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Advanced colonic cancer with clinically suspected bladder invasion: Outcomes and prognosis from a multicentric study of 117 patients from the FRENCH research group

Cindy Vuillermet, H el ene Meillat, Gilles Manceau, Ben Creavin, Clarisse Eveno, St ephane Benoist, Yann Parc, J er emie Lef evre, Sara Arfa, Paul-No el Dumont, et al.

► **To cite this version:**

Cindy Vuillermet, H el ene Meillat, Gilles Manceau, Ben Creavin, Clarisse Eveno, et al.. Advanced colonic cancer with clinically suspected bladder invasion: Outcomes and prognosis from a multicentric study of 117 patients from the FRENCH research group. *Surgery*, 2020, 168 (5), pp.786-792. 10.1016/j.surg.2020.06.021 . hal-03024923

HAL Id: hal-03024923

<https://hal.sorbonne-universite.fr/hal-03024923v1>

Submitted on 26 Nov 2020

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Surgery

Advanced colonic cancer with clinically suspected bladder invasion: outcomes and prognosis from a multicentric study of 117 patients from the FRENCH research group. --Manuscript Draft--

Manuscript Number:	20200270R1
Article Type:	Original Communication
Section/Category:	Clinical
Keywords:	Locally advanced colon cancer; bladder invasion; local recurrence; urinary tract involvement; enbloc resection
Corresponding Author:	jeremie H lefevre, MD, PhD Hôpital Saint-antoine Paris, FRANCE
First Author:	Cindy Vuillermet
Order of Authors:	Cindy Vuillermet Hélène Meillat Gilles Manceau Ben Creavin Clarisse Eveno Stéphane Benoist Yann Parc jeremie H lefevre, MD, PhD
Manuscript Region of Origin:	FRANCE
Abstract:	<p>Objective: Report outcomes and identify risk factor for local recurrence (LR) in colon cancer with clinically suspected bladder invasion.</p> <p>Background: Bladder invasion by colon cancer is rare, however, its management is still controversial</p> <p>Methods: A retrospective study was conducted in 23 centers. All patients who underwent colon surgery with bladder resection (2010-2017) were included. Metastatic and recurrent colon cancers were excluded.</p> <p>Results: 117 patients (men=73) were included. Partial cystectomy occurred in 108 patients (92.3%), with a total cystectomy occurring in 9 patients (7.7%). Neoadjuvant treatment was given to 31 patients (26.5%). Major morbidity was 20.5%. R0 resection rates were 87.2%. Histologically confirmed bladder invasion was seen in 47%. 34 patients were pN+, while 60 patients (51.3%) received adjuvant chemotherapy. Mean follow-up was 33.8 months. 3-year OS and DFS were 82.9% and 59.5%. LR and distant recurrence rates were 14.5% and 18.8%, respectively. 64.7% of LR were located in the bladder (11 patients). 4 patients had a bladder recurrence (BR) despite not having histologically confirmed bladder invasion at index surgery. The BR rate after bladder invasion was 12.7% (7/55), while the BR rate without primary bladder invasion was 6.5% (4/62) (p=0.343). The R1 resection rate after partial cystectomy was 57% (4/7), while the R0resection rate was 6.8%. Neoadjuvant treatment, type of cystectomy and adjuvant treatment did not influence LR (p=0.659, p=0.445, p=0.941). R1 bladder resections increased LR (62.5% vs. 10.2%, p<0.0001). Conclusions: Clinically suspected bladder invasion increases LR even in the absence of histologically confirmed bladder invasion. Only optimal surgery with R0 margins reduces LR. Strong surveillance is needed, even without pathological bladder invasion.</p>

To the Editor-in-Chief

Dear Sir,

Please find attached the revised manuscript submission entitled “**Advanced colon cancer with clinical bladder invasion: outcomes and prognosis from a multicentric study of 117 patients from the FRENCH research group.**” (Surgery RE: 20200270)

We have been paying much attention to all the points raised by the reviewers and we have responded to them separately, with some details you will see below.

Regarding the comments of the Co-Editor-in Chief:

First, I am surprised by the lack of important data in the text as outlined comprehensively by Reviewer 1.

Answer: As noted by the reviewer, the tables describe the majority of the results. The manuscript is long and we choose to avoid repetition.

Second, I suggest that you look at the style of presentation of data in other articles published in SURGERY, because there are far too many individual paragraphs. Please either get some help with the organization of the abstract, introduction, and discussion from an outside scientific editing service or group all parts into paragraphs that contain data on the same topic. Third, I would suggest that your co-authors become much more involved in the presentation of the data, which is not well-organized.

Answer: We modified the manuscript to fit more with the editorial request.

Fourth, I just cannot believe that all 26 authors fulfill ALL the ICGME criteria for authorship. Having conducted a prospective randomized trial with 16 other centers (authors) it took me a full 6 months to get every author to read and make suggestions to the text! Here is my suggestion. You should get the four or five co-authors who really were involved in the analysis, the discussion of the topic, and the wiring of the current paper and include them as co-authors. Then, give the study a name, like "French Study group of Bladder Invasion from Colon Cancer." The other contributors who probably only provided patients, but really didn't participate in the actual data collection, analysis of the data, planning on how to organize the paper, and really were not involved in writing of the paper could then be listed in a footnote. I will ask you--did everyone who is listed as an author really read the paper and make suggestions? I am not saying that they may not have received a copy, but, honestly, how many really read it, made substantive suggestions for improvement, and thereby really met ALL the ICGME criteria for authorship? By listing contributors as members of a study group, those other "authors" who really did not participate much can claim authorship if they so desire, but you do not need to include their names as actual authors and thereby have to claim (inappropriately) that they did fulfill all the criteria of the ICGME. Do you understand my approach? You can tell all the other "co-authors" that I demanded this. Those who really did not participate will understand.

I fully understand your point of view.

As stated, all the authors listed in the article contributed patients, reviewed the manuscript and gave constructive criticism on the manuscript. We made the majority of the corrections and signed off on it during a national meeting where almost all co-authors were in attendance.

If you can put some of them as collaborators so they can have their work recognized with an indexed publication on Pubmed it would be fine for us.

If possible, the list of authors would be:

- Cindy Vuillermet, H el ene Meillat, Gilles Manceau, Ben Creavin, Clarisse Eveno, St ephane Benoist, Yann Parc, J er mie H. Lefevre; on behalf of the FRENCH research group.

The list of collaborators of the FRENCH research group would be:

- Sara Arfa⁶, Paul-No el Dumont⁷, Hortense Boullenois⁸, David Fuks⁹, Mehdi Ouaisi¹⁰, Leonor Benhaim¹¹, Marie Selvy¹², Jean-Jacques Tuech¹³, Zaher Lakkis¹⁴, Renato Lupinacci¹⁵, Antoine Epin¹⁶, Sophie Deguelte¹⁷, Guillaume Passot¹⁸, Bertrand Trilling¹⁹, C ecile Jarlot-Gas²⁰, Muriel Mathonnet²¹, David Moszkowicz²², Leila M'Harzi²³, Laura Beyer Berjot²⁴.

Concerning the Reviewers' Comments:

Reviewer #1: Thank you for allowing us to review your manuscript. This is an important topic, and is generally under-represented in the current literature.

Comments:

- The manuscript needs minor orthographic revision.

Answer: The manuscript has been completely reread by a native English speaker (BC).

- Introduction is brief and helpful.

Answer: Thank you for this nice comment.

- Preop details: please discuss if cases were discussed at multidisciplinary conferences, when is neoadjuvant therapy indicated in France? Is local imaging such as MR used in France? Is has been proven to be helpful to determine the extent of cystectomy in selective cases.

Answer:

- *We do not know if cases were discussed preoperatively in each center in a multidisciplinary conference, as this information was not sought from each center. The cases were likely discussed in a post-operative MDT where decisions on adjuvant therapy would have been made.*
- *Regarding the indication for neo adjuvant treatment for colonic cancer, the French guidelines "TNCD" (Ref n o 24) recommend surgery first for all non metastatic tumors, unless there is a doubt on the resectability, in which case neo adjuvant chemotherapy would be discussed. There was indeed a lack of information on this subject, so we added it into the manuscript.*

- *MRI is not used routinely in France for preoperative assessment of colonic tumors. Hence it was not utilized in our study. We add some references on this subject, using comparisons with other pelvic tumors, including prostate, rectal or cervical cancers.*

- Please provide details of neoadjuvant therapies, including type and duration of chemotherapy, as well as XRT dose. Would also discuss time interval in-between neoadjuvant therapy and surgery.

Answer: We added this information to the text.

- Where any of the conversions started as a diagnostic laparoscopy to rule out carcinomatosis? If so would change this but if indeed a 65% conversion rate, this is an important point of your study.

Answer: There was no diagnostic laparoscopy for carcinomatosis in this study, as metastatic disease at diagnosis was an exclusion criteria. A 65% conversion rate does not seem remarkable to us, as only a few surgical teams perform laparoscopic bladder resections (partial, or total).

- How many patients had prophylactic ureteral stent placement?

Answer: We do not have the information about pre-operative ureteral stent placement.

- Change ileal pouch to ileal diversion.

Answer: Done

- Please list organs (including abdominal wall) and extent of resection for patients undergoing multivisceral resection.

Answer: For multivisceral resection, we added the list in Table 2 to the text. We do not have information about the extent of multivisceral resection.

- Did any patients have carcinomatosis? If there were isolated small bowel mets, I would consider this as such and group there prognosis differently.

Answer: No patient had carcinomatosis as it was an exclusion criteria in the study.

- Why was only 86% resected en bloc? This defies the principles of oncologic resection. This should be looked at as a risk factor for R1 resection and poor oncologic outcomes.

Answer: As the R1 resection variable encompasses this data, we did not include an en-bloc resection in the univariate analysis.

- Please round up percentages. Reads much better.

Answer: We modified the manuscript.

- Please describe Bricker if you are going to label it that way. Many readers will not know what you're talking about.

Answer: We removed this term to talk only about total cystectomy.

- Did neoadjuvant therapy impact postop complications? Would group all and also have a separate analysis of chemo and XRT patients.

Answer: The morbidity rate was not impacted by neoadjuvant treatment. As the numbers are small, we were reluctant to detail these subgroups.

- Did sending frozen sections impact final pathology results? Discuss in results.

Answer: We added a sentence in the results section

- Did any patients undergo fecal diversion, temporary or permanent? Would also add this.

Answer: Information about temporary stoma formation is in Table 2, we have added this to the text also.

- Histologic variables should also include degree of differentiation, mucinous features, and signet-cell features; and LR or metastatic disease should be analyzed according to tumor biology as this tends to be one of the most important factors.

Answer: Information about histological features such as histologic type and grade of differentiation can be found in Table 3.

- What was the definition of confirmed vs. non confirmed bladder invasion? This is confusing to me.

Answer: Confirmed bladder invasion includes a pathological confirmation of infiltration of the bladder by colonic cancer.

- Please provide details regarding duration of adjuvant chemotherapy. Would also be helpful to provide interval between surgery and start of adjuvant chemotherapy, adverse events, and any interruptions; and how all this impacted oncologic outcomes.

Answer: We have added some details about adjuvant chemotherapy. We do not have any information about the adverse events of adjuvant chemotherapy, as it was not the subject of our study.

- The neoadjuvant effect should be highlighted in the abstract.

Answer: done.

- How do you explain the non significant differences in 3-year bladder LR in R0 and R1 patients? Neoadjuvant therapy? Tumor biology? Adjuvant chemo?

Answer: We were surprised by this important finding and have given some possible explanation in the discussion.

- Explain "bladder boundary". Very confusing.

Answer: We removed this term from the article.

- How many surgeons were involved in the treatment of these patients? Please add.

Answer: We do not have the exact number of surgeons involved in this study. It was multicentric including 23 centers.

- Discussion: would emphasize differences in function and QoL a bit more between partial and total cystectomy patients, and potentially reference a paper with this. Comment on the use of MR to predict bladder invasion.

Answer: We added to the discussion regarding quality of life after radical cystectomy. As explained earlier, we added some references, mainly using comparisons with other pelvic tumors, including prostate, rectal or cervical cancers.

- Additional limitations: multiple different centers and surgeons treating these patients, different work-up algorithms, as well as different neoadjuvant and adjuvant strategies.

Answer: We agree with this point. We added the multicentric nature of the study in the limitation section.

- Tables and Figures are helpful and partially address some of the questions/comments above.

Answer: We thank the reviewer for this gentle remark.

Reviewer #2: The authors present a retrospective multicenter observational study of patients with colon cancer invading the bladder. There 117 patients included in the analysis. 92% were treated with partial cystectomy, 26% received neoadjuvant therapy and interestingly only 47% were confirmed to have T4b tumors with direct invasion into the bladder. 3 year DFS was low at 59%. Local recurrence was higher after R1 vs R0 resection and was the only predictor of local recurrence. This is interesting data but there are several issues that need to be addressed.

Answer: We thank the reviewer for this nice comment on our work.

1) Methods -- Did all patients meet inclusion criteria prior to their resection? Specifically, differentiating between a planned partial cystectomy and an intra-operative decision can greatly impact the extent of resection so understanding this is important to understanding a 13% R1 resection rate. Also, specify if patients were included based on imaging, path or both. How the study group was defined needs to be more clearly defined.

Answer: We gave specific and clear inclusion and exclusion criteria to all centers. If patients did not fit with all the criteria, they were excluded from the study. In fact, 253 patients were screened in the 23 centers, and 117 patients were included in the end. The primary inclusion

criteria was a bladder resection for colorectal cancer. It explains why 37% of patients had no work-up before surgery and may, at least in part, explain also the R1 rate.

2) Results -- 63% of patients had suspected bladder involvement so what about the other 37%? What did the work up for those suspected involvement -- imaging...?

Answer: Only 74 patients (63%) were suspected of having a clinical invasion of the bladder in the pre-operative setting, so for the rest of the cohort (37%), it was an intraoperative diagnosis of a T4 tumor adherent to the bladder.

3) Results -- Only 47% of patients truly had T4 disease so shouldn't the denominator be 55 patients? The title of paper should reflect the total patient population -- Suspected bladder invasion. An analysis of all patients with subset analysis of those with T4 (a and b) and T3 would be most helpful. Inclusion of T3 tumors must have impacted your LR rate for R0 resections.

Answer: We agree with this important observation. However, all patients had a clinical bladder invasion justifying the resection. We modified the title to highlight this point. Therefore, we do not agree to using 55 patients as a denominator, because it reflects only the final classification after surgery and definitive histology, and not the daily clinical practice when you have to deal with this kind of clinical situation. Our aim with this study was to help surgeons propose the best strategy for a patient with a pre-operative suspicion of bladder invasion, or an intra-operative finding, and how to deal with the local recurrence risk. Hence the study is presented this way.

4) Results -- It would be helpful to present your data in a manner that supports a partial cystectomy in the face of poor pre-operative predictability bladder involvement.

Answer: We agree with this important observation and added this point in the conclusion.

5) Results -- For bladder recurrence, how did T stage impact recurrence rates?

Answer: We cannot say that the T stage impacted bladder recurrence, as bladder recurrence was found even without histologically confirmed invasion at index surgery (4 patients, 36%).

6) Discussion -- The discussion is too long and needs to focus on the findings of this study. The references should then be used to support and enhance the specific findings of this study.

Answer: We modified the discussion as requested.

7) Discussion -- The major limitation of this study is the study group is not well defined. Based on the title, the reader is expecting this to be exclusively T4 tumors but only 47% were in fact T4. So context of the study becomes confusing. Also, as mentioned above, differentiate between pre- and intra-operative identification of patients. The major take home message of the study is be prepared to resect bladder with the tumor if suspected involvement and neoadjuvant therapy is good. The issues above cloud that message.

Answer: To cope with these remarks, the title has been modified and we clarified the aim of the study.



To the Editor-in-Chief

Dear Sir,

Please find attached a manuscript entitled “**Bladder invasion in advanced colonic cancer: outcomes and prognosis from a multicentric study of 117 patients. A multicentric series of the FRENCH research group.**” which is submitted to *Surgery* as an original article.

We present a multicentric study of 117 advanced colonic cancers with a bladder invasion from 23 centres.

To our knowledge, there is a lack of studies examining the management of bladder involvement in colorectal cancer, mainly due to the relatively limited frequency of the problem in most institutions.

We believe that this work will have a clinical impact for the surgeons. Indeed, Clinical bladder invasion is at risk for local recurrence even without pathological bladder invasion. Only optimal surgery with R0 margins was the only protecting factor for local recurrence. In all cases a strong surveillance is needed, even without pathological bladder invasion.

By submitting the manuscript, the authors understand that the material presented in this paper has not been published before, has not been submitted for publication to another scientific journal, and will not be sent to another journal until a decision is made concerning publication. I attest that this work has been approved by all co-authors. The authors also understand that should the submitted material be accepted for publication in the journal, they will automatically transfer the copyright to the publisher. Authors have no conflicts of interests and no funding source to declare.

Thank you for considering this manuscript for publication in *Surgery*.

Yours sincerely,

The authors

Advanced colonic cancer with clinically suspected bladder invasion: outcomes and prognosis from a multicentric study of 117 patients from the FRENCH research group.

Cindy Vuillermet¹, H  l  ne Meillat², Gilles Manceau³, Ben Creavin⁴, Clarisse Eveno⁵,

St  phane Benoist⁶, Yann Parc¹, J  r  mie H. Lefevre¹; on behalf of the FRENCH research group.

¹ Sorbonne Universit  , Department of Digestive Surgery, AP-HP, H  pital Saint Antoine, F-75012, Paris, France.

² Department of Surgical Oncology, Institut Paoli-Calmettes, Marseille, France

³ Department of Digestive Surgery, Piti   Salp  tri  re Hospital, AP-HP, Sorbonne University, Paris, France

⁴ Department of Surgery, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

⁵ Department of Digestive and Oncological Surgery, University Hospital C. Huriez, Lille, France

⁶ Department of Digestive Surgery, Bic  tre Hospital, University Paris Sud XI, 7, Le Kremlin-Bic  tre, France

List of collaborators of the FRENCH research group:

- *Sara Arfa*, Department of Digestive Surgery, University Hospital of Dijon, Dijon, France
- *Paul-No  l Dumont*, Department of General Surgery and Liver Transplantation, H  pital de la Croix-Rousse, Hospices Civils de Lyon, University Lyon 1, Lyon, France
- *Hortense Boullenois*, Department of Digestive Surgery, Bic  tre Hospital, University Paris Sud XI, 7, Le Kremlin-Bic  tre, France.
- *David Fuks*, Department of GI Surgery, Institut Mutualiste Montsouris, Paris, France
- *Mehdi Ouaiissi*, Department of Digestive Surgery, Tours, France
- *Leonor Benhaim*, Department of Visceral and Oncological Surgery, Gustave Roussy, Villejuif, France
- *Marie Selvy*, Digestive Surgery and Oncological Department, Hospital Estaing, Clermont-Ferrand, France

- 1 • *Jean-Jacques Tuech*, Department of Digestive Surgery, Rouen University Hospital, Rouen,
2 France
- 3 • *Zaher Lakkis*, Department of Digestive Surgery, Besançon University Hospital,
4 Besançon, France
- 5 • *Renato Lupinacci*, Department of Digestive, Visceral and Endocrine Surgery, Groupe
6 Hospitalier Diaconesses - Croix Saint-Simon, France
- 7 • *Antoine Epin*, Department of Digestive and Oncologic Surgery, CHU Nord Saint-Etienne,
8 Saint-Priest en Jarez
- 9 • *Sophie Deguelte*, Department of General and Digestive Surgery, Robert Debré Hospital,
10 Centre Hospitalier Universitaire de Reims, University of Reims Champagne-Ardenne,
11 Reims, France
- 12 • *Guillaume Passot*, Department of Digestive Surgery, Centre Hospitalier Lyon Sud,
13 University Claude Bernard Lyon 1, Lyon, France
- 14 • *Bertrand Trilling*, Department of Surgery, Colorectal Unit, Michallon University Hospital,
15 University Grenoble Alps, Grenoble, France
- 16 • *Cécile Jarlot-Gas*, Department of Visceral Surgery, Toulouse-Rangueil University
17 Hospital, Toulouse, France
- 18 • *Muriel Mathonnet*, Department of Digestive, General and Endocrine Surgery, CHU de
19 Limoges - Dupuytren Hospital, Limoges, France
- 20 • *David Moszkowicz*, Department of Digestive, Oncologic and Metabolic Surgery,
21 Ambroise-Paré Hospital, Boulogne-Billancourt, AP-HP, University of Versailles-
22 Saint-Quentin-en-Yvelines, France
- 23 • *Leila M'Harzi*, Department of Digestive, Oncologic and Bariatric Surgery, AP-HP,
24 Hôpital Européen Georges Pompidou and University Paris Descartes, Paris
- 25 • *Laura Beyer Berjot*, Department of Digestive Surgery, APHM, Hôpital Nord, Aix-
26 Marseille University, Marseille, France

35 Correspondance and reprint requests:

36
37
38 Pr Jérémie H. Lefèvre, Department of Digestive Surgery, Hôpital Saint-Antoine, Assistance
39 Publique Hôpitaux de Paris, Université Pierre et Marie Curie, Paris VI, 184 rue du Faubourg
40 Saint-Antoine, 75012, Paris, France

41
42
43
44
45
46 Tel: 0033 1 49 28 25 47, Fax: 0033 1 49 28 25 48

47
48
49 e-mail: jeremie.lefevre@aphp.fr

50
51
52
53 **ORCID:** <https://orcid.org/0000-0001-7601-7464>

54 55 56 Original article

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59 **Running head:** Bladder invasion in advanced colon cancer.
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Disclosure: No authors reported conflict of interest.

Keywords: Locally advanced colon cancer; bladder invasion; local recurrence; urinary tract involvement; enbloc resection.

Word count: 2833

Abstract count: 249

ABSTRACT

Objective: Report outcomes and identify risk factor for local recurrence (LR) in colon cancer with clinically suspected bladder invasion.

Background: Bladder invasion by colon cancer is rare, however, its management is still controversial

Methods: A retrospective study was conducted in 23 centers. All patients who underwent colon surgery with bladder resection (2010-2017) were included. Metastatic and recurrent colon cancers were excluded.

Results: 117 patients (men=73) were included. Partial cystectomy occurred in 108 patients (92.3%), with a total cystectomy occurring in 9 patients (7.7%). Neoadjuvant treatment was given to 31 patients (26.5%). Major morbidity was 20.5%. R0 resection rates were 87.2%. Histologically confirmed bladder invasion was seen in 47%. 34 patients were pN+, while 60 patients (51.3%) received adjuvant chemotherapy. Mean follow-up was 33.8 months. 3-year OS and DFS were 82.9% and 59.5%. LR and distant recurrence rates were 14.5% and 18.8%, respectively. 64.7% of LR were located in the bladder (11 patients). 4 patients had a bladder recurrence (BR) despite not having histologically confirmed bladder invasion at index surgery. The BR rate after bladder invasion was 12.7% (7/55), while the BR rate without primary bladder invasion was 6.5% (4/62) (p=0.343). The R1 resection rate after partial cystectomy was 57% (4/7), while the R0 resection rate was 6.8%. Neoadjuvant treatment, type of cystectomy and adjuvant treatment did not influence LR (p=0.659, p=0.445, p=0.941). R1 bladder resections increased LR (62.5% vs. 10.2%, p<0.0001).

Conclusions: Clinically suspected bladder invasion increases LR even in the absence of histologically confirmed bladder invasion. Only optimal surgery with R0 margins reduces LR. Strong surveillance is needed, even without pathological bladder invasion.

INTRODUCTION

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2
3 Local invasion into adjacent organs by primary colorectal cancer occurs in 5-20% of cases,¹⁻⁴
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5 with urinary tract involvement accounting for 10-30% of this.⁵⁻⁹ En-bloc resection of all
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7 involved organs to leave no residual cancer is recognized as the gold standard treatment for
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9 locally advanced colorectal cancer.^{10,11} Improved survival is associated with an R0 resection
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11 in these cases, however, achieving this is challenging.¹² Furthermore, bladder invasion can be
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13 encountered intra-operatively without patients undergoing neoadjuvant therapy or appropriate
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15 staging which can further impact on resection margins and patient outcomes. Total cystectomy
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17 with urinary diversion is the oncologic resection of choice for bladder invasion, although this
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19 is associated with significant morbidity and quality of life issues.¹³⁻¹⁵ Therefore, the choice of
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21 a partial or total cystectomy becomes an important consideration when balancing both
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23 oncological outcomes and quality of life.
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30 Management of bladder invasion is still controversial. Local recurrence is not uncommon
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32 (roughly 10-30%), with no definitive contributing factors being identified.^{6,8,9,14,16-19} Seeding
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34 of tumor cells into the bladder may go unnoticed for a long time prior to resection due to the
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36 bladder being a hollow viscus. Furthermore, the rate of bladder recurrence is rarely detailed in
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38 previous publications. To our knowledge, there is a lack of studies examining the management
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40 of bladder involvement in colorectal cancer, mainly due to the relatively limited frequency of
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42 the problem in most institutions. Table 1 summarizes the published data to date on this topic.
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48 The aim of this study was to report surgical and oncological outcomes and identify potential
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50 risk factors of local recurrence after bladder invasion in primary advanced colon cancer.
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METHODS

Patients

All patients who underwent colonic resection for a primary advanced adenocarcinoma with bladder resection for clinically suspected bladder invasion between 2010 and 2017 were retrospectively included from 23 digestive oncologic surgery departments in France, belonging to the FRENCH Group. Exclusion criteria included patients <18 years old, resections for local recurrences, mid or low rectal cancer, synchronous metastatic disease and emergency surgery. Each center sent data through an anonymized database or secure online survey. Information regarding demographic data, clinical symptoms leading to diagnosis, type of surgery, neoadjuvant and adjuvant oncological treatments, postoperative outcomes and follow-up were recorded.

Management

Pathological staging of the tumor was in accordance with the AJCC Cancer Staging 8th edition.²⁰ Modified Dworak Tumor Regression Grade system was used to analyze tumor response to neoadjuvant therapy. Clavien Dindo's classification was used to grade morbidity.²¹ The RECIST 1.1 classification was used as imaging criteria for assessing tumor response.²² Data regarding neoadjuvant treatment was retrieved retrospectively. Indications for neoadjuvant treatment were discussed in each center individually, in line with French guidelines. Neoadjuvant chemotherapy is recommended in non-metastatic disease where tumor resectability is questioned.²³ Data regarding adjuvant treatment was retrieved retrospectively. Adjuvant chemotherapy regimens were chosen at individual centers in accordance with French and European guidelines.²⁴ Currently, adjuvant chemotherapy is recommended for stage III or stage II disease with risks factors. Follow-up was conducted according to each centers preference. French guidelines recommend physical examination and CT scan every 3 months for the first three years, then 6 monthly thereafter for 2 years.²³ Local recurrence was defined

1 as a recurrence near the primary site of resection, with a bladder recurrence defined as a
2 recurrence inside or on the bladder after partial cystectomy. All data was anonymized. The
3
4 study was declared with the CNIL (no: 2212340).
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7 *Statistical analysis*

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10 Qualitative variables were described as number (%) and were compared between groups using
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12 Pearson Chi² test or Fisher's exact test. Quantitative variables were described as mean ± SD.
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14 Positive and negative predictive values were calculated to assess the accuracy of the
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16 preoperative examinations. Survival curves were plotted using the Kaplan–Meier method. Log-
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18 rank test was used to compare survival curves. Potential prognostic factors were evaluated
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20 using Cox proportional hazard regression models. Survival time was the interval between the
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22 intervention date and a new event or last follow-up. Patients who did not experience any event
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24 and were still alive at the end of follow-up were right censored at this time. For each outcome,
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26 factors achieving a p value < 0.20 in the univariate analysis were included in the multivariate
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28 model. Hazard ratio were presented with 95% confidence intervals. All statistical tests were
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30 two-sided and performed using SAS software version 9.3; SAS Institute Inc., Cary, NC, USA.
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41 **RESULTS**

42 *Patients and preoperative management*

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45 From January 2010 to December 2017, 117 patients across 23 French centers who underwent
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47 colectomy with bladder resection for primary advanced colon cancer were included. Patient
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49 characteristics are detailed in Table 2. 73 patients were male (62%). Mean age was 70.3 years
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51 (+/13.4). Bladder invasion (clinically T4) was suspected on preoperative investigations and/or
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53 with clinical symptoms in 74 (63%) patients. 23 patients had a preoperative cystoscopy (20%),
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55 with a macroscopic bladder invasion found in 15 patients. Histological confirmation of bladder
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1 invasion was confirmed in 5 of these patients. Intra-operative bladder invasion was found in
2 43 patients (37%) who were either asymptomatic or not suspected of having invasion on pre-
3 operative investigations. 31 patients had neoadjuvant therapy (26%), with the majority having
4 chemotherapy alone (n=22; 71%). Chemotherapy consisted mainly of folinic acid-fluorouracil
5 and oxaliplatin (Table 2). After neoadjuvant therapy, 20 (64%) patients were RECIST 2 with
6 partial response. No patient had a complete response. The median time between the end of
7 neoadjuvant treatment and surgery was 5 weeks (IQR 4.8-6.7).
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21 *Oncological resection and postoperative course*

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23 34 (29%) patients underwent laparoscopic resection, of which, 22 (65%) were converted to
24 open (Table 2). Nine patients (8%) had a total cystectomy with definitive urinary ileal conduit
25 with 108 patients having a partial cystectomy. 54 patients (46%) had an associated procedure
26 with another organ resected, the most frequent being a small bowel resection (22 patients,
27 41%). Intra-operative frozen section was utilized in 26 patients (22%), with 6 (23%) positive
28 results. En-bloc resection was performed in 101 patients (86%). Overall morbidity was 55%,
29 with severe morbidity encountered in 18% (Table 3). There was 3 postoperative deaths (3%),
30 all after partial cystectomy (one due to a pulmonary embolism and two for unknown causes).
31 10 patients (10%) had an anastomotic leak, with 25 patients (21%) having urinary related
32 morbidity. After partial cystectomy, overall and severe morbidity was 55% and 18%
33 respectively. Bladder leak occurred in 11 patients (10%) after partial cystectomy. Following
34 total cystectomy and urinary ileal conduit, overall and severe morbidity was 55% and 22%
35 respectively, with an ileal-diversion related morbidity of 44%. There was no significant
36 difference in overall (p=1) and severe morbidity (p=0.663) after partial or total cystectomy.
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Pathological outcomes and adjuvant treatment

Pathological invasion of the bladder was confirmed in 55 patients (47%). The negative predictive value of the cT stage for the diagnosis of histologically proven bladder invasion was 70%, with a positive predictive value of 53%. An R0 resection was achieved in 87% of the cohort. R1 resections differed significantly between patients with a confirmed bladder invasion (13/54) and those without confirmation (2/62) ($p < 0.0001$) (Table 3). 60 patients (51%) received adjuvant chemotherapy, with the majority undergoing a FOLFOX regimen ($n=49$, 82%). Median number of administered cycles was 8 (4-12), with the mean interval between surgery and initiation of adjuvant chemotherapy of 8.5 ± 4 weeks. Factors associated with adjuvant chemotherapy administration included lymph node invasion (N+ stage) in 24 patients, T4b stage without lymph node invasion in 29 patients and adverse pathological features in 7 patients (T4a, low differentiation grade, T3).

Long term follow-up and recurrences

Mean follow up was 33.8 ± 24.3 months. Mortality rate was 15% (18 patients). 3-year OS and DFS were 83% and 59%, respectively. 3-year local and distance recurrence rates were 17% and 24%, respectively (figure 1A & 1B). Median time to recurrence was 10.5 months (IQR= 6.1-16.6). 17 patients (53%) had a LR (14% after partial cystectomy and 22% after total cystectomy). Among the 74 patients with cT4 stage, 27 patients received neoadjuvant treatment. LR rate was not influenced by either neoadjuvant treatment (15% vs. 21%, $p=0.762$) or adjuvant treatment (15% vs. 14%, $p=1$). Eleven (10%) patients had recurrence inside the bladder following partial cystectomy after a median interval of 11.9 months (IQR= 7.6-14.1). 4 patients (36%) developed a bladder recurrence who did not have histologically confirmed invasion at index surgery. Bladder recurrence rates after partial cystectomy with invasion of

1 the bladder margin (R1) was 57% (4/7), while recurrence rates were 7% for R0 resections. The
2 3-year bladder recurrence rate was similar between patients with an invaded bladder and R0
3 resection margin to those without bladder invasion (9% vs. 8%) (Figure 2). In univariate
4 analysis, factors significantly associated with local recurrences were R1 resections ($p < 0.001$)
5 and invasion of the bladder margin ($p < 0.01$). Performing a partial instead of a total cystectomy
6 was not associated with a higher local recurrence. Furthermore, bladder invasion on
7 histological analysis was not associated with a higher LR risk (Table 4). In multivariate
8 analysis, the only independent factor associated with a LR was an R1 bladder resection (62.5%
9 vs. 10.2%, $p < 0.0001$).

10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 **DISCUSSION**

27
28 This multicentric retrospective study reported both surgical and oncological outcomes of 117
29 patients with a clinically suspected bladder invasion from a locally advanced colon cancer. The
30 study showed that histologically proven bladder invasion was found in less than half of patients
31 undergoing a partial or total cystectomy with a colonic resection. Furthermore, after partial
32 cystectomy, bladder local recurrence rates were 9% even without confirmed bladder invasion
33 on histological exam.

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44 117 patients were included from 23 FRENCH research group centers over 8 years, from 2010
45 to 2017, in order to collect recent data on surgical management of these patients. This is, to our
46 knowledge, the largest series to date with a short and recent time period examining this topic.
47 Patients in the study were mostly men (62%), with a mean age at diagnosis of 70.3 years. These
48 results are in concordance with previous studies.^{2, 12, 14-16, 18, 25-28} As the inclusion criteria for
49 the present study was a clinically suspected invasion of the bladder, the rate of pathological
50 bladder invasion at the time of the histological analysis was 47%. This result is in concordance
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1 with most studies where less than half of patients have true pathological invasion. This is well
2 demonstrated in Eveno *et al.* study on cT4 colorectal cancers where a pathological invasion
3 rate of 64% for all organs was encountered. ⁷ This observation may explain in part the R1
4 resection rate observed in the study. Intraoperative assessment of bladder adherence is often
5 inaccurate and should not be considered relevant for choosing the type of bladder resection. In
6 fact, even without pathological bladder invasion, a clinical T4 tumor should not be considered
7 as a simple T3 in adjuvant treatment decision making and follow-up due to a high risk of local
8 recurrence. Gao *et al.* found that both groups, with and without pathological bladder invasion,
9 have similar survival outcomes. ¹⁴

10 The 3 years overall survival was 82.9% which was higher than the survival rates found in the
11 previous literature. This can be explained by the exclusion of metastatic disease at the time of
12 diagnosis and emergency surgery which is a known adverse prognostic factor. The LR rate of
13 14%, with 65% of these located in the bladder, in the present study is in keeping with previous
14 reports (Table 1). Surprisingly, the LR rate inside the bladder after pathological bladder
15 invasion (13%) was higher, but nonetheless not significantly different (p=0.342) without
16 pathological bladder invasion (7%). Moreover, after exclusion of R1 resection, the rate was
17 similar between the groups. Yoshida *et al.* recently found that bladder recurrence is related to
18 a transfixing bladder invasion at the time of surgery. ¹⁹ This was not the case in the present
19 study, possibly due to the lack of data regarding the depth of bladder invasion. However,
20 several patients in the present study who did not have bladder invasion at index surgery had a
21 recurrence within the bladder several years later. An R1 resection is a known risk factor for
22 LR, something that was encountered again in the present study. ^{4, 12, 18} Bladder recurrence rates
23 following a partial cystectomy with R1 resection was 57% compared with 7% in the R0 group.
24 Completion total cystectomy may be warranted in these cases due to the poor prognostic
25 outcomes. Close follow up of all patients is also extremely important even if there is no

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consensus on the frequency or modalities required for follow up, however, an annual cystoscopy may be **warranted** after partial cystectomy. Mechanisms leading to bladder recurrence without proof of bladder invasion by tumor cells at the time of histological analysis is still unknown. A physiopathological hypothesis of this may be that some colonic tumor cells are circulating within the bladder cavity in the urine and would not be seen on histological examination. This circulation of tumor cells inside the bladder is probably helped by inflammation due to the bulky colonic tumoral mass nearby, although, the presence of a colovesical fistula may be present in some instances.

An overall morbidity of 55% was encountered in this study. Morbidity rates vary across the studies, with rates between 10-70% being reported.^{2, 3, 7, 14-16, 18, 19, 25, 27-29} Severe morbidity was slightly lower after partial cystectomy compared to total cystectomy with urinary ileal conduit (18% versus 22%). The rate of bladder leak after partial cystectomy was 10%, whereas the rate of morbidity related to ileal conduit was 44%. It is known that urinary diversion, such as **ileal conduit or replacement enterocystoplasty**, carry additional morbidity.^{14, 25} Gao *et al.* found a significantly higher morbidity after total cystectomy than partial cystectomy.¹⁴ Li *et al.* found a higher complication rate after reconstruction (81%) than simple suture (45%).¹⁵ These results would favor a simple suture partial cystectomy over an enterocystoplasty or ileal conduit if possible. **Furthermore, it has been demonstrated that radical cystectomy with ileal conduit can have a major impact on health-related quality of life, especially in the early stages.**³⁰⁻³² Voiding dysfunction can occur after simple suture due to impaired bladder volume, although this is not frequent.²⁸ Long-term functional results were not evaluated in this study.

Neoadjuvant treatment did not influence LR in univariate analysis (p=0.659) in the present study. Dehal *et al.* showed that neoadjuvant chemotherapy improves 3-year overall survival in a subgroup of T4b cancers, although this was not seen in T3 or T4a tumors.³³ **This may explain the discrepancy seen in the present study as only 55% of pT4a tumors were encountered.** A

1 prospective study published by Qiu *et al.* reported an R0 resection rate of 95.2% after
2 neoadjuvant chemoradiotherapy in unresectable locally advanced colon cancers, with a
3 pathological complete response rate of 38%.³⁴ A phase III prospective randomized clinical
4 trial is currently underway to validate the role of neoadjuvant therapy in locally advanced
5 primary colon cancer.³⁵ However, neoadjuvant treatment needs a preoperative diagnosis of
6 bladder invasion, however, as observed in the present study, pre-operative investigations are
7 not accurate at identifying this. The positive and negative predictive values of CT imaging was
8 53% and 70%. Luo *et al.* found that a positive preoperative CT scan is a significant predictor
9 for pathological bladder invasion, as well as a colovesical fistula.²⁷ In a retrospective study
10 published by Woranisaraku *et al.*, haematuria, visible tumor on cystoscopy and CT findings
11 were predictive factors for invasion, with specificity around 70%- 90%, although a low
12 sensitivity of 50%.²⁶ Regarding the usefulness of a preoperative pelvic MRI, this was not
13 evaluated in this study as it is not used routinely in France for colon cancer. Indeed, in prostate
14 and cervical cancer, MRI has proven its efficacy in confirming bladder invasion^{36,37}. Further
15 studies on the precise preoperative investigations are required to provide a consensus on this
16 issue.

17 This study is limited by its retrospective nature. As this is a rare occurrence the sample size
18 was limited, however, it is strengthened by combining multiple centers. Follow up was short,
19 although the authors feel the majority of recurrences were captured within the time frame.
20 Another limitation, resulting from the multicentric and retrospective nature of the study, is the
21 variety of procedures, strategies and habits in each center, which add to the heterogeneity of
22 the study.

23 Partial cystectomy seems to be the procedure of choice in cases of bladder invasion by a colon
24 cancer if safe and clear margins can be obtained. Strong surveillance is needed, even without
25 pathological bladder invasion as local recurrence may occur. Questions such as neoadjuvant

1 treatment, details regarding surveillance and preoperative investigations still need to be
2 explored.
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Figure Legends

Figure 1A. Disease Free survival (DFS)

Figure 1B. Distant, Local and Bladder recurrence

Figure 2. Bladder recurrence, depending on the presence of bladder invasion or not, and R1 or R0 margin

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Author	Inclusion	n	cystectomies		Pathological results		Morbidity		Oncological outcomes (5 years)			
			Partial Total		pT4b	R0 rate	Overall	Severe	OS	DFS	Local recurrence	Bladder recurrence
Balbay	1986-1996	81	9		60%	94%	29%	-	55%	-	17%	-
Fujisawa	1970-2001	36	46		-	-	10%	-	91% (3y)	-	-	-
Kobayashi	1995-2000	17	19		29%	-	-	-	-	-	-	-
Carne	1984-1999	53	12		39%	-	-	-	75%	55%	16%	-
Winter	1985-2000	63	2		54%	89%	18%	-	57%	-	14%	-
Gao	1995-2000	33	45		45%	-	33%	-	39%	30%	27%	-
Li	1987-2004	72	5		47%	-	61%	-	59%	71%	15%	-
Luo	2000-2011	84	58		40%	-	-	-	-	-	-	8.3%
Hartwig	1997-2012	31	14		52%	77%	71%	39%	70%	-	11%	6.2%
Nerli	2001-2016	9	8		100%	100%	-	-	-	-	-	-
Yoshida	2001-2015	89	1		39%	100%	12%	-	70%		37%	8.2%
Present study	2010-2017	117	49		45%		50%		72%		34%	
			108		47%	87%	55%	18%	83% (3y)	56% (3y)	17% (3y)	10%
			9									

Table 1. Literature review on the prognosis and management of colonic cancer with bladder invasion

Characteristics	n (%)
Age (mean +/- SD)	70.3 +/- 13.4
Male	73 (62.4)
BMI (mean +/- SD)	25.1 +/- 4.4
ASA n (%)	
1 / 2	15 (12.8) / 57 (48.7)
3 / 4	33 (28.2) / 1 (0.8)
Previous urological intervention (TURP, TURB, radical prostatectomy)	10 (8.5%)
Previous hysterectomy	6 (13.6%)
Left Colonic tumor	110 (94%)
Urinary symptoms	42 (35.9)
Urinary tract infection	27 (23.1)
Dysuria	17 (14.5)
Pneumaturia / Faecaluria	17 (14.5) / 13 (11.1)
Haematuria	9 (7.7)
Pre-operative cystoscopy	23 (19.7)
Macroscopic invasion	15 (65.2)
Histologic invasion on biopsy	5 (21.7)
Suspected bladder invasion (cT4)	74 (63.2)
Suspected lymph node invasion (cN+)	35 (29.9)
Neoadjuvant treatment	31 (26.5)
Chemotherapy Alone	22 (71%)
FOLFOX	11
FOLFOX + Erbitux	5
FOLFIRINOX	6
Chemoradiotherapy (45-50 Gy+ 5FU)	7 (23%)
Radiotherapy alone (45 or 25 Gy)	2 (6%)
Laparoscopic approach	34 (29.1)
Conversion rate	22 (64.7)
Left colectomy	106 (90.6)
Right colectomy	6 (5.1)
Subtotal colectomy	5 (4.3)
Bowel anastomosis	96 (82.0)
Loop ileostomy	44 (45.8)
Location of bladder invasion	
Apex	84 (71.8)
Posterior side	20 (17.1)
Uretero vesical junction	11 (9.4)
Neck	8 (6.8)
Total cystectomy and ileal conduit	9 (7.7)
Partial cystectomy	108 (92.3)
Type of reconstruction after partial bladder resection	
Suture	99 (84.6)
Enterocystoplasty	3 (2.6)
Psoic bladder	4 (3.4)
Unknown	2 (1.7)
Associated procedures	54 (46.1)
Small bowel resection	22 (40.7)
Uterus and/or adnexa resection	18 (33.3)
Vaginal cuff resection	5 (9.3)
Segmental colectomy	7 (13.0)
Abdominal wall resection	7 (13.0)
Other (Epiploon, appendix, duodenum, vas deferens)	8 (14.8)

Table 2. Patient characteristics and surgical procedures. (TURP: Transurethral resection of the prostate, TURB: Transurethral resection of the bladder)

Characteristics	N (%)
Overall morbidity	64 (54.7)
Clavien Dindo 1	11 (9.4)
Clavien Dindo 2	29 (24.8)
Clavien Dindo 3a	3 (2.6)
Clavien Dindo 3b	12 (10.3)
Clavien Dindo 4	6 (5.1)
Post-operative mortality (Clavien Dindo 5)	3 (2.6)
Bowel anastomotic leak	10 (10.4)
Peritonitis	6 (5.1)
Surgical revision	17 (14.5)
Urinary specific morbidity	25 (21.4)
Bladder leak	11 (10.2)
Postoperative urinary retention	5 (4.6)
Ileal pouch related morbidity	4 (44.4)
Length of stay (days)	18.7 +/- 17.1
Histological type	
Lieberkuhnian adenocarcinoma	93 (79.5)
Colloid	22 (18.8)
Others	6 (5.2)
Grade of differentiation	
Low grade	29 (24.8)
Intermediate grade	58 (49.6)
High grade	24 (20.5)
pT stage	
pT1-pT2	2 (1.7)
pT3	37 (31.6)
pT4a	13 (11.1)
pT4b	65 (55.6)
Total lymph node count (mean +/- SD)	24.4 +/- 11.4
pN+	34 (29.1)
Size of bladder resection (mm)	45.8 +/- 22.2
Pathological invasion of the bladder	55 (47.0)
Depth of the bladder invasion	
Peritoneum or fat tissue	10 (18.2)
Detrusor muscle	14 (25.4)
Urothelium	12 (21.8)
Fistula	13 (22.2)
Unknown	6 (10.9)
R0 resection	102 (87.2)
Invasion of bladder boundary	7 (6.0)
Bladder margin (mm)	6.3 +/- 8.5
TRG 1	4 (12.9)
TRG 2	9 (29.0)
TRG 3	7 (22.6)
TRG 4	0
MSI	7 (6.0)
Adjuvant chemotherapy	60 (51.3)
Folfox	49 (81.7)

Table 3. Post-operative course (30 days) and histologic features.

Variables	No local recurrence (n=100)	Local recurrence (n=17)	p
Age > 65 years	68 (88)	9 (12)	0.35
Age < 65 years	32 (80)	8 (20)	
Male	63 (86)	10 (14)	0.95
Female	37 (84)	7 (16)	
Partial cystectomy	93 (86)	15 (14)	0.62
Total cystectomy	7 (78)	2 (22)	
Bladder invasion	44 (80)	11 (20)	0.19
No bladder invasion	56 (90)	6 (10)	
R1 resection	8 (53)	7 (47)	<0.001
R0 resection	92 (90)	10 (10)	
pN+	26 (76)	8 (24)	0.089
pN0	74 (89)	9(11)	
Adjuvant chemotherapy	51 (85)	9 (15)	1
No adjuvant chemotherapy	49 (86)	8 (14)	

Table 4. Univariate analysis of local recurrence after colon cancer resection with bladder invasion.

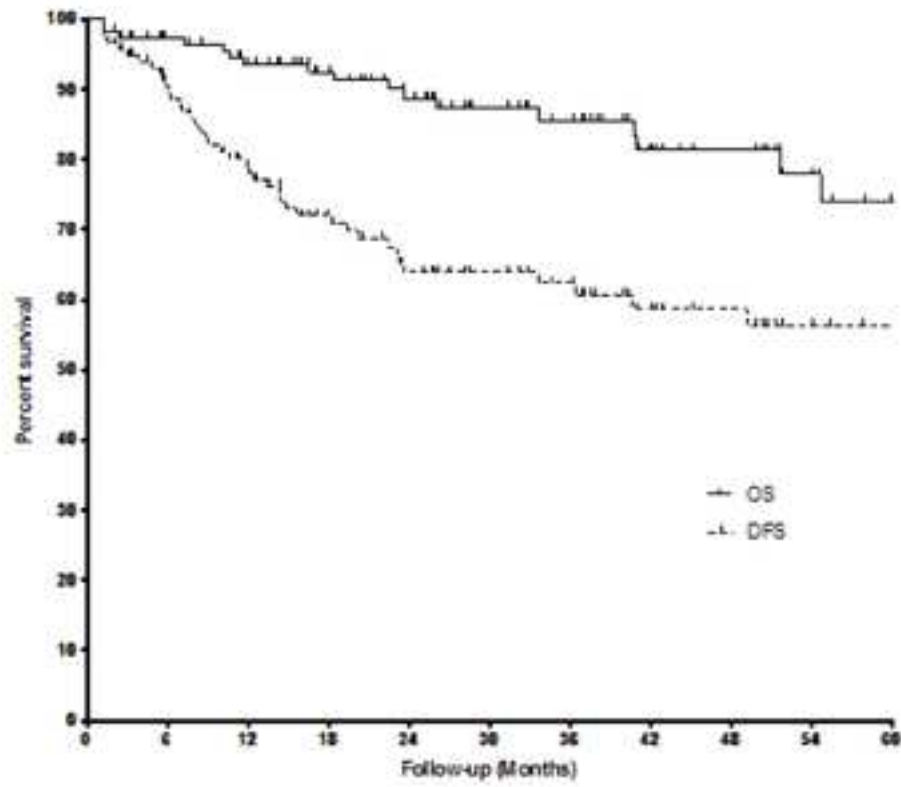


Figure 1A. Disease Free survival (DFS)

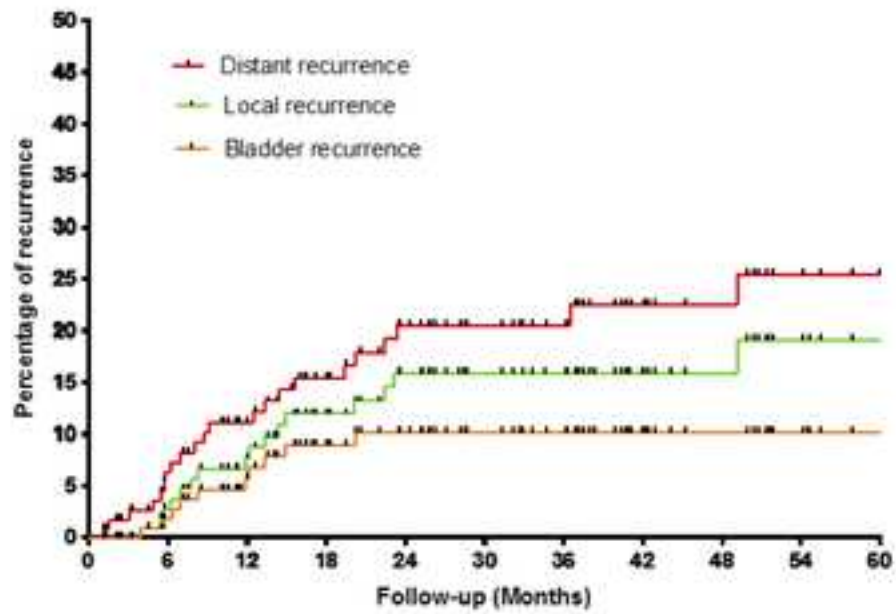


Figure 1B. Distant, Local and Bladder recurrence

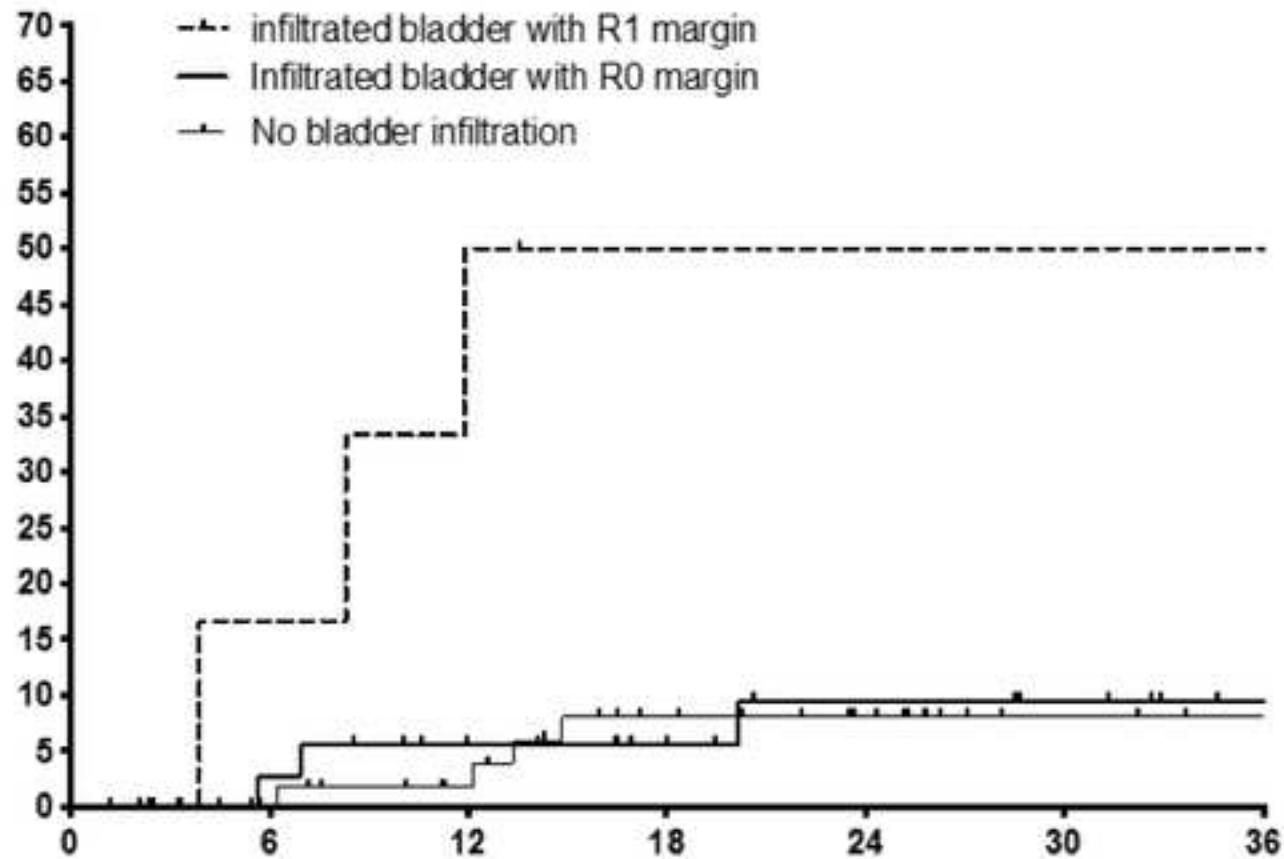


Figure 2. Bladder recurrence, depending on the presence of infiltration of the bladder or not, and R1 or R0 margin.

1. Please confirm that you have mentioned all organizations that funded your research in the Acknowledgements section of your submission, including grant numbers where appropriate.
I confirm that I have mentioned all organizations that funded my research in the Acknowledgements section of my submission, including grant numbers where appropriate.

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Please provide two sentences; the first sentence should briefly summarize what you did or your findings (remember, one sentence). The second sentence should start out with "The importance of this (report or finding) is..." and then add your short justification to the end of this sentence. Please make this the same as your article summary in the manuscript, these two sentences should be verbatim in both places.

Clinical bladder invasion by colorectal cancer is at risk for local recurrence even without pathological bladder invasion and only an optimal surgery with R0 margins reduces LR.

The importance of this study is to show with a large cohort that a en-bloc partial cystectomy is sufficient in case of bladder invasion by a colorectal cancer.

-
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