Table 3: Results of subgroup analyses

no-chemotherapy group, a difference of 7 months (2 to 13). It should be noted that the reliability of this endpoint could be questioned as discussed below.

567 patients developed locoregional disease or died. The hazard ratio was 0.87 (0.73–1.02, $p=0.087$; figure 5), which showed a 13% decrease in the risk of locoregional disease or death with chemotherapy. The absolute difference in 3-year locoregional disease-free survival was 5% (-1 to 11), 42% in the no-chemotherapy group and 47% in the chemotherapy group. Median locoregional disease-free survival for the chemotherapy group was 23.5 months and for the no-chemotherapy group was 20.0 months, a difference of 3.5 months (-0.5 to 7.5). 282 patients had locoregional recurrences followed by death, 203 died with no previously recorded locoregional recurrences, and 82 had locoregional recurrences and are still alive. There was no evidence of a difference between treatments for locoregional control (hazard ratio 0.97 [0.79–1.19], $p=0.738$).

Locoregional disease or metastases, or death occurred in 584 patients. The hazard ratio was 0.82 (0.70–0.97, $p=0.019$; figure 6), which showed an 18% decrease in the risk of locoregional relapse, metastases, or death. The absolute difference in 3-year disease-free survival was 7% (1–13), 39% in the no-chemotherapy group and 46% in the chemotherapy group. The calculated median disease-free survival for the chemotherapy group was 20 months and for the no-chemotherapy group was 16.5 months, a difference of 3.5 months (0.5–7.0). Since this calculation includes the time to development of metastases, it should be interpreted with caution.

The impact of therapy given when disease progression was suspected during follow-up could have influenced survival. The trial placed no restrictions on salvage therapy, which was given to 347 (36%) patients; chemotherapy (cisplatin, methotrexate, vinblastine) was given to 37 patients, other systemic chemotherapy to 51 patients, radiotherapy to 68 patients, and salvage cystectomy to 61 patients. 130 patients underwent various other procedures, including endoscopic and percutaneous relief of urinary obstruction, intravesical chemotherapy, and other major urinary and bowel surgery. As would be expected, more patients received chemotherapy as their first subsequent treatment during follow-up in the no-chemotherapy group than in the chemotherapy group (67 vs 21). Given the small number of patients treated in this way, however, the possible effect of delayed chemotherapy compared with immediate chemotherapy on the overall result would have been small.

The results of the subgroup analyses are shown in table 3. The only subgroups in which there seemed to be some evidence of an effect of chemotherapy on overall survival were histology and renal function. There was no significantly greater or lesser effect of chemotherapy on overall survival in any of the other subgroups investigated.

Discussion

This randomised trial, the largest so far of neoadjuvant cisplatin-based chemotherapy for muscle-invasive bladder cancer, was powered to detect a 10% improvement in survival. The results show no evidence of a survival benefit, with only a possible 5.5% difference in 3-year survival between the groups. To reliably confirm this benefit, which was smaller than expected, would require a trial of about 3500 patients (power 90%, type I error 5%).

We did not compare patients assigned radiotherapy and those assigned cystectomy. These treatments were not randomly assigned to patients and such comparisons were inappropriate. There was no evidence to suggest that the effect of chemotherapy was more or less for patients treated with cystectomy than for those treated with radiotherapy.

In the subgroup analyses, there was some evidence of a greater effect of chemotherapy over no chemotherapy on overall survival in patients with cancers of histological grade G3 than in those with G1 or G2 cancers. There was also some evidence of an increasing effect of chemotherapy compared with no chemotherapy with increasing glomerular filtration rate. Biological hypotheses for these results would not be difficult to postulate, but the subgroup analyses were exploratory and, therefore, the results should be regarded only as hypothesis-generating. Future studies should test these hypotheses prospectively.

Although clinical findings and information on development of metastases were recorded every 6 months during follow-up, the frequency and indications for imaging investigations were not specified by the trial protocol and were left to clinicians' discretion. Many patients underwent further investigation only if they developed symptoms that suggested metastases. Use of second-line chemotherapy for bladder-cancer metastases was generally limited, variable, and had no proven survival benefit. By contrast, chemotherapy with cisplatin, methotrexate, and vinblastine, with methotrexate, vinblastine, doxorubicin, and cisplatin, or with a similar regimen was used more often in chemotherapy-naïve patients who developed metastases, to lessen symptoms and possibly to lengthen survival by a few months. In these patients, clinicians may have started investigations sooner and, therefore, diagnosed metastases earlier. Thus, the difference in time to the development of metastases seen in this trial may be a group-dependent artefact that is apparent rather than real.

Although this trial was large, several criticisms may be pertinent. Some previous studies have shown apparent benefit with adjuvant chemotherapy in patients who have especially poor-risk cancers (pT3, pN+).^{14,15} We recruited a high proportion of patients with disease of good prognosis (34% were staged T2; node-positive patients were excluded) in whom the benefit of adjuvant therapy may be less easily demonstrable. However, since 49.7% of the patients in the study died (79% because of bladder

cancer), our trial was large enough to detect the 10% improvement in survival that was thought to be desirable to justify clinical application. Furthermore, subgroup analyses suggested that our chemotherapy regimen was similarly active in T2, T3, and T4a patients, with similar decreases in the relative risks of death seen in T2 and T3 patients.

Deaths from other causes or from treatment toxicity may confound a small but positive outcome if potentially toxic treatment is tested in an elderly population, especially in a multicentre trial. Since only 5% (24 of 485) of deaths were related to treatment (chemotherapy mortality 1%), our results show that death related to toxic effects was not a concern.

The combination of cisplatin, methotrexate, and vinblastine is an active regimen² but a combination including doxorubicin might have been more effective. Regimens with and without doxorubicin have never, however, been compared by randomised study. We modified the cisplatin, methotrexate, and vinblastine regimen used by Harker and colleagues² by the addition of folinic acid rescue. Browman and colleagues²⁰ reported that the addition of folinic acid to high-dose methotrexate for head and neck cancer may lower efficacy. The cisplatin, methotrexate, and vinblastine regimen, with only 70 mg/m² cisplatin and the same rescue produces a significant survival benefit in patients with metastatic bladder cancer compared with methotrexate and vinblastine.⁴ About 12% of patients in our no-chemotherapy group had no residual cancer in the bladder on histological assessment of the cystectomy sample. The cancer may, therefore, have been removed completely by the diagnostic transurethral resection on entry to the study, which has been noted in some previous trials.²¹ The pathological complete-response rate of 32.5%, shown by tumour-free cystectomy samples, was the result of chemotherapy and the diagnostic transurethral-resection biopsy. In accordance with other data, however, this pathological complete-response rate in the primary bladder tumour did not translate into a significant increase in survival. Similar pathological complete responses of the primary tumour have been reported with a chemotherapy regimen including doxorubicin,⁵⁻⁷ but an intergroup trial⁸ yielded only a 3.4% increase in 5-year survival in patients with metastases. Susceptibility to chemotherapy of malignant urothelial cells that metastasise may therefore differ from that of the parent cancer cells in the bladder.

In previous trials of adjuvant chemotherapy in muscle-invasive bladder cancer, compliance with the chemotherapy regimen was difficult to achieve¹⁴ and the adequacy of the total chemotherapy dose was questionable.²² In our study, treatment compliance and the amount of chemotherapy received by patients would be generally thought to be good, although 12% of patients received fewer than two cycles and 20% fewer than the intended three cycles of chemotherapy. Compliance could have been greater, but this trial reflected clinical practice in 106 institutions, and despite the limitations, the overall percentage of the drugs administered compared with the planned dose was higher than in the Medical Research Council protocol BA07,⁴ which did yield a survival advantage in patients with metastases. The adequacy of the chemotherapy doses in our study was supported by the pathological complete-response rate rate that has already been noted. We cannot

conclude whether more cycles of chemotherapy or alternative regimens would have been more beneficial. The results of smaller randomised trials are contradictory and inconclusive, and the optimum number of chemotherapy cycles that should be given as adjuvant therapy is not known. We chose three cycles as a compromise between a maximum systemic cytotoxic benefit, compliance with treatment, and keeping the potentially harmful delay in starting radiotherapy or cystectomy to a minimum. No other trial has used more than three cycles of neoadjuvant chemotherapy, and the response rate we recorded showed that three cycles of chemotherapy constitute an active regimen by current standards.

Since this trial was designed, nearly 10 years ago, substantial experience of cisplatin, methotrexate, and vinblastine and methotrexate, vinblastine, doxorubicin, and cisplatin regimens has been gained, such that many of the unwanted toxic effects can be overcome. Neoadjuvant chemotherapy that offers a smaller percentage survival benefit may therefore change clinical practice. A survey of clinicians who had participated in this trial and who knew the preliminary result was carried out in September and October, 1997. 77 responses were received, 74% of which stated that they would require a 10% or more survival difference before routine use of the neoadjuvant therapy would be recommended; 13% of the responders required a survival difference of 15% or more. A trial (or meta-analysis) of about four times the size of our trial would be necessary to assess reliably whether the trend we observed is real. The main objection to giving neoadjuvant chemotherapy before surgery or radiation is that the cancer may progress during the treatment. We found no evidence to support this view. The numbers of patients who did not undergo local radical therapy were similar in the two groups and, therefore, are unlikely to have affected the outcome. Adjuvant chemotherapy administered after radiation or cystectomy could, however, still succeed if neoadjuvant treatment has failed. Chemotherapy before local radical treatment may have a harmful effect on normal tissues that could increase the risk of metastasis or enable chemoresistant cancers to metastasise before the primary cancer is removed or destroyed. Others suggest that chemotherapy is most effective if the tumour burden is small rather than for tumours of several centimetres in diameter.

The Nordic 1 trial²³ found a 15% survival benefit in 137 T3 and T4a patients treated with two cycles of neoadjuvant cisplatin and doxorubicin, but there was only marginal benefit for patients with T1 or T2 cancers. The Radiation Therapy Oncology Group Trial 89-03 randomly assigned 123 patients with T2-T4a bladder cancer to two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine or no chemotherapy before radiotherapy with concomitant cisplatin. With median follow-up of 60 months, actuarial 5-year survival was 48% for patients treated with chemotherapy compared with 49% for the control group.²⁴ Abol-Enein and colleagues²⁵ reported an increase in 5-year survival (62 vs 42%; $p=0.013$) from the addition of two cycles of neoadjuvant carboplatin, methotrexate, and vinblastine in a randomised trial of 196 patients with T2 or higher-grade transitional-cell carcinoma. Median follow-up was 32 months. Only 14% of patients in that study achieved pathological complete response after this regimen, compared with 32.5% in our

study, yet the estimated survival benefit was apparently three times more.

The South West Oncology Group has completed accrual to a phase III trial of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin before cystectomy. The outcome of that trial is awaited but a note of caution seems appropriate. The South West Oncology Group trial is powered to detect a large survival benefit and the Nordic, Radiation Therapy Oncology Group, and Egyptian studies have all recruited similar or smaller numbers of patients. Although such trial design may be realistic in terms of feasible accrual of patients, the size of the trial leads to insufficient power to address the most plausible outcome, which would probably be an increase in survival of less than 10%. Three previous studies tested adjuvant chemotherapy after cystectomy in patients with extravesical or node-positive disease.¹⁴⁻¹⁶ Collectively, those studies suggested a delay in time to metastatic progression but did not show improved survival, although because of their small sizes plausible differences may not have been detected.

This trial failed to yield clear evidence that neoadjuvant chemotherapy will increase survival. We observed a possible improvement in 3-year survival (5.5% [-0.5 to 11.0]), but this is not certain because the trial had sufficient power to detect only a larger survival benefit.

Participating centres

Australia and New Zealand (28 patients)—Allamanda Hospital (P McDougall), Dunedin Hospital (G M Jeffery, D Perez), Palmerston North Hospital (S G Allan), Princess Alexandra Hospital (D Nicol, E Walpole), Peter MacCallum Cancer Institute (T Sandeman, K H Tai, M Tong), Prince of Wales Hospital (C Lewis, M Friedlander), Royal Adelaide Hospital (I Olver), Royal Brisbane Hospital (Q Walker), Royal Prince Alfred Hospital (D Raghavan), Geelong Hospital (V Ganju, R McLennan).

Austria (three patients)—Donauspital Der Stdt Wien (G Studler), Kaizer Franz Josef Spital (J Pont).

Belgium (34 patients)—Algemeen Ziekenhuis Middelheim (L Denis), Cliniques Universitaires St Luc (P J Van Cangh), Lierse Ziekenhuizen (K E J Lantsoght), Onze Lieve Vrouw Ziekenhuis (P Carpentier), Sint Josef Kliniek (J Casselman), Universitair Ziekenhuis Gent (A Verbaeys), UZ Gasthuisberg (H Van Poppel).

Canada (69 patients)—BCCA-Vancouver Cancer Centre (C Coppin, N Murray), Cross Cancer Institute (P Venner), Hotel Dieu Hospital, St Catherine's (B Findlay), Northwestern Ontario Regional Cancer Centre (H S Dhaliwal), Penticton Regional Hospital (J H Chritchley), Saskatoon Cancer Centre (G Armitage), The Princess Margaret Hospital (M Gospodarowicz, M Moore, M A S Jewett, I Tannock, W A Wells), Tom Baker Cancer Centre (S Ernst, D A Stewart), Toronto-Sunnybrook Regional Cancer Centre (R Choo).

Finland (six patients)—Helsinki University Central Hospital (O Alfthan).

France (87 patients)—Centre Hospitalier D'Auxerre (R O Fourcade), CHU Besancon Hopital St Jacques (H Bittard), CMC Foch (H Botto), CMC Porte De Choisy (G Vallencian), Gouin (B Callet), Hopital Bichat-Claude Bernard (L Boccon-Gibod), Hopital Edouard Herriot (M Marechal), Institute Gustave Roussy (C Theodore).

Italy (122 patients)—Ospedale Di Circolo E Fondazione Macchi (A V Bono), Ospedale Molinette (A Tizzani), San Raffaele Scientific Institute (C Sternberg, V Pansadoro), Universita Di Palermo (M Pavone-Macaluso).

Malta (four patients)—St Luke's Hospital (C L Cutajar).

Netherlands (87 patients)—AZ Der Vrije Universiteit Amsterdam (C J Van Groenigen), AZ Leiden (H J Keizer), Academisch Medisch Centrum Amsterdam (C H N Veenhof), Maastricht (C Van de Beek), Erasmus University Hospital Dijkzigt Rotterdam (W Kirkels, T A W Splinter), Groot Ziekengasthuis's Hertogenbosch (A P M Van der Meijden), Onze Lieve Vrouw Gasthuis Amsterdam (P P M Karthaus), St Ignatius Ziekenhuis Breda (G A Dijkman), Academisch Ziekenhuis Nijmegen (F Debruyne), Ziekenhuis De Baronie Breda (H Jansen), Zuider Ziekenhuis Rotterdam (C G C Boeken Kruger).

Norway (85 patients)—Norwegian Radium Hospital (S D Fossa, A Aass, H Wahre).

Poland (25 patients)—Szpital Morski I M Pck (J Rzepecki), The Maria Sklodowska-Curie Memorial Cancer Center (G Madej), Warsaw School of Medicine (A Borkowski).

Slovakia (six patients)—Comenius University School of Medicine (J Kliment).

South Africa (one patient)—Groote Schuur Hospital (R P Abratt).

Spain (85 patients)—Hospital Civil de Basurto (N Flores), Hospital De Mutua De Terrassa (R Bastus), Hospital "La Paz" (J A Martinez-Pineiro), Hospital Marques de Valdecilla (B Martin, J Portillo), Hospital Miguel Servet (L A Rioja), Hospital Nuestra Señora Del Pino (S Isorna), Hospital Regional Carlos Haya De Malaga (A Santos Garcia Vaquero), Hospital Virgen de las Nieves (M Tallada).

Sweden (three patients)—University Hospital Lund (P Flodgren).

Switzerland (one patient)—Kantonsspital (F Recker).

Turkey (21 patients)—Dokuz Eylul University School of Medicine (Z Kirkali), Marmara University Hospital (A Akdas).

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USA (one patient)—University of Florida (Z Wajzman).

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COMMENTARY

Perioperative chemotherapy in locally advanced bladder cancer

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In today's *Lancet*, Claire Vale and colleagues present a meta-analysis of randomised phase 3 studies that investigated neoadjuvant chemotherapy (given before local treatment) in locally advanced bladder cancer. Their meta-analysis shows that neoadjuvant cisplatin-based combination chemotherapy provides a survival advantage over definitive local therapy alone. There are several reasons why the conclusion of this landmark meta-analysis should be considered valid. First, the investigators obtained primary data from each individual study rather than depending on published summary information. Second, they have identified and included data from unpublished studies. Third, they did a sensitivity analysis showing that the overall results were not unduly influenced by results from any individual study. Although unfortunate that primary data from a US study addressing this question were unavailable, it is comforting that the conclusions of the US study are very similar to those reached here. Inclusion of at least the preliminary summary data from the American study does not significantly alter the results of the meta-analysis. Fourth, the meta-analysis results are consistent with randomised trials in metastatic transitional cell cancer in which cisplatin-combination therapy provides a survival advantage over single-agent therapy.¹

Thus, after almost two decades of investigation, the conclusion is that neoadjuvant chemotherapy for patients with locally advanced bladder cancer is a standard of care. A declaration of victory would, however, be out of place. The relative benefit of potentially toxic chemotherapy is extremely modest, with a 95% CI for the hazard ratio that comes perilously close to one, and an absolute survival improvement at 5 years of 5%.

One obvious way in which to improve these results is simply to improve the chemotherapy. Experience in the metastatic setting for this disease is, however, not encouraging. Several different drugs with activity in transitional cell cancer have been identified in the past several years. Although some modest improvements in toxicity have been shown, no improvements in overall survival have been observed.² Thus mixing and matching of various cytotoxic agents is unlikely to have a major impact. There has been much enthusiasm in the cancer literature for the potential of more "targeted agents", such as drugs that target the epidermal growth-factor receptor. Although studies of these agents in bladder cancer are still ongoing, recent data in other tumours suggest that these drugs will not be a panacea.³

Is it then possible to limit cytotoxic therapy only to patients most likely to benefit? For example, postoperative therapy, when detailed and accurate pathological data are available, would allow therapy to be limited to patients with

the highest risk of relapse. The subgroup analysis of this meta-analysis suggests, however, that the absolute level of benefit is the same in more advanced than in less advanced tumours. Therefore a selective strategy based on pathological staging may not be as selective as imagined. Complete pathological information after surgery may, however, still be useful since patients who are pathologically T2N0 or less have a probability of survival at 5 years ranging from 64% to 83% in contemporary cystectomy series. Thus the incremental survival benefit with chemotherapy may not be worth its toxicity.⁴

Vale and colleagues' meta-analysis also suggests that the benefit with neoadjuvant chemotherapy is independent of the definitive local therapy. However, such an observation does not address the question of the relative effectiveness of surgery versus radiotherapy. The local recurrence rate from all trials in the meta-analysis is 28% (table 3), but the local recurrence rate with radical cystectomy and extended pelvic lymphadenectomy is substantially lower.⁴ In addition to improved local control, a surgical approach also provides more accurate pathological staging and thus more accurate prognostic information, as well as more tissue in which to evaluate molecular markers.

Some investigators have questioned whether chemotherapy in the perioperative setting would still provide a survival advantage if systemic therapy is routinely given to all patients at the first sign of metastatic disease. This question is being directly addressed by a phase 3 trial being done by the European Organisation for Research and Treatment of Cancer and the Southwest Oncology Group. However, the degree of the survival advantage with neoadjuvant chemotherapy in the US study mentioned above, in which most of the patients with metastatic disease presumably did receive systemic therapy, is very similar to studies in the meta-analysis. It thus seems doubtful that delaying chemotherapy until there is evidence of metastatic disease will be an option for limiting therapy to those who need it. This conjecture is supported by the observation that long-term survival of patients with metastatic bladder cancer treated with the combination of methotrexate, vinblastine, doxorubicin, and cisplatin is only 3.7%, and essentially 0% if patients present with visceral metastases and a modestly impaired performance status.^{1,5}

Is there a molecular marker in the tumour that identifies individuals most likely to benefit from chemotherapy? Retrospective analysis of a clinical study suggests that *TP53* mutations may be such a marker, and preclinical studies support the hypothesis that *TP53* mutations predict risk of progression and chemotherapy benefit.⁶⁻⁸ This idea is being directly tested in a large international randomised trial coordinated by the University of Southern California and the Southwest Oncology Group.

In summary, Vale and colleagues' meta-analysis provides strong evidence that neoadjuvant platinum-containing combination chemotherapy improves survival in patients with locally advanced bladder cancer. Their meta-analysis thus defines a new standard of care and is the end of the beginning for combined modality therapy in locally advanced bladder cancer. It is, however, only the beginning of further work, which will need to not only identify far more active regimens in this disease, but also more clearly identify patients who are most likely to benefit from available therapies.

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Cholinergic denervation in diverticular disease

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In today's *Lancet*, Mark Golder and colleagues describe reduced smooth muscle choline acetyltransferase activity, upregulation of M3 receptors, and increased in-vitro sensitivity to acetylcholine in the sigmoid colon of patients with diverticulosis. Their paper is interesting because it suggests a specific defect in cholinergic innervation of the colon in patients with uncomplicated diverticulosis, a previously unreported finding that has clinical implications. Whether the reported changes are primary, or are secondary to injury of another cell type that is tropic to cholinergic nerves, or to diverticulosis itself, remains an open question.

There are some methodological issues in this study that may have influenced some of the results. The investigators focused on M3 receptors expressed on smooth muscle. Several studies have shown that the predominant receptors expressed on intestinal smooth muscle are M2 receptors.¹ However, most of the available data suggest that the predominant pathway in vivo is through the M3 receptor, which validates the decision to focus on the M3 receptor. However, in pathological conditions the contribution of M2 receptors may vary, influencing the reported organ-bath

results and perhaps the differences noted between the muscle layers. The percentage of colon surface area positive for protein gene product 9·5 (PGP 9·5) (reflecting the entire nerve population) reported in Golder's study was lower than in previous reports. About 18% of the volume of the circular muscle layer of the normal sigmoid colon has been reported² as positive for PGP 9·5 compared with the 3·1% in Golder's report. The lower value may have resulted in a higher than expected percentage of total neuronal tissue being reported as positive for choline acetyltransferase. It is also unclear whether the investigators adjusted for any differential change in the thickness of the circular and longitudinal muscle layers occurring as a result of diverticular disease, which would have changed the reported percentages. The values reported for M3 receptors are also open to interpretation. A single receptor cannot be visualised by light microscopy, and therefore detectable fluorescence reflects clusters of receptors. Several hundred receptors can fit within the size of a given pixel, even at the limits of light resolution. Therefore if, for the sake of argument, the preparation had 100 receptors, the digitised image was made up of 100 pixels, and all the receptors were clustered together within one pixel, then the reported percentage of surface area positive for receptors would be 1%. If after denervation there were 20 evenly-spaced clusters of five receptors each, then the surface area occupied by the same number of receptors would be reported as 20%. While smooth muscle cholinergic denervation hypersensitivity has been suggested in studies on mouse stomach lacking interstitial cells of Cajal, it is not known whether such hypersensitivity is accompanied by changes in receptor distribution.

To determine the implications of the findings of Golder and colleagues', one must first consider the medical burden of diverticular disease. A report in 1975³ estimated the prevalence of diverticulosis to be 5% by the age of 40 years, increasing to 65% at 80 years, but there are no recent studies. This supposedly "benign" disease generates considerable morbidity and mortality. Although most people with diverticular disease remain asymptomatic, 10–25% develop symptoms, and of these, 15% will develop clinically significant complications.⁴ Of patients requiring the Hartmann procedure (resection of the sigmoid with formation of colostomy and rectal stump), a third never regain intestinal continuity.⁵ Furthermore, this morbidity may be the tip of the iceberg, because many surgeons will see patients who have been treated for diverticulitis on many previous occasions by primary-care physicians. Diverticular disease is also a major consideration in terms of health-care resources—it is one of the five most costly gastrointestinal disorders affecting the US population.⁶

The development of diverticulae is thought to result from a combination of disorders of both bowel-wall structure and motility. How are structure and function tied together? Goldberg and colleagues postulate that increased expression of M3 receptors is a compensatory mechanism in response to reduced cholinergic innervation and that this increased expression maintains normal tone, until there is external stimulation resulting in increased motility responses. Differential deposition of elastin in the colonic taeniae may result in an inability of this layer to contract in response to acetylcholine, leading to uncoordinated contractions between circular and longitudinal muscle layers and the subsequent outpouching of diverticulae alongside the vasa recta adjacent to the taeniae.

Obviously, this model does not explain why cholinergic innervation is decreased, or even if this decrease is the first step in the disease process. But it does suggest further clinically relevant studies. Does blockade of external stimuli