ORIGINAL ARTICLE

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

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ABSTRACT

BACKGROUND

Radiotherapy is an alternative to cystectomy in patients with muscle-invasive bladder cancer. In other disease sites, synchronous chemoradiotherapy has been associated with increased local control and improved survival, as compared with radiotherapy alone.

METHODS

In this multicenter, phase 3 trial, we randomly assigned 360 patients with muscle-invasive bladder cancer to undergo radiotherapy with or without synchronous chemotherapy. The regimen consisted of fluorouracil (500 mg per square meter of body-surface area per day) during fractions 1 to 5 and 16 to 20 of radiotherapy and mitomycin C (12 mg per square meter) on day 1. Patients were also randomly assigned to undergo either whole-bladder radiotherapy or modified-volume radiotherapy (in which the volume of bladder receiving full-dose radiotherapy was reduced) in a partial 2-by-2 factorial design (results not reported here). The primary end point was survival free of locoregional disease. Secondary end points included overall survival and toxic effects.

RESULTS

At 2 years, rates of locoregional disease–free survival were 67% (95% confidence interval [CI], 59 to 74) in the chemoradiotherapy group and 54% (95% CI, 46 to 62) in the radiotherapy group. With a median follow-up of 69.9 months, the hazard ratio in the chemoradiotherapy group was 0.68 (95% CI, 0.48 to 0.96; P=0.03). Five-year rates of overall survival were 48% (95% CI, 40 to 55) in the chemoradiotherapy group and 35% (95% CI, 28 to 43) in the radiotherapy group (hazard ratio, 0.82; 95% CI, 0.63 to 1.09; P=0.16). Grade 3 or 4 adverse events were slightly more common in the chemoradiotherapy group than in the radiotherapy group during treatment (36.0% vs. 27.5%, P=0.07) but not during follow-up (8.3% vs. 15.7%, P=0.07).

CONCLUSIONS

Synchronous chemotherapy with fluorouracil and mitomycin C combined with radiotherapy significantly improved locoregional control of bladder cancer, as compared with radiotherapy alone, with no significant increase in adverse events. (Funded by Cancer Research U.K.; BC2001 Current Controlled Trials number, ISRCTN68324339.)

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Bladder cancer, with more than 385,000 new cases worldwide in 2008,[1] is a major cause of cancer complications. The median age at diagnosis is over 70 years, and since the tumor often is related to smoking, many patients have a substantial number of coexisting illnesses that pose risks for radical surgical approaches. Survival rates are poor for muscle-invasive bladder cancer, with around 45% of patients surviving for 5 years regardless of the type of treatment.[2-4] Although surgery is considered the standard therapy, considerable interest in bladder preservation has led to the use of radiotherapy as an alternative, particularly in less fit patients. However, radical radiotherapy is associated with a relatively high rate of incomplete response or local recurrence (up to 50%),[5] with salvage cystectomy for treatment failures. Even in the absence of more effective systemic therapy, improving bladder-preservation treatments could provide patients with a choice of treatments and improve quality of life.

Synchronous chemoradiotherapy may have advantages over radiotherapy alone,[6-9] although only one randomized trial has compared these two approaches in bladder cancer.[10] In that study, 99 patients were randomly assigned to undergo radiotherapy with or without cisplatin, followed by elective cystectomy or further radiotherapy. The chemoradiotherapy group had improved survival without pelvic disease progression, but the number of patients was too small to provide reliable estimates of overall survival effects.

Radiosensitization with cisplatin is not ideal for patients with bladder cancer, since many patients who are referred for radiotherapy have impaired renal function or poor performance status. In the Bladder Cancer 2001 (BC2001) trial, we tested the hypothesis that on the basis of our previous phase 1 and 2 data,[11,12] synchronous chemoradiotherapy with fluorouracil and mitomycin C would be more efficacious than radiotherapy alone. In a concurrent randomization, we examined whether reducing the high-dose radiotherapy volume could reduce toxic effects without compromising local control. We report here on the principal analysis of the comparison between chemoradiotherapy and radiotherapy alone.

Methods

Patients

Patients were at least 18 years of age with histologically confirmed stage T2, T3, or T4a bladder cancer (adenocarcinoma or transitional or squamous-cell carcinoma) with no signs of lymph-node involvement or metastasis. The main inclusion criteria were a performance status of 0 to 2, according to World Health Organization criteria; a white-cell count of more than 4000 per cubic millimeter; a platelet count of more than 100,000 per cubic millimeter; a glomerular filtration rate of more than 25 ml per minute; and levels of serum bilirubin and aminotransferase values of less than 1.5 times the upper limit of the normal range. On the basis of results of a meta-analysis[2] and the Medical Research Council BA06 trial (Current Controlled Trials number, ISRCTN82694463),[13] platinum-based neoadjuvant chemotherapy was permitted but not mandatory. The main exclusion criteria were pregnancy, a previous cancer or radiotherapy that was likely to interfere with the protocol treatment, or inflammatory bowel disease.

Trial Design

This unblinded, phase 3 trial was conducted at 45 centers in the United Kingdom. The trial had a partial 2-by-2 factorial design. Patients were randomly assigned (in a 1:1 ratio) to undergo radiotherapy with or without synchronous chemotherapy with fluorouracil and mitomycin C and either whole-bladder radiotherapy or modified-volume radiotherapy to uninvolved bladder. Recruitment to the double randomization was encouraged but optional, since recruitment in this population is challenging.

Independent randomization was conducted by telephone to the Clinical Trials and Statistics Unit at the Institute of Cancer Research. Computer-generated random permuted blocks were used, with stratification according to center, use or nonuse of neoadjuvant chemotherapy, and entry to one or both randomizations. All drugs that were administered in the study were purchased by participating hospitals through standard procurement routes. All patients provided written informed consent. The study protocol is available with the full text of this article at NEJM.org.

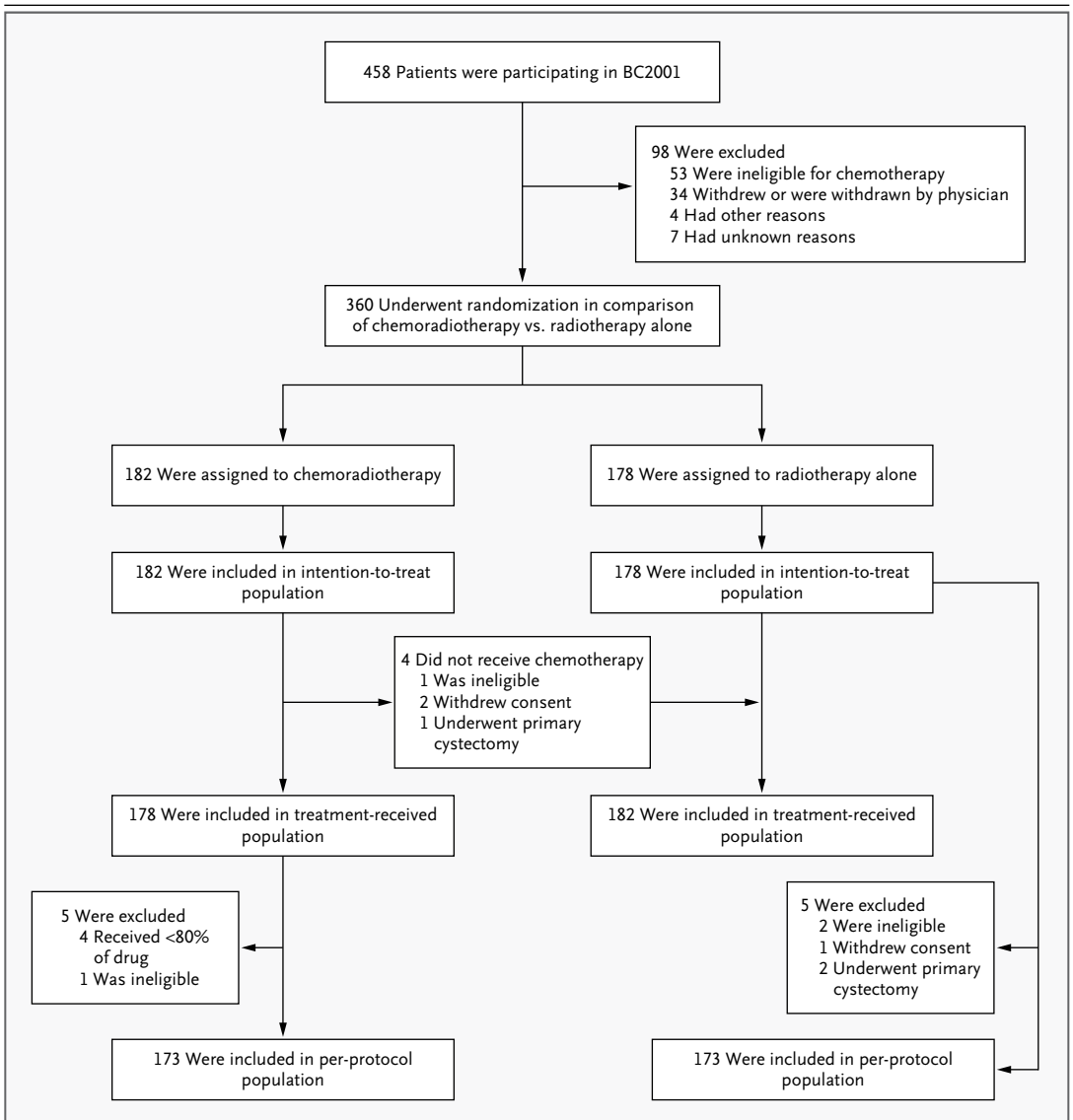


Figure 1. Enrollment and Outcomes.

TREATMENT

Two radiotherapy fractionation schedules were permitted. At the outset of the study, centers could opt to administer either 55 Gy in 20 fractions over a 4-week period or 64 Gy in 32 fractions over a 6.5-week period in all patients. Fluorouracil was administered as a continuous infusion (500 mg per square meter of body-surface area per day) during fractions 1 to 5 and 16 to 20 of radiotherapy (10 days in total). For a majority of patients, this treatment was performed on an outpatient basis through a central catheter. Mitomycin C was administered as an intravenous bolus dose of 12 mg per square meter on day 1.

Dose modifications for both chemotherapy and radiotherapy were permitted. In brief, the protocol recommended reducing or omitting chemotherapy before interrupting radiotherapy in an effort to maximize delivery of the core therapy.

ASSESSMENTS

At baseline, all patients underwent physical examination, hematologic and biochemical analyses, assessment of bladder capacity, computed tomography (CT) of the abdomen and pelvis, chest radiography or CT, and examination under anesthesia plus cystoscopic resection of tumor and biopsy. The tumor–node–metastasis classification (1997)[14] was used for staging purposes.

TUMOR CONTROL

We assessed tumor control by means of physical examination, chest radiography, and rigid or flexible cystoscopy at 6, 9, and 12 months after randomization and annually for up to 5 years. Biopsy of the tumor bed and normal bladder was mandated at 6 months and was repeated as indicated at subsequent visits. CT of the abdomen and pelvis was performed at 1 and 2 years after randomization and then as indicated.

ADVERSE EVENTS

We graded acute side effects weekly during treatment using National Cancer Institute Common Toxicity Criteria, version 2.[15] We assessed late toxicity using the criteria of the Radiation Therapy Oncology Group (RTOG)[16] and Late Effects of Normal Tissue (Subjective, Objective, and Management

Table 1. Patient and Tumor Characteristics at Baseline.*

Characteristic	Chemoradiotherapy (N=182)	Radiotherapy (N=178)	All Patients (N=360)
Radiotherapy — no. (%)†			
Whole-bladder radiotherapy (randomized)	31 (17.0)	32 (18.0)	63 (17.5)
Modified-volume radiotherapy	33 (18.1)	25 (14.0)	58 (16.1)
Whole-bladder radiotherapy (not randomized)	118 (64.8)	121 (68.0)	239 (66.4)
Sex — no. (%)			
Male	149 (81.9)	140 (78.7)	289 (80.3)
Female	33 (18.1)	38 (21.3)	71 (19.7)
WHO performance status — no. (%)‡			
0	114 (62.6)	118 (66.3)	232 (64.4)
1	63 (34.6)	54 (30.3)	117 (32.5)
2	5 (2.7)	6 (3.4)	11 (3.1)
Age — yr			
Median	72.3	71.2	71.9
Interquartile range	65.1–76.6	63.7–75.9	64.1–76.2
Pathological stage of primary tumor — no. (%)			
1	0	1 (0.6)§	1 (0.3)
2	154 (84.6)	143 (80.3)	297 (82.5)
3a	10 (5.5)	15 (8.4)	25 (6.9)
3b	11 (6.0)	11 (6.2)	22 (6.1)
4a	7 (3.8)	7 (3.9)	14 (3.9)
Unknown	0	1 (0.6)	1 (0.3)
Transitional-cell carcinoma — no. (%)	177 (97.3)	175 (98.3)	352 (97.8)
Tumor resection — no. (%)¶			
Not resected	5 (2.7)	4 (2.2)	9 (2.5)
Biopsy	22 (12.1)	9 (5.1)	31 (8.6)
Complete resection	103 (56.6)	95 (53.4)	198 (55.0)
Incomplete resection	48 (26.4)	67 (37.6)	115 (31.9)
Unknown	4 (2.2)	3 (1.7)	7 (1.9)

Table 1. (Continued.)

Characteristic	Chemoradiotherapy (N=182)	Radiotherapy (N=178)	All Patients (N=360)
Residual mass after resection — no. (%)¶			
Yes	48 (26.4)	52 (29.2)	100 (27.8)
No	122 (67.0)	117 (65.7)	239 (66.4)
Unknown	12 (6.6)	9 (5.1)	21 (5.8)
Neoadjuvant chemotherapy planned — no. (%)‖			
Yes	57 (31.3)	61 (34.3)	118 (32.8)
No	125 (68.7)	117 (65.7)	242 (67.2)
Planned radiotherapy schedule — no. (%)			
55 Gy in 20 fractions	71 (39.0)	71 (39.9)	142 (39.4)
64 Gy in 32 fractions	111 (61.0)	106 (59.6)	217 (60.3)
Unknown	0	1 (0.6)	1 (0.3)

* There were no significant differences between groups except that a higher proportion of patients in the chemoradiotherapy group underwent tumor biopsy (P=0.01). WHO denotes World Health Organization.
† Participation in the full 2-by-2 randomization was encouraged but not mandatory, and some patients (e.g., those with multiple tumors) were eligible only for the comparison between chemoradiotherapy and radiotherapy alone; these patients all received standard whole-bladder radiotherapy. In addition, the radiotherapy-volume randomization was closed in September 2006, and all patients who were subsequently enrolled received whole-bladder radiotherapy.
‡ WHO performance status ranges from 0 to 5, with 0 indicating perfect health and 5 indicating death.
§ This tumor was deemed to be pathological stage T1, but radiologic staging confirmed the tumor as T3. Therefore, the patient was not considered to be ineligible for the trial.
¶ Findings are from cystoscopy before radiotherapy but may have been obtained after primary debulking or neoadjuvant chemotherapy and hence are not always for the first cystoscopy.
‖ Two patients (one each in the chemoradiotherapy and radiotherapy groups) planned to receive neoadjuvant chemotherapy but did not receive it. One patient in the radiotherapy group did not plan to receive neoadjuvant chemotherapy but did receive it.

elements) (LENT/SOM)[17,18] at 6, 9, and 12 months after randomization and annually thereafter (as described in the Supplementary Appendix, available at NEJM.org). Bladder capacity was measured at 1 and 2 years after randomization.

END POINTS

The primary end point was locoregional disease–free survival, which was defined as the rate of survival free of recurrence in pelvic nodes or bladder, with data censored at the first sign of metastasis (if this occurred ≥30 days before locoregional failure), a second primary tumor, or death. Secondary end points were disease-free survival (with data censored at the occurrence of a second primary tumor or death from a cause other than bladder cancer), metastasis-free survival, and toxic effects at 1 year, 2 years, and throughout follow-up, as assessed by the worst grade of toxicity, change in bladder capacity, and quality of life (data not shown). Tertiary end points were acute toxic effects (worst grade during treatment); cystoscopic local control at 6 months, 1 year, and 2 years; the rate of salvage cystectomy; and overall survival. We also analyzed exploratory end points of the time to invasive locoregional recurrence and death from bladder cancer. Survival outcomes were measured from the time of randomization.

STATISTICAL ANALYSIS

We originally determined that an enrollment of 460 patients (194 events) would provide a power of 90% to detect an improvement of 15 percentage points (from 50% to 65%) in the primary end point in the chemoradiotherapy group, as compared with the radiotherapy group, at 2 years (hazard ratio, 0.62) with a two-sided alpha level of 0.05. In 2005, with the support of the independent trial steering committee, we reduced the power to 80% because of slow recruitment. The revised target sample size was 350 patients (140 events).

Primary analyses included all patients who underwent randomization and were conducted on the intention-to-treat principle for efficacy outcomes and according to treatment received for toxicity end points. A P value of 0.05 was considered to

indicate statistical significance, and 95% confidence intervals were used unless otherwise stated. All analyses were adjusted for randomization to a radiotherapy group (whole-bladder radiotherapy, modified-volume radiotherapy, or no randomization).

We used a stratified log-rank test to analyze survival end points and time to cystectomy. For survival end points, we used the Cox model to calculate absolute differences and hazard ratios (with a hazard ratio <1 favoring chemoradiotherapy). The proportional hazards assumption of the Cox model, which was tested with the use of Schoenfeld residuals, held for the primary end point and two secondary end points (disease-free survival and time to invasive locoregional recurrence) but did not hold for the time to cystectomy, and there were slight departures for overall, bladder-cancer–specific, and metastasis-free survival.

We analyzed adverse events by comparing the proportion of grade 3 or 4 adverse events using a stratified Mantel–Haenszel test. To avoid interpreting disease symptoms as side effects, late toxicity data were censored 3 months before recurrence, occurrence of a second primary tumor, or death from bladder cancer. To adjust for multiple testing, a significance level of 1% was used for all toxicity end points; accordingly, 99% confidence intervals are provided.

The presence of an interaction between chemotherapy and radiotherapy volume was tested for all survival and toxicity outcomes, but the tests had low power as only 121 patients were randomly assigned to both comparisons.

Sensitivity analyses were conducted in patients without major protocol violations (i.e., per protocol). Hazard ratios that were adjusted for the use of neoadjuvant chemotherapy, age, radiotherapy dose, tumor stage, performance status, and tumor grade were calculated to assess robustness of the results. A frailty model adjusting for center was fitted but showed no significant center effect on any outcome. A competing risks analysis was conducted for the primary outcome with the use of distant events (metastasis or death from bladder cancer) and nondisease events (second primary tumor or death from a cause other than bladder cancer) as competing risks. Consistency of treatment effect was assessed, fitting interaction terms with four prespecified demographic or clinical characteristics into Cox models for all survival outcomes; these tests are reported for the primary outcome only. Post hoc interaction tests were conducted for two further characteristics but these showed no clinically important results and so are not presented. No formal adjustments for multiplicity were used. These sensitivity analyses provided results similar to those in the main analysis (data not shown).

Time-to-event analyses were based on a database snapshot taken on November 2, 2011. All other analyses were based on a database snapshot taken on April 27, 2010. All analyses were conducted with the use of Stata 10 software (StataCorp) except competing risk analyses, conducted in R (R Development Core Team).

RESULTS

PATIENTS

From August 2001 through April 2008, a total of 458 patients were recruited (Fig. 1). Of these patients, 360 (from 43 centers) underwent randomization to either the chemoradiotherapy group (182 patients) or the radiotherapy group (178 patients). In addition, 219 patients underwent randomization to two radiotherapy groups (either whole-bladder or modified-volume); 121 patients underwent randomization in both comparisons. Baseline characteristics were well balanced in the two study groups (Table 1). Median follow-up in the chemoradiotherapy randomization was 69.9 months (interquartile range, 50.1 to 84.1). Compliance with follow-up was good, with no evidence of differences between the two study groups.

Overall, 173 of 182 patients (95.1%) in the chemoradiotherapy group and 170 of 178 patients (95.5%) in the radiotherapy group completed radiotherapy at the target dose, with 172 patients (94.5%) and 166 patients (93.3%), respectively, receiving the target dose with a delay of less than 1 week. In the chemoradiotherapy group, 174 patients (95.6%) received at least 80% of the target mitomycin C dose; 171 patients (94.0%) and 146 patients (80.2%) received 80% of the fluorouracil dose during week 1 and week 4, respectively. Another 6 patients (3.3%) received a reduced fluorouracil dose in week 1, and 10 patients (5.5%) received a reduced fluorouracil dose in week 4. Reasons for chemotherapy noncompliance were mostly toxicity-related.

Table 2. Worst Grade of Toxic Effects, According to Toxicity Criteria.*

Toxicity Criteria and Worst Grade	Chemoradiotherapy (N=178)	Radiotherapy (N=182)	Odds Ratio (99% CI)†	P Value‡
	no. (%)			
NCI CTCAE				
Any event				
Patients with data	178 (100.0)	182 (100.0)		
Grade 3–5	64 (36.0)	50 (27.5)	1.51 (0.83–2.74)	0.07
Genitourinary				
Patients with data	178 (100.0)	182 (100.0)		
Grade 3–5	38 (21.3)	39 (21.4)	1.00 (0.52–1.95)	0.99
Gastrointestinal				
Patients with data	178 (100.0)	182 (100.0)		
Grade 3–5	17 (9.6)	5 (2.7)	3.84 (0.97–15.19)	0.007
RTOG				
At 1 yr				
Patients with data	92 (51.7)	78 (42.9)		
Grade 3–4	3 (3.3)	1 (1.3)	2.88 (0.15–56.95)	0.34
At 2 yr				
Patients with data	65 (36.5)	58 (31.9)		
Grade 3–4	3 (4.6)	3 (5.2)	0.90 (0.11–7.21)	0.90
Overall follow-up§				
Patients with data	120 (67.4)	108 (59.3)		
Grade 3–4	10 (8.3)	17 (15.7)	0.48 (0.16–1.42)	0.07
LENT/SOM				
At 1 yr				
Patients with data	77 (43.3)	75 (41.2)		
Grade 3–4	29 (37.7)	22 (29.3)	1.42 (0.58–3.48)	0.31
At 2 yr				
Patients with data	61 (34.3)	53 (29.1)		
Grade 3–4	21 (34.4)	19 (35.8)	0.94 (0.35–2.55)	0.87
Overall follow-up§				
Patients with data	117 (65.7)	100 (54.9)		
Grade 3–4	63 (53.8)	51 (51.0)	1.10 (0.54–2.25)	0.72

* Four patients in the chemoradiotherapy group did not actually receive chemotherapy, so they were included in the radiotherapy group for the safety analysis. LENT/SOM denotes Late Effects of Normal Tissue (Subjective, Objective, and Management elements), NCI CTCAE National Cancer Institute Common Toxicity Criteria for Adverse Events, and RTOG Radiation Therapy Oncology Group.
† Odds ratio are for the chemoradiotherapy group, as compared with the radiotherapy group.
‡ P values were calculated by means of the stratified Mantel–Haenszel test.
§ Follow-up includes all visits from 6 months to 5 years after randomization.

ADVERSE EVENTS

Four patients in the chemoradiotherapy group did not actually receive chemotherapy, so they were included in the radiotherapy group for the safety analysis. There was weak evidence of increased acute grade 3 or 4 adverse events in the chemoradiotherapy group (Table 2). Grade 3 or 4 toxic effects occurred in 64 of 178 patients (36.0%) in the chemoradiotherapy group, as compared with 50 of 182 patients (27.5%) in the radiotherapy group (P=0.07). These events were primarily gastrointestinal toxic effects, with 17

events (9.6%) in the chemoradiotherapy group versus 5 events (2.7%) in the radiotherapy group (P=0.007).

Grade 3 or 4 RTOG adverse events occurred at some point during follow-up in 10 of 120 patients (8.3%) in the chemoradiotherapy group and 17 of 108 (15.7%) in the radiotherapy group at some point during follow-up (Table 2). At 1 year, grade 3 or 4 RTOG adverse events (all genitourinary symptoms) were reported in 3 of 92 patients (3.3%) in the chemoradiotherapy group and 1 of 78 patients (1.3%) in the radiotherapy group (P=0.34) (Table 2). Grade 3 or 4 LENT/SOM toxicity occurred in 29 of 77 patients (37.7%) in the chemoradiotherapy group and 22 of 75 patients (29.3%) in the radiotherapy group (P=0.31). When sexual dysfunction was excluded, the corresponding numbers were 13 of 77 patients (16.9%) in the chemoradiotherapy group and 12 of 75 (16.0%) in the radiotherapy group (P=0.91). At 1 and 2 years, there was no significant between-group difference in changes in bladder volume. The reduction in bladder volume in the chemoradiotherapy group was 1.3 ml (99% CI, –112.1 to 114.8) less than in the radiotherapy group at 1 year and 55.6 ml (99% CI, –64.3 to 175.5) less at 2 years, although data were available for only 78 of 360 patients (22%) at 1 year and 51 of 360 patients (14%) at 2 years.

PRIMARY OUTCOME

Locoregional disease–free survival was significantly better in the chemoradiotherapy group than in the radiotherapy group, with 2-year recurrence-free rates of 67% (95% CI, 59 to 74) in the chemoradiotherapy group versus 54% (95% CI, 46 to 62) in the radiotherapy group, for an estimated absolute difference of 12 percentage points (95% CI, 1.3 to 20) (hazard ratio in the chemoradiotherapy group, 0.68; 95% CI, 0.48 to 0.96; P=0.03) (Fig. 2A). The hazard ratio for the primary end point (after adjustment for neoadjuvant chemotherapy, age, radiotherapy dose, tumor stage, performance status, and tumor grade) was 0.66 (95% CI, 0.46 to 0.95; P=0.03). The chemotherapy effect did not vary significantly between radiotherapy subgroups or with neoadjuvant therapy (Fig. 3). Relapses that contributed to reductions in the primary outcome were invasive bladder cancer in 20 patients (11.0%) in the chemoradiotherapy group and 34 (19.1%) in the radiotherapy group, non–muscle-invasive bladder cancer in 26 patients (14.3%) in the chemoradiotherapy group and 30 (16.9%) in the radiotherapy group, and pelvic node relapse in 9 patients (4.9%) in the chemoradiotherapy group and 12 (6.7%) in the radiotherapy group.

Figure 2 (facing page). Kaplan–Meier Analysis of Survival.

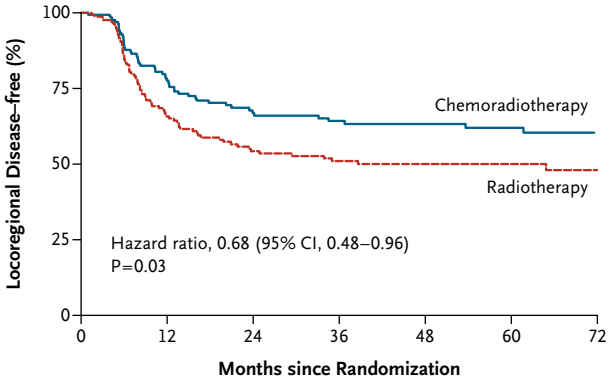
Shown are the patients' rates of survival free of locoregional disease (Panel A), survival free of invasive locoregional disease (Panel B), and overall survival (Panel C) during 72 months of follow-up. P values were calculated by log-rank test stratified according to the radiotherapy treatment group.

SECONDARY OUTCOMES

For the secondary outcomes, an exploratory analysis of invasive locoregional disease showed a 2-year relapse rate of 18% in the chemoradiotherapy group versus 32% in the radiotherapy group (hazard ratio, 0.57; 95% CI, 0.37 to 0.90; P=0.01) (Fig. 2B). Chemoradiotherapy was associated with a trend toward a reduction in cystectomy, with a 2-year rate of 11.4% (95% CI, 7.1 to 18.0) in the chemoradiotherapy group versus 16.8% (95% CI, 11.6 to 23.9) in the radiotherapy group (P=0.07), although the comparison was underpowered. Of the 51 cystectomies that were performed, 41 (80.4%) were for recurrence (27 for invasive disease, 9 for non–muscle-invasive disease, and 5 for an unknown type of recurrence); 4 were performed for late effects of radiotherapy.

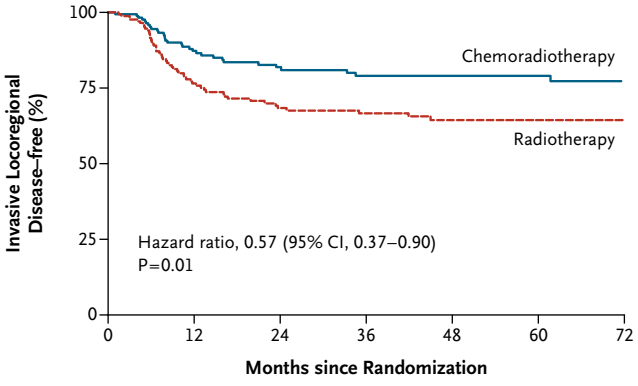
Overall, there were 208 deaths (98 in the chemoradiotherapy group and 110 in the radiotherapy group). Five-year overall survival rates were 48% (95% CI, 40 to 55) in the chemoradiotherapy group versus 35% (95% CI, 28 to 43) in the radiotherapy group, for an estimated absolute difference of 7% (95% CI, –3 to 17). The hazard ratio for overall survival in the chemoradiotherapy group was 0.82 (95% CI, 0.63 to 1.09; P=0.16) with little between-group divergence until at least 2 years (Fig. 2C). There were 166 deaths from bladder cancer: 74 in the chemoradiotherapy group and 92 in the radiotherapy group (hazard ratio, 0.77; 95% CI, 0.57 to 1.05; P=0.10). Disease-free and metastasis-free survival data are provided in Figures 1A and 1B in the Supplementary Appendix.

A Locoregional Disease–free Survival



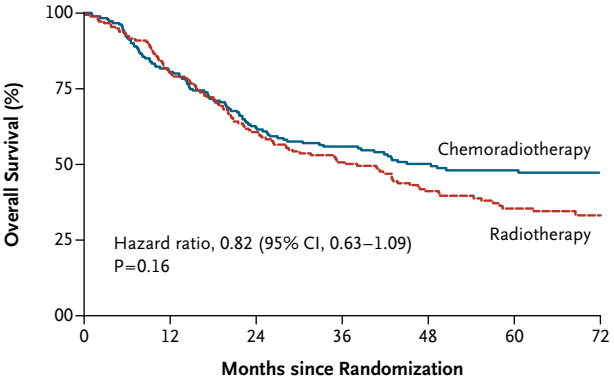
No. at Risk (no. of events)							
Chemoradiotherapy	182 (35)	108 (14)	76 (3)	66 (1)	56 (1)	46 (1)	25
Radiotherapy alone	178 (54)	96 (16)	69 (4)	58 (1)	44 (0)	35 (1)	18

B Invasive Locoregional Disease–free Survival



No. at Risk (no. of events)							
Chemoradiotherapy	182 (20)	121 (7)	93 (3)	79 (0)	66 (0)	54 (1)	32
Radiotherapy alone	178 (37)	109 (11)	85 (2)	74 (2)	52 (0)	39 (0)	20

C Overall Survival



No. at Risk (no. of events)							
Chemoradiotherapy	182 (35)	144 (33)	111 (11)	94 (9)	75 (3)	62 (1)	39
Radiotherapy alone	178 (35)	141 (34)	104 (17)	85 (15)	60 (7)	41 (2)	20

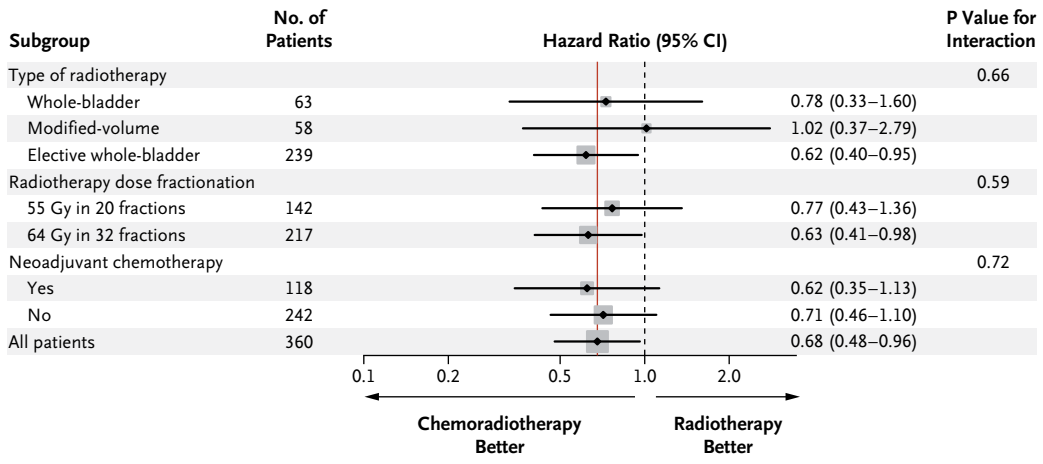


Figure 3. Effect of Chemoradiotherapy on Locoregional Disease–free Survival, According to Subgroup.

The initial randomization to either whole-bladder or modified-volume radiotherapy closed in September 2006, after which all patients underwent randomization into the chemoradiotherapy group or the radiotherapy group and received whole-bladder radiotherapy. The red vertical line indicates the hazard ratio from the primary analysis.

DISCUSSION

In this randomized, phase 3 trial with a median follow-up of 69.9 months, the addition of chemotherapy to standard-dose radiotherapy was associated with a relative reduction of 33% in the risk of locoregional recurrence with a reduction of almost 50% in invasive recurrence. This benefit appeared consistent in preplanned subgroup analyses and was not affected by a history of previous neoadjuvant chemotherapy, which suggests that neoadjuvant and concomitant chemotherapy confer separate benefits on distant and local control, respectively. The improvement in locoregional control was achieved with modest increases in acute toxic effects that did not reach statistical significance with respect to grade 3 or 4 outcomes. We were concerned that the more intensive therapy, particularly when given after neoadjuvant chemotherapy, would result in impaired late bladder function. However, late toxicity, as measured with the use of RTOG and LENT/SOM scales, showed no significant increase in the chemoradiotherapy group. Likewise, we were unable to detect any significant effect of chemoradiotherapy on bladder volume.

We chose locoregional disease–free survival as the primary outcome measure because it is known that there is a high rate of micrometastasis in apparently localized disease, as evidenced by the poor 5-year survival rate seen with surgery alone and the effect on survival of neoadjuvant chemotherapy.[2,13] Fluorouracil and mitomycin C are known to radiosensitize tumors but would not be expected to have significant activity on systemic disease at the dose and schedule tested. The early separation of curves for locoregional disease–free survival is consistent with the expected mode of action. A reduced rate of invasive locoregional relapse might translate into improved survival (especially if salvage cystectomy cannot be used) but would be expected to occur late. However, there was a trend toward an increased rate of salvage cystectomy in the radiotherapy group (20 patients in the chemoradiotherapy group vs. 31 in the radiotherapy group) for a hazard ratio of 0.58 (95% CI, 0.33 to 1.03; P=0.07). This increased rate of cystectomy might be expected to reduce any overall survival benefit for chemoradiotherapy over radiotherapy, an effect also seen in the trials involving patients with anal cancer.[9] The overall survival curves begin to separate at around 2 years, but with a hazard ratio that did not reach statistical significance (0.82; 95% CI, 0.63 to 1.09; P=0.16), consistent with this hypothesis. Similar effects have been seen in other studies with disease-free survival as the primary outcome and the availability of salvage therapies (e.g., in trials of pazopanib in renal cancer).[19] Patients continue to be followed in order to fully understand the effect of chemo-

radiotherapy on survival. Our data show that effective radiosensitization in this tumor type can be achieved without the need to use cisplatin, and the findings duplicate those in studies involving patients with anal cancer.[9,20,21] The low overall rate of isolated nodal relapse is also noteworthy, since no attempt was made to include pelvic nodes in the radiotherapy planning target volume. Given issues of comorbidity, hydronephrosis and impaired renal function in many patients with bladder cancer, the combination of fluorouracil and mitomycin C might be a suitable choice for radiosensitization in bladder-cancer treatment.

An alternative approach to radiosensitization would be to address tumor hypoxia, as reported in another phase 3 trial, the Bladder Carbogen Nicotinamide (BCON) study (ISRCTN45938399), in the United Kingdom. In that trial, 333 patients were randomly assigned to undergo either radiotherapy alone or radiotherapy with synchronous nicotinamide and carbogen.[22] Analysis of the primary outcome of 3-year locoregional relapse–free survival (including invasive locoregional disease recurrence and death as events) did not meet statistical significance (54% for combined therapy vs. 43% for radiotherapy alone; hazard ratio, 0.88; 95% CI, 0.76 to 1.01; P=0.06), although significant improvements in 3-year overall survival were reported (59% for combined therapy vs. 46% for radiotherapy alone; hazard ratio, 0.86; 95% CI, 0.74 to 0.99; P=0.04). No increase in the rate of acute toxic effects was noted with combined therapy.

Although further clinical trials to refine and improve chemoradiotherapy schedules are warranted, our study shows that the addition of chemotherapy to radiotherapy improved local control, particularly freedom from invasive recurrence, as compared with radiotherapy alone, and resulted in good long-term bladder function and low rates of salvage cystectomy, all of which are of major importance in this elderly, relatively frail group of patients. The benefit of synchronous chemotherapy was consistent across both radiation fractionation schedules. Thus, it may be time to reevaluate the relative roles of bladder preservation and surgery in the treatment of muscle-invasive bladder cancer, particularly for patients at high risk for complications from surgery.

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REFERENCES

1. GLOBOCAN 2008: cancer incidence, mortality and prevalence worldwide in 2008. Lyon, France: International Agency for Research on Cancer (http://globocan.iarc.fr).
2. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-66. [Erratum, N Engl J Med 2003;349:1880.]
3. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666-75.
4. Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002;20:3061-71.
5. Cooke PW, Dunn JA, Latief T, Bathers S, James ND, Wallace DM. Long-term risk of salvage cystectomy after radiotherapy for muscle-invasive bladder cancer. Eur Urol 2000;38:279-86.
6. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-61. [Erratum, N Engl J Med 1999;341:708.]
7. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-53. [Erratum, N Engl J Med 1999;341:708.]
8. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-43.
9. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin. Lancet 1996;348:1049-54.
10. Coppin CM, Gospodarowicz MK, James K, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. J Clin Oncol 1996;14:2901-7.
11. Hussain SA, Moffitt DD, Glaholm JG, Peake D, Wallace DM, James ND. A phase II study of synchronous chemoradiotherapy for locally advanced bladder cancer. Br J Cancer 2001;85:16.
12. *Idem*. A phase I/II study of synchronous chemoradiotherapy for poor prognosis locally advanced bladder cancer. Ann Oncol 2001;12:929-35.
13. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. Lancet 1999;354:533-40. [Erratum, Lancet 1999;354:1650.]
14. International Union against Cancer. TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss, 2002.
15. National Cancer Institute. Common Toxicity Criteria, version 2 (http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf).
16. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-6.

17. Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH. Overview: Late Effects of Normal Tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys 1995;31:1041-2.
18. Pavy JJ, Denekamp J, Letschert J, et al. Late effects toxicity scoring: the SOMA scale. Radiother Oncol 1995;35:11-5.
19. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2011;28:1061-8.
20. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008; 299:1914-21.
21. Olivatto LO, Cabral V, Rosa A, et al. Mitomycin-C- or cisplatin-based chemoradiotherapy for anal canal carcinoma: long-term results. Int J Radiat Oncol Biol Phys 2011;79:490-5.
22. Hoskin PJ, Rojas AM, Bentzen SM, Saunders MI. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. J Clin Oncol 2010;28: 4912-8.