Impact of hydronephrosis and kidney function on survival in newly diagnosed advanced cervical cancer

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A B S T R A C T

Objectives: To assess the impact of hydronephrosis and kidney function in newly diagnosed advanced cervical cancer patients.

Methods: A retrospective cohort study of newly diagnosed cervical cancer stage IIIB to IVB was conducted in a tertiary hospital in Brazil. Data from clinical records between 2014 and 2018 were reviewed. A total of 285 women with advanced cervical cancer and no previous cancer treatment were included. 108 (37.9%) patients were diagnosed with hydronephrosis (HN) before or during the first treatment, 49 (17.2%) patients underwent ureteral obstruction relief, and emergency hemodialysis was performed in 17 patients due to uremia. The median overall survival (mOS) was 46.9 months for non-HN, 19.2 months for unilateral-HN, and 10.0 months for bilateral-HN (non-HN vs HN-groups, p = 0.0001). Patients with eGFR <60 mL/min/1.73 m² had mOS 23.4 months, 23.5 months, and 11.1 months for non-HN, unilateral-HN and bilateral-HN, respectively (non-HN vs bilateral-HN, p = 0.002). Patients with eGFR <60 mL/min/1.73 m² had mOS 23.4 months, 19.2 months, and 10.0 months for non-HN, unilateral-HN and bilateral-HN, respectively (non-HN vs bilateral-HN, p = 0.003). In the HN group, mOS was 11.2 months among those who underwent urinary diversion and 15.6 months among those who did not; p = 0.2. On multivariate analysis, cancer treatment, FIGO stage, and HN were prognostic factors for OS; however eGFR <60 mL/min/1.73 m² does not appear to be associated with worse survival by itself (p = 0.7).

Conclusion: HN seems to have a negative effect on survival of patients with cervical cancer even after adjustment for FIGO stage and cancer treatment. The mOS does not appear to be worse in patients with HN who required urinary diversion compared to those who did not.

1. Introduction

Cervical cancer is the 4th most common cancer in women and the 9th most frequent cause of cancer death worldwide (Bray et al., 2018). In Brazil, cervical cancer is the third most common malignancy in women and the fourth cause of cancer death in this group (Estimativa, 2020). Around the world an increased incidence and mortality by this disease is found in developing nations when compared to more developed countries; in some of these countries it is still the most common cause of cancer death in women, affecting disproportionately underserved and resource poor populations (Arbyn et al., 2020).

Hydronephrosis is a frequent complication of cervical cancer and is associated with a poorer prognosis (Rose et al., 2010; Logsdon and Eifel, 1999; Chao et al., 1998). Its incidence in advanced cervical cancer ranges from 17% to 48.9% at diagnosis (Pradhan et al., 2011; Maguire et al., 2020) and if not treated it can cause renal dysfunction and death. Patients with renal impairment may have restrictions to receive cisplatin during chemoradiation and are at increased risk of toxicities and treatment complications when compared to patients with normal kidney function (KartiwaHadiNuryanto, 2019; Horan et al., 2006; Rose et al., 1999).

The aim of this study was to determine the impact of hydronephrosis and renal dysfunction on the survival of newly diagnosed patients with stage IIIB to IVB cervical cancer at a high-volume center in Brazil dedicated to breast and gynecologic oncology.

2. Methods and materials

All medical records of patients diagnosed with cervical cancer at Hospital Femina, Porto Alegre, Brazil (tertiary care hospital specialized in gynecological and breast cancer) from January 2014 to December 2018 were retrospectively reviewed. Patients included had to have histologically confirmed cervical cancer and stage IIIB to IVB by FIGO 2018 classification. All staging were reviewed and classified according...
to FIGO 2018 staging for cervical cancer. Lymph node (LN) involvement was determined by computed tomography scan (CT) or magnetic resonance imaging (MRI), as PET/CT was not available and biopsies were not performed in most cases. LNs with short diameters ≥ 10 mm were considered pathologic. Baseline information about disease stage, age at cancer diagnosis (years), height (cm), weight (Kg), performance status (PS), cancer histology, pelvic sidewall involvement, pelvic LN, renal function at diagnosis of cancer and before cancer treatment, cancer treatment modalities and treatment performed for ureteral obstruction relief (if any) were obtained from electronic medical records.

The standard of care for locally advanced cervical cancer at our institution is external pelvic radiation with concurrent weekly cisplatin chemotherapy followed by brachytherapy, which is in accordance with most international guidelines. Presence of LN, whether unilateral or bilateral, was assessed by intravenous pyelography (IP), ultrasound (US), CT scan or MRI. All women that presented with LN before or during the first cancer treatment were included in the LN group. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault Equation at diagnosis, before and after urinary diversion, and before cancer treatment.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25.0 computer software. Overall survival (OS) was calculated using Kaplan-Meier method from the date of the biopsy to death from any cause and was censored at the last follow-up date if the patients were alive. Log-rank test was used to compare the differences in survival between non-HN, unilateral-HN and bilateral-HN patients and between patients with and without renal dysfunction according to the eGFR (eGFR below 60 mL/min/1.73 m² was considered altered). This eGFR cutoff point was chosen according to our institutional protocol which recommends not using cisplatin below this point. Fisher’s exact tests were used to evaluate the association between HN groups and baseline traits. Chi-square tests were used to assess relationships between categorical variables. The Wilcoxon signed rank test was used to compare continuous variables between two level categorical variables. A univariate and multivariate Cox regression model was used to identify prognostic factors for OS. Variables with significance in the univariate test were selected for a multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by Cox proportional hazard regression analysis. The p-values < 0.05 were considered statistically significant.

The study was conducted in accordance with applicable regulatory requirements and was approved by the Ethics Committee of Hospital Nossa Senhora da Conceição/Hospital Femina under the number 19389119.8.0000.5530. The application of the consent form was waived.

### 3. Results

A total of 285 patients were included. Only one patient could not be evaluated in regard to the presence of HN for not having been submitted to any modality of urinary tract imaging exam. The mean age at diagnosis was 49.3 years (range 22.9–92.4 years). One hundred and eight patients (37.9%) were diagnosed with HN before or during the initial treatment for cervical cancer, 57 (52.8%) unilateral-HN and 51 (47.2%) bilateral-HN. Squamous cell carcinoma (SCC) was the most frequent histology in all groups, present in 90.1% of cases. Bilateral pelvic sidewall involvement was more frequent in patients with bilateral-HN than unilateral-HN or non-HN (p = 0.0001). Pelvic positive nodal involvement was identified in 123 (43.3%) patients (81 stage IIC, 8 stage IVA and 34 stage IVB), 87 (30.6%) patients did not have LN evaluated and 74 (26.1%) were LN negative. The majority of patients were diagnosed with stage III: 137 (48.2%) stage IIB, 81 (28.5%) stage IIC, 26 (9.2%) stage IVA and 40 (14.1%) stage IVB. The median eGFR at initial diagnosis of cervical cancer was 107.2, 84.6, and 37.6 mL/min/1.73 m² for women without HN, unilateral-HN and bilateral-HN, respectively (non-HN vs unilateral-HN, p = 0.015; non-HN vs bilateral-HN, p = 0.0001; unilateral-HN vs bilateral-HN, p = 0.001). The eGFR could not be calculated in nine patients because there was no weight or height available in the records.

Treatment with concurrent chemoradiation (CCRT) + brachytherapy was performed in 154 (54.0%) patients, CCRT without brachytherapy in 74 patients (26.0%), radiation therapy (RT) alone in 32 (11.2%), chemotherapy alone in 12 (4.2%), best supportive care (BSC) in 12 (4.2%) and not available 1 (0.4%). Of the 108 patients with LN, 68 (62.9%) patients received CCRT (63 with cisplatin, 3 with gemcitabine and 2 with carboplatin). All 5 patients who received CCRT without cisplatin had eGFR < 30 mL/min/1.73 m³, and all improved kidney function after the end of cancer treatment (3 underwent percutaneous nephrostomy (PCN)). Median time to start treatment with CCRT or RT alone was 71.0 days for non-HN, 77.5 days for unilateral-HN and 65.0 days for bilateral HN, p = 0.16. The baseline patient characteristics and treatment, according to HN status, are seen in Table 1.

On univariate Cox regression analysis, presence of pelvic LN, HN at diagnosis, FIGO stage IVA or IVB, cancer treatment (no CCRT), eGFR < 60 mL/min/1.73 m² prior to cancer treatment were all associated with worse OS (p = 0.0001) (Table 2A). On multivariate analysis adjusted for cancer treatment, FIGO stage and eGFR, women with HN had a 50% increased risk of death compared with women without HN [hazard ratio (HR), 1.50; p = 0.042] (Table 2B). The presence or absence of pelvic LN disease was omitted from multivariate analysis because of a large number (30.6%) of missing data.

Among the 108 patients with HN, there was no statistically significant difference between HN relieved and HN not relieved groups in relation to age, race, histology, pelvic wall involvement, pelvic node, FIGO and PS. Forty-nine patients (45.4%) received renal obstruction relief treatment: 14/49 (28.6%) unilateral PCN, 29/49 (59.2%) bilateral PCN, and 7/49 (14.3%) double J stent (one patient did unilateral PCN + unilateral double J). The median eGFR from patients submitted to urinary diversion treatment increased from 10.6 to 59.7 mL/min/1.73 m² after the procedure (p = 0.0001). Emergent hemodialysis was necessary in 17 (15.7%) patients (15 underwent urinary diversion and 2 did not). All women in the hemodialysis group that received obstruction relief treatment improved their renal function. The median eGFR before hemodialysis was 6.47 mL/min/1.73 m² (17 patients) and improved to 47.4 mL/min/1.73 m² after renal obstruction relief (15/17) (p = 0.004). In total, 9/49 (18.4%) women who underwent urinary diversion were alive in the last assessment, and three of them had received dialysis.

The mOS was 46.9 months for patients without HN, 19.2 months for unilateral-HN and 10.0 months for bilateral-HN (non-HN vs HN groups; p = 0.0001; unilateral-HN vs bilateral-HN; p = 0.094) (Fig. 1). Among patients who underwent CCRT + brachytherapy, mOS was not reached (NR) in patients with non-HN and bilateral-HN and was 66.6 months in patients with unilateral-HN (p = 0.66), while the mOS for patients who underwent CCRT without brachytherapy or RT alone was only 26.3 months for non-HN, 14.5 months for unilateral-HN and 9.0 months for bilateral-HN (p = 0.07 between non-HN and unilateral-HN; p < 0.01 between the other comparison). The mOS was 11.2 months for HN with relief and 15.6 months for HN without relief; p = 0.2 (Fig. 2). Among patients with HN, mOS was 10.0 months for the dialysis group and 14.6 months for the non-dialysis group; p = 0.47. Patients with eGFR ≥ 60 mL/min/1.73 m², before or during the first cancer treatment, had mOS of 46.9 months, 23.5 months, and 11.1 months for non-HN, unilateral-HN, and bilateral-HN groups, respectively (p = 0.002 between non-HN and bilateral-HN; p = 0.09 between non-HN and unilateral-HN; there was no statistically significant difference in other comparisons) and the mOS for patients with eGFR < 60 mL/min/1.73 m² was 23.4 months, 19.2 months, and 10.0 months for non-HN, unilateral-HN and bilateral-HN, respectively (p = 0.003 between non-HN and bilateral-HN; there was no statistically significant difference in the other comparisons).
Table 1
Characteristics of the Patients by Hydronephrosis Status.

|                      | Non-Hydronephrosis (N = 176) no(%) | Unilateral Hydronephrosis (N = 57) no(%) | Bilateral Hydronephrosis (N = 51) no(%) | p-value |
|----------------------|----------------------------------|----------------------------------------|----------------------------------------|---------|
| Mean age (range) - Yr| 48.4 (25.0–92.4)                | 50.1 (23.5–79.7)                      | 51.5 (22.9–88.3)                      | 0.35    |
| Race *               |                                  |                                        |                                        | 0.97    |
| White                | 145 (82.4)                       | 48 (84.2)                             | 42 (82.4)                             |         |
| Black                | 21 (11.9)                        | 7 (12.3)                              | 7 (13.7)                              |         |
| Other                | 10 (5.7)                         | 2 (3.5)                               | 2 (3.9)                               |         |
| Histology *          |                                  |                                        |                                        | 0.97    |
| Adenocarcinoma       | 10 (5.7)                         | 2 (3.5)                               | 2 (3.9)                               |         |
| Squamous             | 158 (89.8)                       | 52 (91.2)                             | 46 (90.2)                             |         |
| Other                | 8 (4.5)                          | 3 (5.3)                               | 3 (5.9)                               |         |
| Pelvic wall involvement * |                          |                                        |                                        | 0.0001  |
| None                 | 42 (23.9)                        | 18 (31.6)                             | 9 (17.6)                              |         |
| Unilateral           | 66 (37.5)                        | 13 (22.8)                             | 3 (5.9)                               |         |
| Bilateral            | 62 (35.2)                        | 23 (40.4)                             | 36 (70.6)                             |         |
| Yes (without specification) |                          | 2 (1.1)                              | 0 (0.0)                               |         |
| Not available        | 4 (2.3)                          | 3 (5.3)                               | 2 (3.9)                               |         |
| Pelvic node status * |                                  |                                        |                                        | 0.48    |
| Negative             | 51 (29)                          | 11 (19.3)                             | 12 (23.5)                             |         |
| Positive             | 70 (39.8)                        | 29 (50.9)                             | 24 (47.1)                             |         |
| FIGO 2018 *          |                                  |                                        |                                        | 0.0001  |
| IIIB                 | 97 (55.1)                        | 23 (40.4)                             | 17 (33.3)                             |         |
| IIIC                 | 59 (33.5)                        | 12 (21.1)                             | 10 (19.6)                             |         |
| IVA                  | 6 (3.4)                          | 8 (14.0)                              | 12 (23.5)                             |         |
| IVB                  | 14 (8.0)                         | 14 (24.6)                             | 12 (23.5)                             |         |
| Performance status*  |                                  |                                        |                                        | 0.0001  |
| 0                    | 73 (41.5)                        | 11 (19.3)                             | 7 (13.7)                              |         |
| 1                    | 92 (52.3)                        | 35 (61.4)                             | 30 (58.8)                             |         |
| 2                    | 9 (5.1)                          | 8 (14.0)                              | 10 (19.6)                             |         |
| 3                    | 1 (0.6)                          | 3 (5.3)                               | 4 (7.8)                               |         |
| 4                    | 1 (0.6)                          | 0 (0.0)                               | 0 (0.0)                               |         |
| eGFR group at diagnosis ¶ |                          |                                        |                                        | 0.0001  |
| > 60 mL/min/1.73 m²  | 158 (92.4)                       | 44 (80.0)                             | 20 (40.8)                             |         |
| 30–60 mL/min/1.73 m² | 12 (7.0)                         | 11 (20.0)                             | 10 (20.4)                             |         |
| < 30 mL/min/1.73 m²  | 1 (0.6)                          | 0 (0.0)                               | 19 (38.8)                             |         |
| Cancer treatment     |                                  |                                        |                                        |         |
| CCRT + BT            | 120 (68.2)                       | 21 (36.8)                             | 13 (25.5)                             | 0.0001  |
| CCRT without BT      | 40 (22.7%)                       | 20 (35.1)                             | 14 (27.5)                             | 0.28    |
| RT alone*            | 9 (5.1)                          | 7 (12.3)                              | 16 (31.4)                             | 0.0001  |
| Palliative CHT       | 5 (2.8)                          | 3 (5.3)                               | 4 (7.8)                               | 0.44    |
| Best supportive care | 2 (1.1)                          | 6 (10.5)                              | 4 (7.8)                               | 0.009   |

* Fisher’s exact test was used for statistical significance.

BT: Brachytherapy; CHT: Chemotherapy; CCRT: Concurrent Chemoradiation; BSC: best supportive care.
¶ 9 women did not have eGFR calculated because they had no available weight and/or height in the medical record.

Table 2a
Univariate Analysis for evaluation of prognostic factors for Overall Survival.

|                      | Univariate analysis | p Value |
|----------------------|---------------------|---------|
| Pelvic node status   |                     |         |
| (negative vs positive) | 2.52 (1.60–3.96)    | 0.0001  |
| Hydronephrosis at diagnostic (absent vs present) | 2.38 (1.75 – 3.25) | 0.0001  |
| FIGO 2018            |                     |         |
| (IIIB vs IIC)        | 1.22 (0.83–1.82)    | 0.31    |
| (IIIB vs IVA)        | 2.71 (1.66–4.44)    | 0.0001  |
| (IIIB vs IVB)        | 3.88 (2.55–5.91)    | 0.0001  |
| Cancer Treatment     |                     |         |
| CCRT vs RT           | 3.85 (2.56–5.80)    | 0.0001  |
| CCRT vs Others*      | 9.09 (5.68–14.55)   | 0.0001  |
| Hydronephrosis relief (No vs Yes) | 1.30 (0.83–2.02) | 0.24    |
| eGFR prior cancer treatment (>60 vs < 60 mL/min/1.73 m²) | 2.10 (1.46–3.01) | 0.0001  |

* Chemotherapy alone and best supportive care.

Table 2b
Multivariate Analysis for evaluation of prognostic factors for Overall Survival.

|                      | Multivariate analysis | p Value |
|----------------------|-----------------------|---------|
| FIGO 2018            |                       |         |
| (IIIB vs IIC)        | 1.42 (0.94–2.15)      | 0.09    |
| (IIIB vs IVA)        | 2.10 (1.15–3.86)      | 0.016   |
| (IIIB vs IVB)        | 2.44 (1.44–4.10)      | 0.001   |
| Hydronephrosis at diagnostic (absent vs present) | 1.50 (1.01–2.23) | 0.042   |
| Cancer Treatment     |                       |         |
| CCRT vs RT           | 4.32 (2.48–7.55)      | 0.0001  |
| CCRT vs Others*      | 4.55 (2.10–9.96)      | 0.0001  |
| eGFR prior cancer treatment (>60 vs < 60 mL/min/1.73 m²) | 0.91 (0.56–1.51) | 0.73    |

* Chemotherapy alone and best supportive care.

Logistic regression model to predict OS.
Gynecologic Oncology Reports 39 (2022) 100934

4. Discussion

To our knowledge, this is one of the largest cohorts of patients with HN secondary to cervical cancer in the literature so far. The findings corroborate much of what has been previously published in other studies that demonstrated a worse overall survival for patients with urinary obstruction (Rose et al., 2010; Pradhan et al., 2011; Mishra et al., 2009 Jan; Pergialiotis et al., 2019 Jan 14; van Aardt et al., 2017). The prevalence of hydronephrosis in this study was 37.9\%, very similar to that described in the literature (Rose et al., 2010; Chao et al., 1998).

Like in Goklu MR et al. (Goklu et al., 2015), this study showed that patients with HN have worse mOS than patients without HN, but there
was no statistically difference whether HN was unilateral or bilateral. Also, it was observed that patients with HN had the same mOS regardless of having been submitted to urinary diversion or not, which may be explained by baseline differences between the groups and a poor prognosis overall in this population. Nonetheless, this procedure should always be performed when required, as it may allow treatment with concurrent cisplatin plus radiotherapy, a cornerstone of improving overall survival in locally advanced disease, and to avoid serious complications from kidney failure, including death.

Other publications such as Rose et al. (Rose et al., 2010) have reported that patients with stage IIIB and hydronephrosis at diagnosis present worse survival and that hydronephrosis relief is correlated with outcome improvement. Differently from our study, they included only patients with creatinine < 2.0 mg/dl and all patients received radiotherapy with or without chemotherapy. In this study, it was possible to see that patients who were able to undergo standard treatment for cervical cancer had similar survival regardless of the presence of hydronephrosis. When performing urinary tract relief is a question not yet answered, but every effort must be made to ensure that patients can perform standard treatment. Patients with locally advanced cervical cancer with suspected or confirmed HN should always have renal function assessed and monitored and be referred for a diverting procedure urgently when required. We have to acknowledge that in most instances the procedure (either PCN or duple J) was performed in a timely fashion.

This study has some limitations, the first of them being its retrospective design. Second, the sample size limited the possibility of analyzing the different disease stages separately. Third, RT technique and the total dose received could not be evaluated. The prevalence of more advanced stages in patients with HN may be an explanation for the worse survival in this group regardless of renal function and of having been submitted to urinary diversion or not. Finally, it represents a cohort from a single institution and it is representative mostly of the population treated at this center.

Cervical cancer is still an important health issue in developing nations and a major cause of cancer related death in some parts of the world. The grim outcome of locally advanced disease stresses the importance of screening practices to enable treatment before the disease progresses to more advanced stages. As such cases are still an important health problem, physicians treating patients with cervical cancer should be able to recognize and properly treat the complications of the disease in the later stages. Hydronephrosis is one of the most frequent and most serious of these complications; it is of surmount importance to detect and treat it when necessary without further delays.

5. Conclusion

HN seems to have a negative effect on survival of patients with cervical cancer even after adjustment for FIGO stage and cancer treatment. Every effort should be made to improve renal function in patients with HN as this will allow women to receive cancer standard treatment.

CRediT authorship contribution statement

Fernanda Bronzon Damian: Formal analysis, Conceptualization, Methodology, Investigation, Writing – original draft. Fernando Kude de Almeida: Conceptualization, Writing – original draft. Fernando Schmidt Fernandes: Writing – original draft. Mirela Foresti Jimenez: Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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