# Surgical treatment for clinical node-positive bladder cancer patients treated with radical cystectomy without neoadjuvant chemotherapy

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ORIGINAL ARTICLE

# Surgical treatment for clinical node-positive bladder cancer patients treated with radical cystectomy without neoadjuvant chemotherapy

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## Abstract

**Objective** Growing literature supports good survival expectancies in bladder cancer (BCa) patients affected by clinical node metastases (cN+) treated with multimodal therapy. We evaluated the role of adjuvant chemotherapy in cN+BCa patients treated with radical cystectomy (RC) and pelvic lymph node dissection (PLND) without neoadjuvant chemotherapy (NAC).

**Methods** We evaluated a total of 192 patients with BCa and cN+. All patients were treated with RC and PLND without NAC between 2001 and 2013. Kaplan–Meier analyses and Cox regression analyses were used to assess the impact of adjuvant chemotherapy (ACT) on recurrence, cancer-specific mortality (CSM) and overall mortality (OM) after surgery.

**Results** Overall, 99 patients (51.6%) were found without node metastases at RC, while 18 (9.4%), 58 (30.2%) and 17 (8.9%) patients were found pN1, pN2 and pN3, respectively. With a median follow-up of 48 months, in cN+ patients we recorded 5-year recurrence, CSM and OM of 55, 53 and 51%, respectively. Overall, 36 (18.8%) patients were treated with adjuvant chemotherapy. At univariable analyses, ACT was associated with improved overall survival [Hazard ratio (HR): 0.42, confidence interval (CI) 0.20–0.86, $p = 0.02$) in pN+ subgroup only. These results were confirmed at multivariable analyses, where ACT was associated with improved CSS (HR: 0.45, CI 0.21–0.89, $p = 0.03$) and OS (HR: 0.37, CI 0.17–0.81, $p = 0.01$).

**Conclusions** We report good survival outcomes in cN+ patients treated with RC. The use of ACT after surgery increases survival expectancies, especially in those patients with pathological node disease. Our data need to be further evaluated in prospective setting.

**Keywords** Clinical metastases · Radical cystectomy · Bladder cancer · Clinical node positive · Metastases · Survival

## Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is considered the standard of care for high-risk non-muscle invasive unresponsive to intravesical therapies, and for muscle invasive BCa [1]. Despite treatments, life expectancy is only 58% at 5 years [2–4]. Lymph node metastases exert the greatest impact on survival expectancies after RC [2, 5, 6]. In this context, literature is growing assessing that the presence of clinical metastases (cN+) does not invariably impair oncological outcomes [7–10], especially if treated with a multimodal approach. Although clinical trials on neoadjuvant chemotherapy(NAC) excluded patients with clinical node involvement [11, 12], Zargar-Shoshtari et al. [10] recently reported survival benefits for clinical node-positive BCa patients treated with NAC followed by RC suggesting a role for cisplatin-based chemotherapies in the multimodal approach of nodal disease. On the other hand, no data support at the time the use of surgery without NAC with the subsequent use of adjuvant chemotherapy when the node metastases are pathologically confirmed. This approach might overcome the reported low sensitivity of cross-sectional imaging regarding nodal staging [7].

To this aim, we benefit from a large cN+ population treated at a single center with RC and PLND without NAC. We evaluated the role of adjuvant chemotherapy on cN+ and cN+pN+ patients treated with surgery.

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## Materials and methods

After institutional review board (Milan-San Raffaele Hospital, bladder/2012) approval was obtained, we retrospectively reviewed data of 192 consecutive patients with non-metastatic clinical node-positive BCa patients treated with RC and PLND at a single tertiary care referral center between January 2001 and December 2013 without NAC. Patients with incomplete follow-up or without proper informed consent were excluded from the series.

Patients were staged preoperatively with pelvic/abdominal computerized tomography, bone scan when indicated and chest X-ray. Clinical N status was defined as pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, as detected by computer tomography or magnetic resonance imaging within 3 months prior RC [13]. Lymph nodes were removed and evaluated separately and subsequently processed by a dedicated experienced uropathologist. Briefly, fat tissue containing lymph nodes were fixed in 10% buffered formalin. The macroscopic specimen assessment was based on tactile and visual criteria. Large nodes (> 2 cm) were sampled in multiple blocks. If no lymph nodes were macroscopically detected, all fat tissue was processed. All blocks were embedded in paraffin, cut at 3 µm, and stained with hematoxylin–eosin. Pathologic data included tumor grade (according to 1998 WHO/ISUP consensus classification), tumor and nodal stage (according to VI edition TNM classification) [14], lymphovascular invasion (LVI) [15], carcinoma in situ and soft tissue surgical margin (STSM) status [16]. Adjuvant chemotherapy was administered on the bases of patients' characteristics and physicians' preferences.

### Primary and secondary end points

The primary end-point was to evaluate the survival effects of adjuvant chemotherapy in cN+ and cN+pN+ patients treated with RC and PLND. The secondary end-point was to describe survival outcomes of cN+ patients treated without NAC.

### Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and Interquartile Ranges (IQR) were reported for continuously coded variables. The Mann–Whitney test and Chi square test were used to compare the statistical significance of differences in medians and proportions, respectively. The Kaplan–Meier method was used to compare recurrence, cancer-specific mortality (CSM) and overall mortality (OM)-free rates cN+ and cN+pN+ patients. Univariable and multivariable Cox regression analyses tested the impact adjuvant chemotherapy in cN+ and cN+pN+ patients. Statistical significance was considered at $p < 0.05$. Statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA) and STATA 13 (Stata Corp., College Station, TX, USA).

## Results

### Baseline characteristics

Patients' characteristics of the cohort are depicted in Table 1. Of the 192 individuals included in the study, 93 (48.4%) were found with pathologically node metastases at RC. Median age of the population was 67 [Interquartile range (IQR): 61–74]. The median number of nodes removed and

**Table 1** Descriptive statistics of 192 patients treated with radical cystectomy and pelvic lymph node dissection without neoadjuvant chemotherapy for bladder cancer

| Variables | cN+ (192, 100.0%) |
|---|---|
| Age, years | |
| Mean | 67 |
| Median (IQR) | 67 (61–74) |
| Gender | |
| Male | 156 (81.3%) |
| Female | 36 (18.8%) |
| Body mass index | |
| Mean | 25.7 |
| Median (IQR) | 25.4 (23.2–28.6) |
| Nodes removed, number | |
| Mean | 22 |
| Median (IQR) | 21 (13–30) |
| Nodes positive, number | |
| Mean | 5 |
| Median (IQR) | 0 (0–6) |
| Pathologic stage (%) | |
| pT0-pT2 | 68 (35.4) |
| pT3 | 75 (39.1) |
| pT4 | 49 (25.5) |
| Concomitant CIS | 44 (22.9) |
| Positive STSM | 33 (17.2) |
| LVI | 11 (5.7) |
| LNI | 93 (48.4) |
| Grade (%) | |
| 1–2 | 9 (4.7) |
| 3 | 150 (78.1) |
| Adjuvant chemotherapy | 36 (18.8) |

*IQR* interquartile range, *STSM* soft tissue surgical margin, *CIS* carcinoma in situ, *LVI* lymph vascular invasion, *LNI* lymph node invasion

positive were, respectively, 22 and 5. Overall, 36 (18.8%) cN+ patients were treated with adjuvant chemotherapy.

### Cox regression analyses and survival estimates

During a median follow-up of 48 months, 65 recurrences, 67 CSM and 80 OM were reported. The 1-, 3- and 5-year cN+ recurrence-free, CSM-free and OM-free survival were 92.9, 77.6 and 55.0% vs. 93.4, 77.7 and 53.2% vs. 92.9, 74.4, and 51.9% (Fig. 1). Considering cN+pN+ patients, 1-, 3- and 5-year recurrence-free, CSM-free and OM-free survival were 85.4, 45.6 and 37.4% vs. 85.1, 35.2 and 24.1% vs. 89.3, 46.2, and 22.9% (Fig. 2).

At univariable Cox regression analyses considering cN+ patients, pT stage 4 vs. pT 0-2 [Hazard Ratio (HR): 3.68, confidence interval (CI) 1.90.7.12, $p < 0.001$], pT3 vs. pT0-2 (HR: 2.14, CI 1.18–3.88, $p = 0.01$), concomitant LVI (HR:2.90, CI 1.14–7.39, $p = 0.02$), positive STSM (HR: 1.99, CI 1.05–3.76, $p = 0.03$), pN+ vs. pN0 (HR: 1.85, CI 1.13–3.01, $p = 0.01$), and number of positive nodes (HR: 1.04, CI 1.01–1.06, $p = 0.004$) were associated with CSM. Adjuvant chemotherapy was not associated with recurrence, CSM or OM ($p > 0.2$; Table 2). Considering cN+pN+, at univariable Cox regression analyses adjuvant chemotherapy was associated with improved CSM (HR: 0.48, CI 0.25–0.92, $p = 0.02$) and OM (HR: 0.42, CI 0.20–0.86, $p = 0.02$; Table 3).

Table 4 shows multivariable Cox regression analyses in cN+ and cN+pN+ patients. Adjuvant chemotherapy was associated with improved CSM (HR: 0.45, CI 0.21–0.89, $p = 0.03$) and OM (HR: 0.37, CI 0.17–0.81, $p = 0.01$) considering cN+pN+ patients. An association was also reported considering cN+ patients, where adjuvant chemotherapy was associated with improved OM survival (HR: 0.57, CI 0.33–0.99, $p = 0.04$).

## Discussion

Node metastases in BCa severely affect survival outcomes [2, 5, 6]. Although NAC trials exclude all patients with cN+ disease [11, 12], recently some series suggest a role for NAC or adjuvant chemotherapy also in this setting [10, 8]. In our series, we evaluated a large single-center population of patients affected by cN+ treated with RC and PLND without NAC.

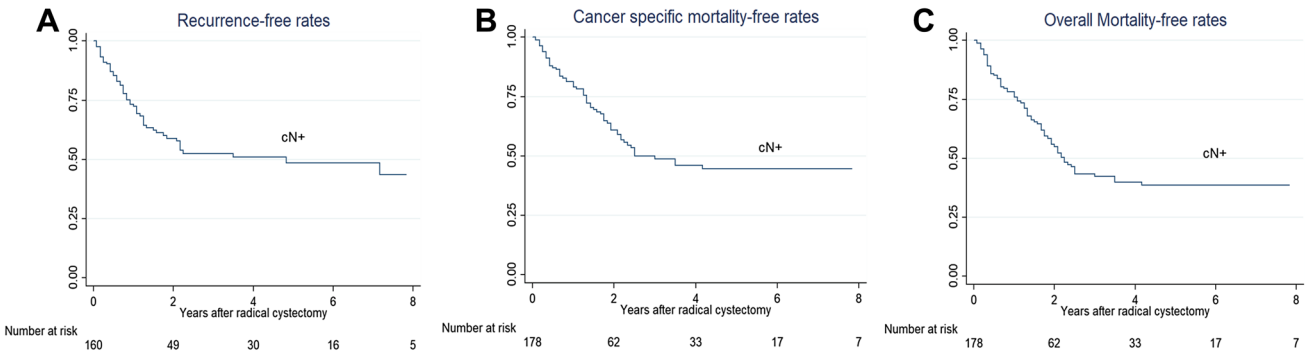


**Fig. 1** Kaplan–Meier analysis assessing recurrence (**a**), cancer-specific mortality (**b**) and overall mortality (**c**)—free rates in patients affected by clinical node metastatic bladder cancer treated with radical cystectomy and pelvic lymph node dissection

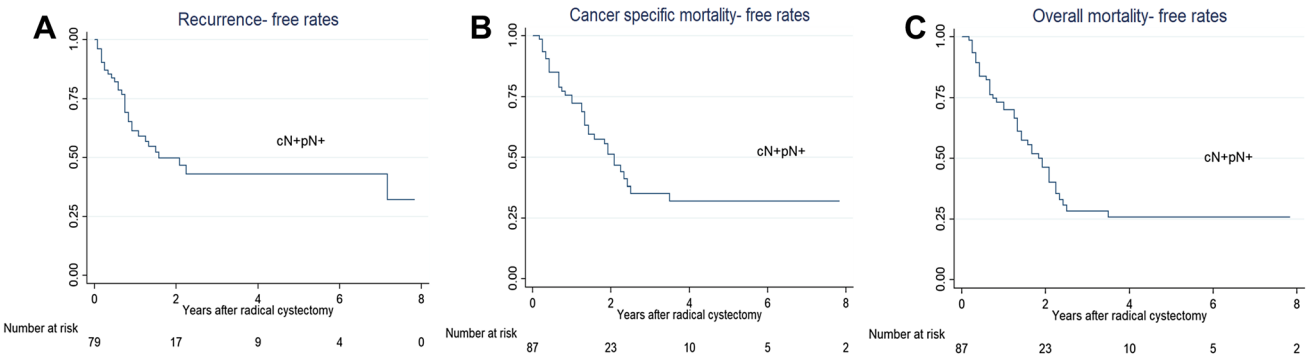


**Fig. 2** Kaplan–Meier analysis assessing recurrence (**a**), cancer-specific mortality (**b**) and overall mortality (**c**)—free rates in patients affected by clinical and pathological node metastatic bladder cancer treated with radical cystectomy and pelvic lymph node dissection

**Table 2** Univariable Cox regression analyses predicting the risk of recurrence, cancer-specific mortality (CSM) and overall mortality (OM) in patients treated with radical cystectomy for cN+BCa disease

| Variables | Univariable recurrence | | Univariable CSM | | Univariable OM | |
|---|---|---|---|---|---|---|
| | HR (CI 95%) | *p* value | HR (CI 95%) | *p* value | HR (CI 95%) | *p* value |
| Age, years | 1.00 (0.97–1.03) | 0.9 | 1.01 (0.98–1.04) | 0.5 | 1.03 (1.01–1.03) | 0.02 |
| Gender (Ref: female) | 0.76 (0.37–1.54) | 0.4 | 1.05 (0.56–1.96) | 0.9 | 1.10 (0.63–1.94) | 0.7 |
| CCI | | | | | | |
| 0 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 1 | 1.64 (0.90–2.99) | 0.1 | 1.48 (0.84–2.61) | 0.2 | 1.28 (0.76–2.17) | 0.3 |
| ≥ 2 | 1.15 (0.54–2.44) | 0.7 | 0.95 (0.45–1.99) | 0.9 | 1.05 (0.56–1.99) | 0.9 |
| Pathological stage | | | | | | |
| pT0-pT2 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| pT3 | 2.32 (1.25–4.33) | 0.008 | 2.14 (1.18–3.88) | 0.01 | 2.00 (1.16–3.45) | 0.01 |
| pT4 | 4.08 (2.06–8.07) | < 0.001 | 3.68 (1.90–7.12) | < 0.001 | 3.51 (1.93–6.39) | < 0.001 |
| Concomitant LVI | 0.91 (0.22–3.77) | 0.9 | 2.90 (1.14–7.39) | 0.02 | 2.92 (1.24–6.84) | 0.01 |
| Concomitant CIS | 1.02 (0.58–1.79) | 0.9 | 1.03 (0.58–1.84) | 0.9 | 0.96 (0.56–1.64) | 0.9 |
| Positive STSM | 2.03 (1.07–3.84) | 0.03 | 1.99 (1.05–3.76) | 0.03 | 2.27 (1.30–3.97) | 0.004 |
| pN+ vs. pN0 | 1.71 (1.04–2.80) | 0.3 | 1.85 (1.13–3.01) | 0.01 | 1.71 (1.09–2.66) | 0.02 |
| Number of positive nodes | 1.02 (1.00–1.05) | 0.1 | 1.04 (1.01–1.06) | 0.004 | 1.04 (1.01–1.06) | 0.002 |
| Number of removed nodes | 0.99 (0.97–1.01) | 0.3 | 1.00 (0.98–1.02) | 0.9 | 1.00 (0.98–1.02) | 0.8 |
| Adjuvant chemotherapy | 1.42 (0.84–2.40) | 0.2 | 1.08 (0.63–1.84) | 0.8 | 0.91 (0.55–1.52) | 0.7 |

*CSM* cancer-specific mortality, *OM* overall mortality, *HR* Hazard ratio, *CI* confidence interval, *CCI* Charlson comorbidity index, *LVI* lymphovascular invasion, *CIS* carcinoma in situ, *PSTSM* positive soft tissue surgical margin

**Table 3** Univariable Cox regression analyses predicting the risk of recurrence, cancer-specific mortality (CSM) and overall mortality (OM) in patients treated with radical cystectomy for cN+pN+BCa disease

| Variables | Univariable recurrence | | Univariable CSM | | Univariable OM | |
|---|---|---|---|---|---|---|
| | HR (CI 95%) | *p* value | HR (CI 95%) | *p* value | HR (CI 95%) | *p* value |
| Age, years | 0.98 (0.94–1.02) | 0.2 | 1.00 (0.96–1.04) | 0.9 | 1.01 (0.98–1.05) | 0.5 |
| Gender (Ref: female) | 0.81 (0.31–2.10) | 0.7 | 0.90 (0.37–2.18) | 0.8 | 1.07 (0.49–2.32) | 0.9 |
| CCI | | | | | | |
| 0 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 1 | 1.64 (0.69–3.87) | 0.3 | 1.76 (0.90–3.87) | 0.2 | 1.68 (0.80–3.54) | 0.2 |
| ≥2 | 1.37 (0.53–3.55) | 0.5 | 1.10 (0.44–2.75) | 0.8 | 1.23 (0.54–2.81) | 0.6 |
| Pathological stage | | | | | | |
| pT0-pT2 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| pT3 | 1.90 (0.44–8.18) | 0.4 | 1.15 (0.34–3.89) | 0.8 | 1.34 (0.40–4.45) | 0.6 |
| pT4 | 2.91 (0.66–12.79) | 0.2 | 1.66 (0.48–5.79) | 0.4 | 2.05 (0.60–7.03) | 0.2 |
| Concomitant LVI | 0.59 (0.08–4.34) | 0.6 | 2.82 (1.03–8.08) | 0.04 | 2.47 (0.87–7.06) | 0.09 |
| Concomitant CIS | 0.78 (0.35–1.73) | 0.5 | 1.00 (0.47–2.14) | 0.9 | 0.83 (0.40–1.74) | 0.6 |
| Positive STSM | 1.12 (0.49–2.58) | 0.8 | 1.21 (0.53–2.77) | 0.7 | 1.56 (0.76–3.19) | 0.2 |
| Number of positive nodes | 1.01 (0.98–1.04) | 0.6 | 1.03 (1.00–1.06) | 0.05 | 1.03 (1.01–1.06) | 0.02 |
| Number of removed nodes | 0.97 (0.94–0.99) | 0.02 | 0.98 (0.95–1.01) | 0.1 | 0.98 (0.96–1.01) | 0.1 |
| Adjuvant chemotherapy | 0.62 (0.41–1.13) | 0.08 | 0.48 (0.25–0.92) | 0.02 | 0.42 (0.20–0.86) | 0.02 |

*CSM* cancer-specific mortality, *OM* overall mortality, *HR* Hazard ratio, *CI* confidence interval, *CCI* Charlson comorbidity index, *LVI* lymphovascular invasion, *CIS* carcinoma in situ, *PSTSM* positive soft tissue surgical margin

**Table 4** Multivariable Cox regression analyses predicting the risk of recurrence, cancer-specific mortality (CSM) and overall mortality (OM) in patients treated with radical cystectomy for cN+or cN+pN+BCa disease

| Variables | Multivariable recurrence | | Multivariable CSM | | Multivariable OM | |
|---|---|---|---|---|---|---|
| | HR (CI 95%) | *p* value | HR (CI 95%) | *p* value | HR (CI 95%) | *p* value |
| Adjuvant CT in cN+ | 0.89 (0.51–1.58) | 0.7 | 0.65 (0.36–1.16) | 0.1 | 0.57 (0.33.0.99) | 0.04 |
| Adjuvant CT in cN+pN+ | 0.73 (0.34–1.53) | 0.4 | 0.45 (0.21–0.89) | 0.03 | 0.37 (0.17–0.81) | 0.01 |

Adjusted for: age, pTstage, STSM status, grading and gender

*CSM* cancer-specific mortality, *OM* overall mortality, *HR* Hazard ratio, *CI* confidence interval, *CT* chemotherapy

We made several findings. First, we found that half patients with clinical node metastases had no pathological confined node metastases. These results confirmed previous findings, assessing the poor sensitivity of cross-sectional imaging in detecting node metastases in BCa patients [17, 7]. In this setting, preoperative characteristics [18] or cross-sectional imaging cannot accurate stage clinical node metastases and cannot represent di per se an indication an accurate parameter to decide to skip surgery, to extend PLND or to treat with NAC. Considering these elements, the decision seems reasonable to exclude cN+ patients from the two trials evaluating the role of NAC in BCa, since cN+ population appears to be very heterogeneous in terms of survival outcomes. More accurate diagnostic tools are required to guide patients' management on the basis of cN status.

Second, 5-year CSM-free rates were 53 and 24% in cN+ and cN+pN+, respectively. Ho et al. [9] evaluated 55 patients with cN+ disease, reporting CSM-free rates of 44%; similar survival outcomes were observed by Zargar-Shoshtari et al. [10]. Our data replicate these survival expectancies in cN+ and demonstrated that pathologically confirmed node-positive patients are those affected by worse survival expectancies. In this setting, it appears unjustified to exclude cN+ from surgery that should be offered to these patients with an extended PLND to guarantee a correct staging, reserving adjuvant chemotherapy when indicated. In this context, Galsky et al. [8] reported data from National cancer database comparing cN+ patients treated with chemotherapy alone, cystectomy alone, NAC followed by RC and RC followed by adjuvant chemotherapy. Overall survival for patients treated with NAC and RC or RC and adjuvant chemotherapy was similar to those reported our series and previous literature. On the other hand, patients treated with RC only or chemotherapy only suffered from worse survival outcomes.

Third, in our series the use of adjuvant chemotherapy was associated with improved survival outcomes in cN+pN+ and in cN+ patients. Specifically, at multivariable analyses adjuvant chemotherapy improved overall survival in cN+ and even more in those with pathologically confirmed node metastases. These data confirm the utility of a multimodal treatment for patients with node metastases, but also suggest that not all patients with cN+ need adjuvant chemotherapy.

The importance of our study consists in several factors. First, in our work we propose an approach consisting in offering RC and PLND to cN+ patients without NAC. Reserving the use of cisplatin-based chemotherapy on the bases of pathological findings, for example only to patients with adverse pathological characteristics. In the absence of prospective trials evaluating NAC for cN+ patients and given the heterogeneity of this population, new data are required to define the patients that might benefit more from this approach. Second, our study benefits from a large single-center experience of patients treated with extended and superextended PLND regardless of preoperative characteristics. The single-center nature of our report overpasses some limitations that can be found in big multicentric collaboration. Despite several strengths, our study is not devoid of limitations. First and foremost, we recognize that our study is limited by its observational nature and, thus, our results should be interpreted within the limits of retrospective design. Second, our data included only patients treated with RC and no patients in our series were treated with chemotherapy alone. Therefore, it is not possible to make any comparison between different types of treatments or to exclude the selection bias that affects this retrospective series. Moreover, no data regarding type of regimens of chemotherapy used were available in our cohort. Third, all patients included in our cohort underwent RC at a high-volume tertiary referral center with a dedicated uro-pathologist. Therefore, our findings are representative of this clinical scenario and might not be applicable to other settings with less experience in identifying positive node metastases.

## Conclusion

In this single-center experience, we report good survival rates in cN+. Only half of the patients with cN+ were found with pathological node disease. Adjuvant chemotherapy appears to be effective, especially in the group of patients with pathological node-positive disease. Physicians should consider these results in the management of cN+ patients.

**Author contributions** MM Project development, Manuscript writing, Data analysis. AM Project development. JC Project development, Data Collection. SFS Manuscript writing, Data analysis. PDO Project development, Data Collection. EZ Project development, Data Collection. AS Manuscript writing, Data analysis. FM Manuscript writing, Data analysis. AB Project development. RC Project development. AG Project development, Manuscript writing.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** All person gave their informed consent to use their data for this retrospective study.

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