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► To cite this version:

Constance Le Goux, Yann Neuzillet, Mathieu Rouanne, Julie Gachet, Fabrice Staub, et al.. Prognosis of patients receiving induction chemotherapy for locally advanced or lymph node metastatic bladder cancer. *Journal of Clinical Urology*, 2020, 13 (6), pp.425-436. 10.1177/2051415819895865. hal-03032266

HAL Id: hal-03032266

<https://hal.science/hal-03032266>

Submitted on 28 Jan 2021

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**PROGNOSIS OF PATIENTS RECEIVING INDUCTION
CHEMOTHERAPY FOR LOCALLY ADVANCED OR LYMPH-NODE
METASTATIC BLADDER CANCER**

Journal:	<i>Journal of Clinical Urology</i>
Manuscript ID	Draft
Manuscript Type:	Cohort Study
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Le Goux, Constance; Hospital Foch, Urology; Versailles Saint-Quentin-en-Yvelines University Faculty of Medicine Paris Ile de France Ouest, Urology</p> <p>Neuzillet, Yann; Hospital Foch, Urology; Versailles Saint-Quentin-en-Yvelines University Faculty of Medicine Paris Ile de France Ouest, Urology</p> <p>Rouanne, Mathieu; Hospital Foch, Urology; Versailles Saint-Quentin-en-Yvelines University Faculty of Medicine Paris Ile de France Ouest, Urology</p> <p>Gachet, Julie; Hospital Foch, Medical Oncology</p> <p>Staub, Fabrice; Hospital Foch, Radiology</p> <p>Hervé, Jean-Marie; Hospital Foch, Urology</p> <p>Yonneau, Laurent; Hospital Foch, Urology</p> <p>Abdou, Ali; Hospital Foch, Urology</p> <p>Ghoneim, Tarek; Hospital Foch, Urology</p> <p>Théodore, Christine; Hospital Foch, Medical Oncology</p> <p>Lebret, Thierry; Hospital Foch, Urology; Versailles Saint-Quentin-en-Yvelines University Faculty of Medicine Paris Ile de France Ouest, Urology</p>
Keywords:	muscle invasive bladder cancer, locally advanced bladder cancer, neoadjuvant chemotherapy, induction chemotherapy, cystectomy
Abstract:	<p>Background Induction chemotherapy is recommended before surgery for unresectable muscle-invasive bladder cancer (MIBC), locally advanced or lymph-node disseminated disease. These patient's prognosis cannot be extrapolated from data regarding neoadjuvant chemotherapy, which is performed in operable patients.</p> <p>Objective We assessed the prognosis of patients undergoing induction chemotherapy for locally advanced or lymph-node metastatic bladder cancer.</p> <p>Methods We analyzed patients with cT4NxM0 or cTxN+M0 bladder cancer treated by induction chemotherapy between 2006 and 2016. The tumor extension and node invasion was determined by imaging or histologically after upfront lymph-node dissection. Clinical, biological, pathological and patient follow up data were identified. Kaplan-Meier survival curves were compared by log rank test. Factors associated with the response to induction chemotherapy, operability of patients and survival were determined by multivariable logistic regression.</p>

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	<p>Results Among 70 patients included in the analysis, 51 (73%) showed response to induction chemotherapy. Progression-free and overall survival were improved in responder patients compared to non-responders ($p < 0.0001$ and $p = 0.025$, respectively) and for patients who underwent surgery compared to the non-operated patients (both $p < 0.001$). On multivariable analysis, poor response was associated with chemotherapy other than methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) ($p = 0.016$), operability with late response ($p = 0.0024$) and overall survival with surgery after induction chemotherapy ($p = 0.0014$).</p> <p>Conclusions Surgery after induction chemotherapy with MVAC may improve prognosis with locally advanced or lymph node metastatic bladder cancer.</p>

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3 Declaration.
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- 6 1. None of the authors has a conflict of interest in the
-
- 7 topic of this study
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- 8 2. No funding received
-
- 9 3. No Research involving Human Participants and/or Animals
-
- 10 4. Written informed consent was obtained from the patient(s)
-
- 11 for their anonymized information to be published in this
-
- 12 article
-
- 13
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- 14 5. Guarantor : Prof. Thierry LEBRET (TL)
-
- 15 6. Contributorship: CLG Data collection, data analysis and
-
- 16 Manuscript writing; YN protocol development, data
-
- 17 analysis and project development and Manuscript writing;
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- 18 MR Data collection; JG Data collection; FS Data
-
- 19 collection; JMH Data collection; LY Data collection; AA
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- 20 Data collection; TG Data collection and Manuscript
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- 21 Writing; CT Protocol/project development; TL
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- 22 Protocol/project development
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- 24 7. Acknowledgements: none
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ABSTRACT*Background*

Induction chemotherapy is recommended before surgery for unresectable muscle-invasive bladder cancer (MIBC), locally advanced or lymph-node disseminated disease. These patient's prognosis cannot be extrapolated from data regarding neoadjuvant chemotherapy, which is performed in operable patients.

Objective

We assessed the prognosis of patients undergoing induction chemotherapy for locally advanced or lymph-node metastatic bladder cancer.

Methods

We analyzed patients with cT4NxM0 or cTxN+M0 bladder cancer treated by induction chemotherapy between 2006 and 2016. The tumor extension and node invasion was determined by imaging or histologically after upfront lymph-node dissection. Clinical, biological, pathological and patient follow up data were identified. Kaplan-Meier survival curves were compared by log rank test. Factors associated with the response to induction chemotherapy, operability of patients and survival were determined by multivariable logistic regression.

Results

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3 Among 70 patients included in the analysis, 51 (73%) showed response to induction
4 chemotherapy. Progression-free and overall survival were improved in responder
5 patients compared to non-responders ($p < 0.0001$ and $p = 0.025$, respectively) and for
6 patients who underwent surgery compared to the non-operated patients (both
7 $p < 0.001$). On multivariable analysis, poor response was associated with chemotherapy
8 other than methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) ($p = 0.016$),
9 operability with late response ($p = 0.0024$) and overall survival with surgery after
10 induction chemotherapy ($p = 0.0014$).
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27 *Conclusions*

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29 Surgery after induction chemotherapy with MVAC may improve prognosis with locally
30 advanced or lymph node metastatic bladder cancer.
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37 Key words: muscle invasive bladder cancer, locally advanced bladder cancer,
38 neoadjuvant chemotherapy, induction chemotherapy, cystectomy
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42 Level of Evidence: 4
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BACKGROUND

Unresectable muscle-invasive bladder cancer (MIBC) are defined by a locally advanced disease or associated lymph node metastasis. Unresectable MIBC patients are not considered suitable for upfront surgery and induction chemotherapy is recommended [1, 2]. The chemotherapy aims to improve the overall survival of the patient, but the potential benefit of the therapy cannot be extrapolated from studies of neoadjuvant chemotherapy, achieved in patients who can immediately undergo surgery. Indeed, within the meta-analysis of 2688 patients that reported a 5% improvement in overall survival with neoadjuvant chemotherapy, only 4% of patients harbored cN1-3 cancers [3]. Nevertheless, the same cisplatin-based regimens are considered as the gold standard treatment, considering some data showed a comparable objective response rates with gemcitabine-cisplatin and with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) regimens in induction chemotherapy [2, 4]. The oncological outcome with chemotherapy regimens without cisplatin have been described as less efficient [5, 6]. Notwithstanding, some authors recommend the use of regimens without cisplatin, acknowledging that 50% of patients are unfit for a cisplatin-based chemotherapy in the locally advanced NMIBC setting [4, 7–9]. The rationale for performing such induction chemotherapy without cisplatin, is that suboptimal chemotherapy is better than nothing.

Irrespective of the kind of chemotherapy regimen, the optimal number of cycles for induction chemotherapy has not been determined. That number must reconcile two objectives: in one hand, an objective response must be observed, meaning that the

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3 amount of cycle is sufficient; in the other hand, the patient's overall health must be
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5 consistent with the radical surgery. In current practices, induction chemotherapy
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7 involves 4 to 8 cycles. No evidence exists regarding the optimal protocol for this
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9 induction chemotherapy and surgery combination, and the subsequent outcome at the
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11 end of this treatment.
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16 Bearing in mind the need investigates the objective response and prognosis of
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18 patients receiving induction chemotherapy for MIBC non-eligible for upfront surgery,
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20 the objectives of this study were to define the objective response rate during induction
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22 chemotherapy, and the subsequent progression-free survival (PFS) and overall survival
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24 (OS) according both to the response to induction chemotherapy, and the completion
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26 of the radical cystectomy.
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38 **MATERIALS AND METHODS**

39 Patients and Samples

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41 Data from patients with locally advanced (cT4NxM0) or lymph-node invasion (cTxN+)
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43 MIBC treated with induction chemotherapy in our center between September 2006 and
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45 February 2016 were collected. The study was approved by the local ethic and research
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47 committee. Tumors were graded according to the OMS 2004 tumor-grading scheme
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49 [10] and were re-staged according to the 2009 TNM classification of bladder tumors
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51 [11]. The tumor and lymph-node invasion were determined by either CT or PET/CT.
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3 Alternatively, lymph-node invasion was determined histologically with a upfront
4 lymph-node dissection.
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8 The objective response to induction chemotherapy was assessed through repeated CT
9 or PET /CT (according to modality used for initial staging), and performed between the
10 third and the sixth cycles of induction chemotherapy. For conventional imaging, the
11 response to induction chemotherapy was defined as complete response or partial
12 response according to RECIST 1.1 criteria [12]. Using PET/CT, complete response was
13 defined by the total disappearance of abnormal uptake [13, 14]. Surgery could be
14 performed when objective response allowed the resection of all lesions defined on
15 imaging. Late response was defined surgery was allowed when achieved after more
16 than 8 courses of induction chemotherapy. Standard follow-up visits were performed
17 according to current guidelines.
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37 The studied variables were:

- 38 • Cinical features:
 - 39 - Number of patients
 - 40 - Age
 - 41 - Sex
 - 42 - Smoking status
 - 43 - Professional exposure
 - 44 - History of bladder tumor
 - 45 - Body Mass Index (BMI)
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- Performance status (PS) according to the WHO classification
 - Biological features:
 - Creatininemia with Cockcroft and Gault creatinine clearance calculation (normal renal function when clearance was ≥ 90 mL/min, renal insufficiency stage I when $60 \leq \text{clearance} \leq 89$ mL/min, stage II when $30 \leq \text{clearance} \leq 59$ mL/min, stage III when clearance < 30 mL/min)
 - Nutritional status (denutrition when albuminemia < 40 g/L)
 - Blood counts (anemia when hemoglobin was < 12 g/dL, normal platelet count between 150 and 400 G/L, normal leukocyte count between 4 and 10 G/L)
 - Induction chemotherapy features:
 - Type of chemotherapy
 - Timing of re-evaluation by imagery
 - Number of cycles
 - Pathologic and operating features:
 - Lymph-node dissection
 - Pathologic data pre and post-cystectomy (in case of cystectomy):
 - Histological type
 - TNM
 - Margins after cystectomy
 - Prostate cancer seen on specimens
 - Follow-up
 - The occurrence of recurrence specifying the site

- Date of latest news
- The date of death and its cause (related or unrelated to urothelial disease)

Statistical analyses

Data are reported with mean (range). The clinicopathologic features of MIBC were tested for their association with induction chemotherapy response and surgery completion by chi-square test. PFS was defined as the time from the date of chemotherapy response to the first local relapse or first metastasis. OS was calculated from the date of diagnosis to death or the last follow-up. Patients were censored if they had not experienced the end-point of interest at the time of the last follow-up. Kaplan-Meier survival curves were compared by log rank test. The impact of clinicopathologic features on induction chemotherapy response, cystectomy and survival was assessed by multivariable analysis with a Cox proportional-hazards regression model, estimating hazard ratios (HRs). Factors significant on univariate analysis at $p < 0.10$ were included in the multivariable analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Patients

In total, we identified 72 patients with locally advanced bladder tumour and/or N+ status who should receive induction chemotherapy over the study period; 70 (mean age 65 years [median 66 years (33-86)]) actually received induction chemotherapy (Figure 1). The mean follow-up was 31 months (median 27 months [5-108]).

Induction chemotherapy protocols and response rates

Induction chemotherapy consisted in cisplatin-based protocols for 52 patients (50 MVAC, 1 Cisplatin-Etoposid, 1 Cisplatin-Laroxel) (74.3%) and taxol-gemcitabine protocol for 18 patients (25.7%). Overall, an objective response to induction chemotherapy were observed in 51 patients (72.9%). The clinical, biologic, and pathologic features of responders and non-responders are reported in Table 1. The mean number of chemotherapy cycles received among responders was 7 (median 5 [4-29]) comparing to 21 (median 16 [4-70]) among non-responders. Clinical factors significantly associated with response to induction chemotherapy were sex, smoking status and induction chemotherapy using MVAC regimen. The only biological factor significantly associated with response to chemotherapy was kidney function. On multivariable analysis, response to induction chemotherapy was associated with MVAC as first-line chemotherapy (Table 2a).

Surgery completion

Forty-seven patients underwent surgery (44/51 responders [86%] and 3/19 non-responders [16%]). The clinical, biologic and pathologic features of the 70 patients

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3 according to surgery completion are reported in Table 3. Among the 3 non-responders,
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6 2 underwent surgery due to an uncontrollable hematuria requiring iterative
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8 transfusions, and the last was operated after an initial unresponsiveness under
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10 induction therapy with laroxel-cisplatin then a response under a second-line therapy
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12 with taxol-gemcitabine. Overall, 45/47 patients underwent lymph-node dissection; The
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15 2 patient who did not have lymph-node dissection were those requiring cystectomy
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17 for bleeding control. There were no deaths in early post-operative period (<30 days).
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19 Factors associated with surgery completion after induction chemotherapy were age,
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21 sex, smoking status, response to chemotherapy, regardless of the time of the response,
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23 and histologic urothelial type. On multivariable analysis, surgery completion inversely
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25 associated with late response to induction chemotherapy (Table 2b).
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32 **Outcome according to response to induction chemotherapy and surgery** 33 **completion** 34 35

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38 Regardless surgery completion, patients with response to induction chemotherapy
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40 showed improved PFS ($p < 0.001$; Figure 2a) and OS ($p = 0.025$; Figure 2b). regardless
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42 response to induction chemotherapy, patients who underwent surgery showed
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44 improved PFS ($p < 0.001$) and OS ($p < 0.001$). Professional exposure was the only
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46 prognostic factor significantly associated with lower PFS (Table 4a).. Surgery
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48 completion after induction chemotherapy was the only prognostic factor significantly
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50 associated with OS (Table 4b). Surgery after induction chemotherapy was protective
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52 for risk of death.
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DISCUSSION

Concept of unresectable MIBC patients includes both locally advanced diseases, which invade pelvic organs, and lymph nodes invasive diseases, where extent of lymph nodes dissection that should be done to achieve a complete resection of the cancer is too morbid and with uncertain efficacy. The possibility to achieve a complete surgical resection of the disease depends both of the ability of the surgical team in performing complex procedure, and the physical capacity and psychological acceptance of the patients regarding the surgical treatment. Each of these criteria may vary widely according to the medico-economic and sociologic environments. Thus, limited epidemiological data on a such heterogeneous disease are available, and therapeutics guidelines in this setting are primarily based on expert advises. Data from Surveillance, Epidemiology and End Results database reported by Abdollah et al. had estimated prevalence and incidence of regional MIBC at 26,014 cases and 4.7 new cases/years/100 000 US citizens [15]. Studies focusing on induction chemotherapy for locally advanced or lymph-node metastatic MIBC are relatively old and have included limited in number of patients, with methodological issues [16-23]. Overall, the objective response rate to induction chemotherapy ranges from 33% within the historical cohort described by Herr et al. [23], to 44%-86% in most recent series [16-22]. In accordance with these previous studies, we report an objective response rate of 72.9%. In most of the previous studies, objective response to induction chemotherapy was associated with improved survival. The results from the present study confirm improvement in

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3 overall survival in patients who obtain an objective response through induction
4 chemotherapy. Moreover, our results showed an independent association between the
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6 response to induction chemotherapy and use of MVAC regimen contrary to others
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8 regimens. Our study also demonstrates an improvement in overall survival in patients
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10 who underwent surgery after induction chemotherapy. In addition, we showed that late
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12 response to induction chemotherapy was independently associated with reduced
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14 probability for surgery completion. Taken together, these results defend a maximalist
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16 approach, combining chemotherapy and surgery in the treatment of unresectable
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18 MIBC.
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30 Use of induction chemotherapy is based on pragmatic principle that as the
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32 extent of cancer is too important for a surgical resection, hence an upfront chemical
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34 reduction of this extend is aimed [24]. Cisplatin based chemotherapy regimens have
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36 demonstrated improvement of overall survival in patients with metastatic diseases [2].
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38 Contrary to chemotherapy, evidences of clinical benefit of surgical resection of tumors
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40 in this setting did not concern overall survival improvement, but control of symptoms,
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42 mainly bleeding. Indeed, in the locally unresectable MIBC setting (i.e. cT4b tumors),
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44 extirpative surgery alone, not combined with chemotherapy, has demonstrated futility
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46 in many studies [25-27]. Pak et al. recently reports results from a retrospective study
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48 comparing survival outcomes in patients with clinically node-positive muscle-invasive
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50 bladder cancer receiving induction chemotherapy followed by surgery and those who
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52 underwent upfront radical cystectomy. Through the analyses of 340 patients, including
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3 106 received induction chemotherapy and 234 underwent upfront surgery, authors
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5 shown that the 5-year cancer-specific survival rate of cN1-2 patients was higher in the
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7 induction chemotherapy group than the upfront surgery group (68.1% vs. 52.9%). Our
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9 results reinforce the conclusion of previous studies, in supporting combination of both
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11 chemotherapy then surgery. Indeed, through a systematic review of literature,
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13 cumulating 7 retrospective studies, Li et al. reported that this strategy may improve
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15 survival in patient with $cT \leq 3bN + M0$ MIBC [28]. The results from the present study bring
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17 new contribution in patients management regarding timing for surgery. Indeed, our
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19 multivariable analysis shown that surgery completion was inversely associated with late
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21 response to induction chemotherapy, meaning that in prolonging the chemotherapy,
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23 probability of completing surgery completion is not improved. Thus, objective
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25 response should be early assessed in order to perform surgery as soon as tumor
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27 removability is obtained.
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41 This study had several limitations. Mainly, this study was retrospective in nature
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43 and may therefore be subject to inherent bias. Inherent limitations may have included
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45 selection bias for induction or adjuvant chemotherapy and the lack of prospective
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47 standardized protocols for lymphadenectomy, chemotherapy regimen, and salvage
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CONCLUSIONS

Patients with unresectable MIBC constitute a problematic group of patients which require a multimodal treatment. If cisplatin-based induction chemotherapy had demonstrated a keen interest regarding overall survival, our study adds argument in favor of benefit of subsequent surgery. This surgery should not be delayed in prolonging induction chemotherapy beyond a sufficient clinical response, allowing to remove the tumors. The extirpability status of tumors could be dependant of the surgical team, thus patients applicant to this kind of surgery could benefit by being performed in tertiary center.

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ABBREVIATIONS

BMI: Body Mass Index

CT: computer tomography

(HD)-MVAC: high-dose methotrexate, vinblastine, doxorubicin and cisplatin

EORTC: European Organisation for Research and Treatment of Cancer

INF α : interferon α

MIBC: muscle-invasive bladder cancer

MRI: Magnetic Resonance Imaging

MVAC: methotrexate, vinblastine, doxorubicin and cisplatin

NMIBC: non-muscle-invasive bladder cancer

OMS: Organisation Mondiale de la Santé

OS: overall survival

PET: positron emission tomography

PFS: progression-free survival

PS: Performans status

RECIST: response evaluation criteria in solid tumours

SEER: The Surveillance, Epidemiology, and End Results

SWOG: Southwest Oncology Group

TNM: Tumor Node Metastasis

Table 1: Clinical, biologic and pathologic features of 70 patients with and without response to induction chemotherapy

	Total	Response	No response	
	n (%)	n (%)	n (%)	p*
	70 (100.0)	51 (72.9)	19 (27.1)	
Clinical features				
Age (years)				
<60	22 (31.4)	19 (37.3)	3 (15.8)	0.085
≥60	48 (68.6)	32 (62.7)	16 (84.2)	
Sex				
Male	53 (75.7)	42 (82.4)	11 (57.9)	0.034
Female	17 (24.3)	9 (17.6)	8 (42.1)	
Smoking status				
No-smoker	15 (21.4)	6 (11.8)	9 (47.4)	0.001
Smoker	55 (78.6)	45 (88.2)	10 (52.6)	
Professional exposure				
Yes	3 (4.3)	2 (3.9)	1 (5.3)	0.805
No	67 (95.7)	49 (96.1)	18 (94.7)	
History of bladder cancer				
Yes	22 (31.4)	17 (33.3)	5 (26.3)	0.573
No	48 (68.6)	34 (66.7)	14 (73.7)	
BMI (kg/m²)				
<18	3 (4.3)	2 (3.9)	1 (5.3)	
18-25	34 (48.6)	23 (45.1)	11 (57.9)	0.713
>25	33 (47.1)	26 (51.0)	7 (36.8)	
Performance status				
0-1	64 (91.4)	49 (96.1)	15 (78.9)	0.372
2-3	6 (8.6)	2 (3.9)	4 (21.1)	
Type of first-line chemotherapy				
MVAC	50 (71.4)	42 (82.4)	8 (42.1)	
TG	18 (25.7)	9 (17.6)	9 (47.4)	0.001
Other	2 (2.9)	0 (0.0)	2 (10.5)	
Biologic features				
Renal failure				
Yes	57 (81.4)	38 (74.5)	19 (100.0)	0.015
No	13 (18.6)	13 (25.5)	0 (0.0)	

Denutrition[£]

Yes	27 (90.3)	17 (81.0)	10 (100.0)	0.139
No	4 (9.7)	4 (19.0)	0 (0.0)	

Anemia^{££}

Yes	27 (40.3)	18 (37.5)	9 (47.4)	0.458
No	40 (59.7)	30 (62.5)	10 (52.6)	

Platelets^{£££}

Thrombocytopenia	3 (4.6)	2 (4.3)	1 (5.6)	
Normal rate	53 (81.5)	38 (80.8)	15 (83.3)	0.908
Thrombocytosis	9 (13.8)	7 (14.9)	2 (11.1)	

Leukocytes^{££££}

Leukopenia	2 (3.3)	1 (22.2)	1 (6.3)	
Normal rate	45 (73.8)	32 (71.1)	13 (81.3)	0.346
Leukocytosis	14 (22.9)	12 (26.7)	2 (12.5)	

Anatomo-pathological features**Histologic type**

Urothelial	66 (94.3)	49 (96.1)	17 (89.5)	
Other	4 (5.7)	2 (3.9)	2 (10.5)	0.290

Tumour stage (cT)

<T3	46 (65.7)	36 (70.6)	10 (52.6)	
T3	9 (12.9)	7 (13.7)	2 (10.5)	0.159
T4	15 (21.4)	8 (15.7)	7 (36.8)	

Lymph node status

N-	6 (8.6)	3 (5.9)	3 (15.8)	0.188
N+	64 (91.4)	48 (94.1)	16 (84.2)	

MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; TG, taxol-gemcitabine

* Chi² test

[£] data available for 31 patients

^{££} data available for 67 patients

^{£££} data available for 65 patients

^{££££} data available for 61 patients

^{£££££} data available for 41 patients

Table 2: a) Multivariable analysis of factors associated with response to induction chemotherapy

Pronostic factor	Response to chemotherapy	
	HR	p
Age	2.98	0.22
Sex	1.90	0.44
Smoking status	3.25	0.16
Type of first-line chemotherapy		0.016
MVAC	1	
TG	0.05	
Other	0.01	
Renal function	0.00	0.98

MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; TG, taxol-gemcitabine
 HR, hazard ratio; 95% CI, 95% confidence interval

Table 2: b) Multivariable analysis of factors associated with surgery completion.

Pronostic factor	Operability	
	HR	p
Age	125.90	0.98
Sex	0.98	0.96
Smoking status	0.40	0.59
BMI (kg/m²)		0.76
<18	1.00	
18-25	0.74	
>25	0.41	
Performance status before chemotherapy	0.12	0.23
Performance status after chemotherapy	0.00	0.98
Response to chemotherapy	3.00	0.44
Late <u>response</u> to chemotherapy	0.01	0.024
Histologic type	1.02	0.99

Table 3: Clinical, biologic and pathologic characteristics of 70 patients after induction therapy with and without cystectomy

	General	Surgery	No Surgery	
	n (%)	n (%)	n (%)	p*
	70 (100.0)	47 (67.1)	23 (32.9)	
Clinical features				
Age (years)				
<60	20 (28.6)	17 (36.2)	3 (13.0)	0.044
≥60	50 (71.4)	30 (63.8)	20 (87.0)	
Sex				
Male	53 (75.7)	40 (85.1)	13 (56.5)	0.009
Female	17 (24.3)	7 (14.9)	10 (43.5)	
Smoking status				
No-smoker	15 (21.4)	6 (12.8)	9 (39.1)	0.001
Smoker	55 (78.6)	41 (87.2)	14 (60.9)	
Professional exposure				
Yes	3 (4.3)	2 (4.3)	1 (4.4)	0.986
No	67 (95.7)	45 (95.7)	22 (95.6)	
History of bladder cancer				
Yes	22 (31.4)	16 (34.0)	6 (26.1)	0.500
No	48 (68.6)	31 (66.0)	17 (73.9)	
BMI (kg/m²)				
<18	3 (4.3)	2 (4.2)	1 (4.3)	
18-25	34 (48.6)	20 (42.6)	14 (60.9)	0.086
>25	33 (47.1)	25 (53.2)	8 (34.8)	
Performance status				
0-1	64 (91.4)	45 (95.7)	19 (82.6)	0.065
2-3	6 (8.6)	2 (4.3)	4 (17.4)	
Type of 1st line chemotherapy				
MVAC	50 (71.4)	37 (78.7)	13 (56.5)	
TG	18 (25.7)	9 (19.1)	9 (39.1)	0.155
Other	2 (2.9)	1 (2.1)	1 (4.3)	
Response to induction chemotherapy				
Yes	51 (72.9)	44 (93.6)	7 (30.4)	<0.001

No	19 (27.1)	3 (6.4)	16 (69.6)	
Late response to chemotherapy[£]				
Yes	7 (13.7)	2 (4.5)	5 (71.4)	<0.001
No	44 (86.3)	42 (95.5)	2 (28.6)	
BMI post-chemotherapy (kg/m²)				
<18	1 (1.4)	1 (2.1)	0 (0.0)	
18-25	42 (60.0)	28 (59.6)	14 (60.9)	0.780
>25	27 (38.6)	18 (38.3)	9 (39.1)	
Performance status post-chemotherapy				
0-1	65 (92.9)	46 (97.9)	19 (82.6)	0.020
2-3	5 (7.1)	1 (2.1)	4 (17.4)	
Biologic features				
Renal failure				
Yes	57 (81.4)	36 (76.6)	21 (91.3)	0.137
No	13 (18.6)	11 (23.4)	2 (8.7)	
Denutrition^{££}				
Yes	27 (90.3)	17 (81.0)	10 (100.0)	0.139
No	4 (9.7)	4 (19.0)	0 (0.0)	
Anemia^{£££}				
Yes	28 (41.8)	18 (40.0)	10 (45.5)	0.670
No	39 (58.2)	27 (60.0)	12 (54.5)	
Platelets^{££££}				
Thrombocytopenia	3 (4.6)	2 (4.5)	1 (4.8)	
Normal rate	53 (81.5)	37 (84.1)	16 (76.2)	0.699
Thrombocytosis	9 (13.8)	5 (11.4)	4 (19.0)	
Leukocytes^{£££££}				
Leukopenia	2 (3.3)	2 (4.3)	0 (0.0)	
Normal rate	45 (73.8)	29 (61.7)	16 (84.2)	0.381
Leukocytosis	14 (22.9)	11 (23.4)	3 (15.8)	
Anatomic-pathological features				
Histologic type				
Urothelial	66 (94.3)	47 (100.0)	19 (82.6)	
Other	4 (5.7)	0 (0.0)	4 (17.4)	0.003
Tumour stage (cT)				
<T3	46 (65.7)	34 (72.3)	12 (52.2)	

	T3	9 (12.9)	6 (12.8)	3 (13.0)	0.149
	T4	15 (21.4)	7 (14.9)	8 (34.8)	
Lymph node status					
	N-	6 (8.6)	4 (8.5)	2 (8.7)	0.979
	N+	64 (91.4)	43 (91.5)	21 (91.3)	

MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; TG, taxol-gemcitabine

* Chi² test

[‡] Among 51 patients responders to induction chemotherapy

^{‡‡} Information available for 31 patients

^{‡‡‡} Information available for 67 patients

^{‡‡‡‡} Information available for 65 patients

^{‡‡‡‡‡} Information available for 61 patients

^{‡‡‡‡‡‡} Information available for 41 patients

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Table 4: a) Multivariable analysis of factors associated with progression-free survival

Pronostic factor	Progression-free survival	
	<i>HR</i>	<i>p</i>
Smoking status	0.60	0.23
Professional exposure	7.29	0.0038
Histologic type	1.19	0.84
Tumour stage (cT)		0.21
<T3	1	
T3	1.29	
T4	1.67	
Platelets		0.093
Thrombocytopenia	1	
Normal rate	0.42	
Thrombocytosis	0.18	
Response to chemotherapy	2.13	0.13
Late response to chemotherapy	1.13	0.081
Cystectomy after chemotherapy	2.31	0.086

Table 4: b) Multivariable analysis of factors associated with overall survival

Pronostic factor	Overall survival	
	<i>HR</i>	<i>p</i>
Sex	0.47	0.23
Platelets		0.50
Thrombocytopenia	1	
Normal rate	0.56	
Thrombocytosis	0.31	
Response to chemotherapy	0.45	0.35
Late response to chemotherapy	0.30	0.22
Cystectomy after chemotherapy	0.21	0.011

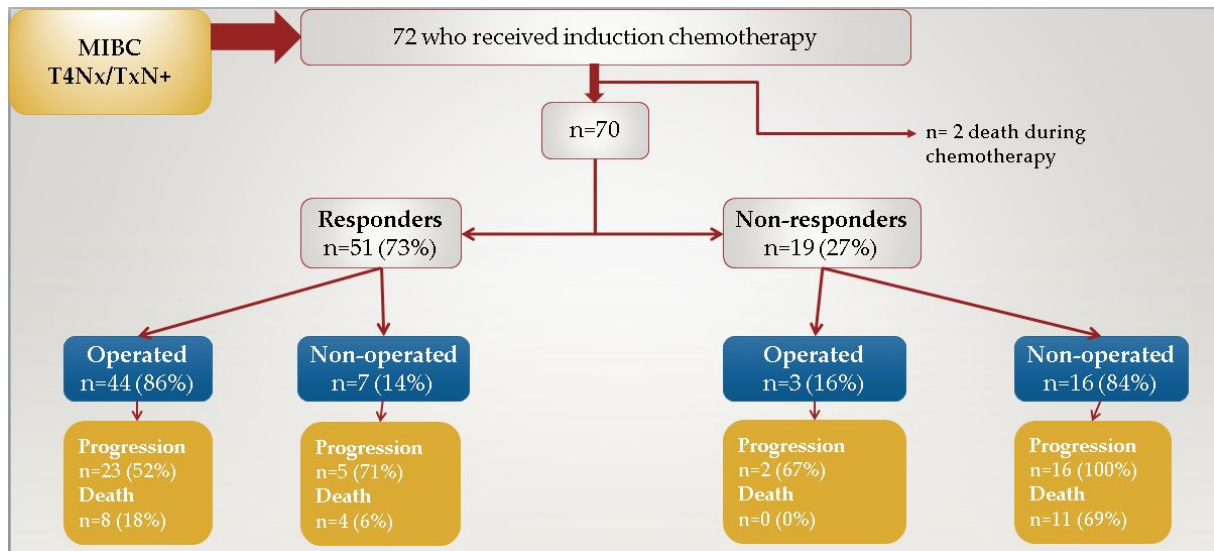
Figure 1: Study flow chart

Figure 2a: Progression-free survival according to the response to induction chemotherapy

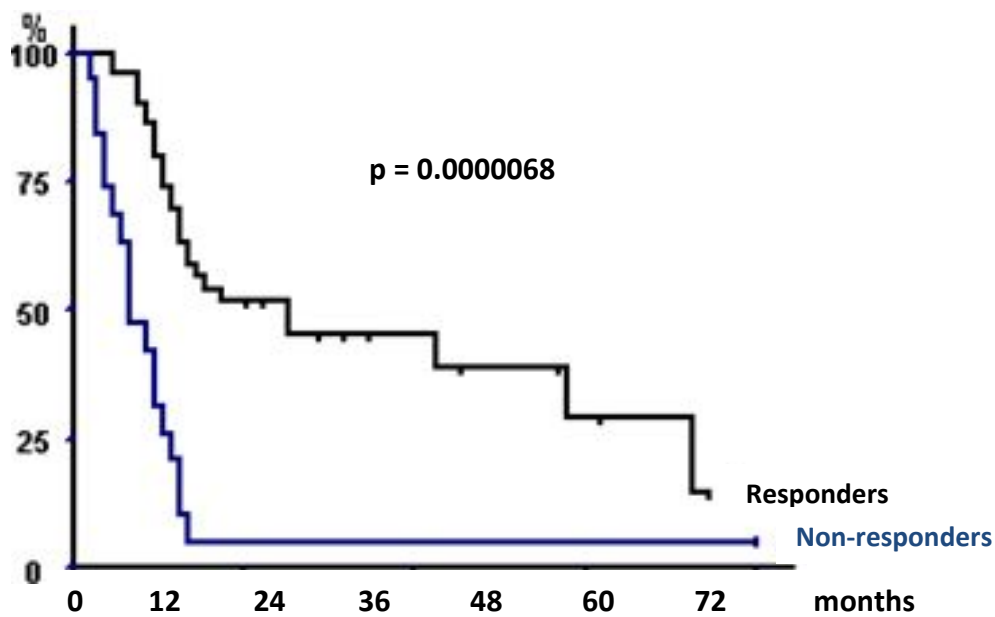


Figure 2b: Overall survival according to the response to induction chemotherapy

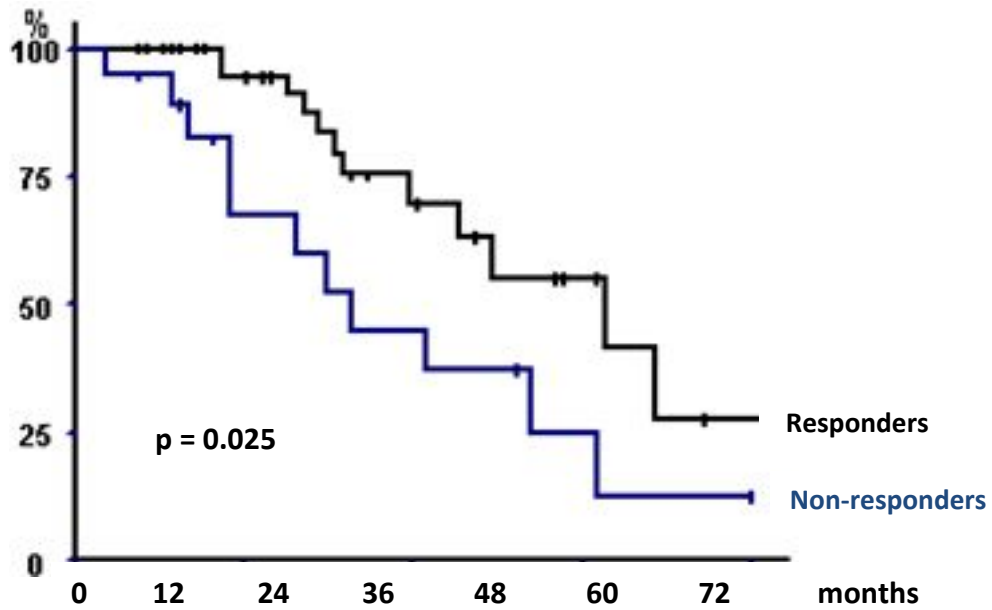


Figure 3a: Progression-free survival according to cystectomy achievement

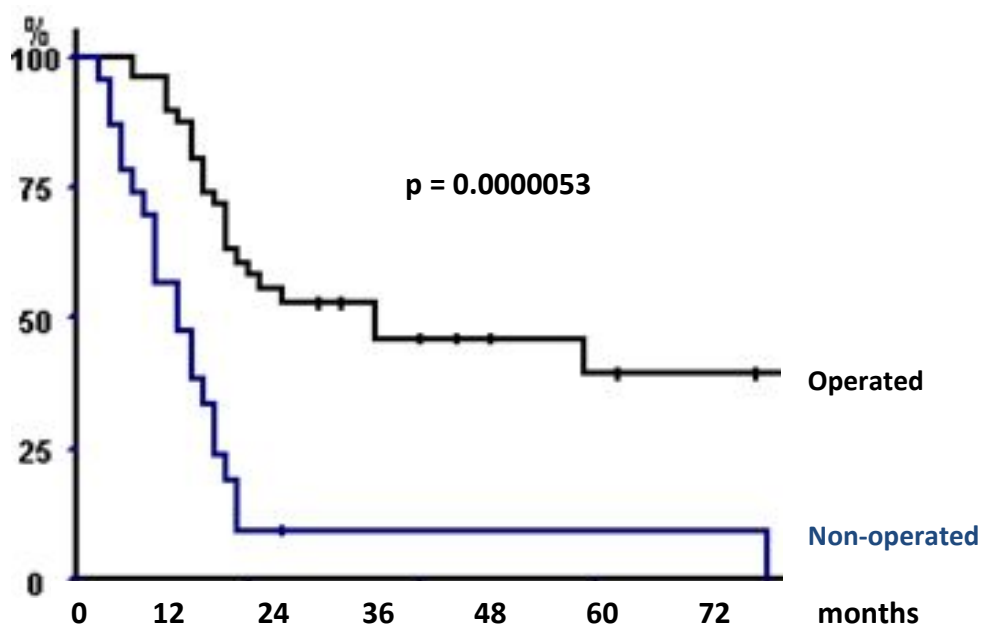
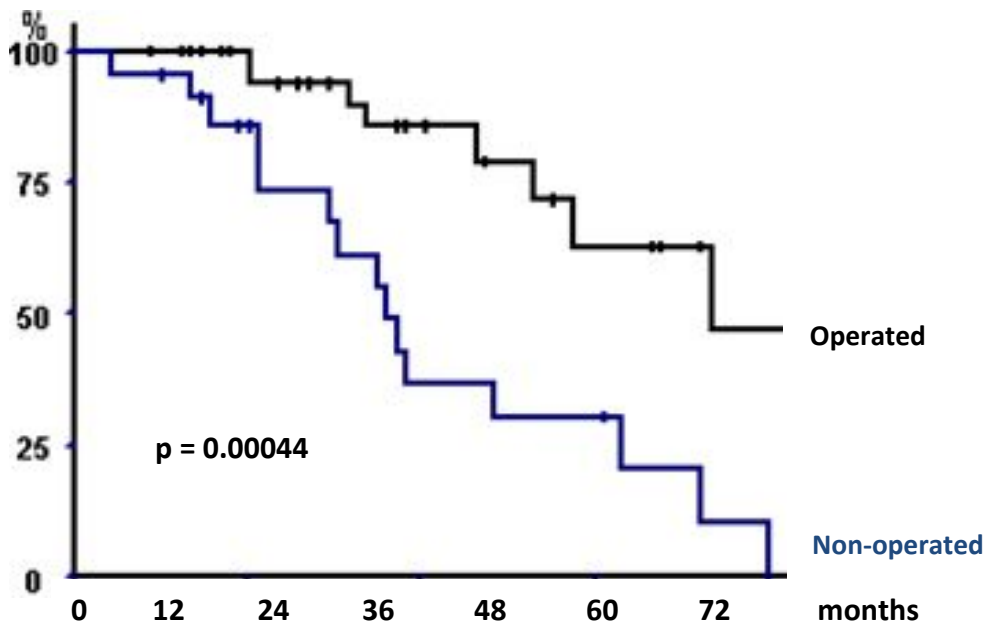


Figure 3b: Overall survival according to cystectomy achievement



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