Submitted: 23 May, 2024 Accepted: 25 June, 2024 Published: 15 December, 2024 DOI:10.22514/ejgo.2024.117

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Management of persistent post-treatment cervical FDG-avidity after definitive chemoradiation for locally advanced cervical cancer

Claire Hoppenot[1,2,*], Yingao Zhang[1], Sarah Tounsi[1], Daniela C Marcano[3], Tracilyn R Hall[1,2]

[1]Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX 77030, USA
[2]Gynecologic Oncology Division, Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX 77030, USA
[3]Baylor College of Medicine, Houston, TX 77030, USA

***Correspondence**
Claire.hoppenot@bcm.edu
(Claire Hoppenot)

Abstract

Fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PETCT) imaging is recommended to assess the response after completion of definitive chemoradiation for the treatment of locally advanced cervical cancer. False-positive residual avidity is common and may lead to further workup or interventions. We aim to describe a cohort of patients treated with definitive chemoradiation for locally advanced cervical cancer with cervical avidity on post treatment PETCT; in particular the patterns of cervical recurrence and concordance with PETCT FDG avidity. This is a retrospective review of patients between 2015–2021 at a safety-net hospital system who underwent definitive chemoradiation for stage IB2–IVA cervical cancer, underwent post-treatment PETCT, and had post-treatment avidity in the cervix. 145 patients were included, of which 79 (55%) patients had post-treatment avidity in the cervix. The median cervical standardized uptake value (SUV) measurement was 5. The work up of these 79 patients with residual cervical avidity varied including biopsy, repeat imaging, or placement on surveillance. 16 (20.5%) patients in the cohort ultimately were diagnosed with persistent or progressive disease. No patients with SUV <5 (49%) had persistent cervical disease. The majority of the recurrences were not detected until more than 11 months after treatment completion in our patient population Persistent cervical FDG-avidity is common after treatment with definitive chemoradiation for locally advanced cervical cancer. However, persistent disease is less common. To triage further work up, our data suggests that patients with SUV <5 are unlikely to have persistent cervical disease and can be considered for repeat imaging alone. Those with cervical SUV of 5 or higher could consider repeat biopsy or exam under anesthesia based on physical exam, versus close follow-up with repeat imaging. The average time to recurrence of almost 1 year makes close surveillance for the two years after treatment crucial.

Keywords

Cervical cancer; Persistent FDG avidity; Chemoradiation

1. Introduction

Cervical cancer is the fourth most common cancer among women in the world, with an estimated 604,000 new cases and 342,000 deaths in 2020 [1]. Locally advanced cervical cancer (LACC) includes FIGO (International Federation of Gynecology and Obstetrics) 2018 stages IB3–IVA [2]. Contemporary treatment for LACC typically includes radiation therapy with concurrent radiosensitizing platinum-based chemotherapy, followed by brachytherapy [3]. After treatment completion patients typically undergo imaging with 18F-FDG-PETCT to determine the response to treatment [3].

While FDG-PETCT is a powerful and sensitive tool in the diagnosis and treatment of most solid organ malignancies, FDG uptake can also be seen in healthy tissues with altered glucose metabolism, such as local inflammation and post-surgical healing [4]. Previous studies have shown up to a 12.5% false positive rate in the first FDG-PET scan after definitive chemoradiation [5]. This is not an insignificant rate as additional workup and potential treatment for presumed persistent disease may increase patient morbidity, create financial toxicity, and result in adverse long-term outcomes.

While the current recommendations indicate post-treatment surveillance imaging at 3–6 months, most institutions, including our safety-net county health system, employ a 3-month follow-up to maximize the detection of persistent or progressive disease. This study aims to describe our management of persistent post-treatment cervical FDG-avidity for a cohort of women treated for locally advanced cervical cancer with definitive chemoradiation.

2. Materials and methods

2.1 Cohort selection

This was a retrospective review of all patients diagnosed with locally advanced cervical cancer between 2015–2021 in a safety-net county health system. All included patients had biopsy proven stage IB2–IVA cervical cancer and underwent definitive chemoradiation at our institution followed by post-treatment imaging with PETCT to assess treatment response. Patients were identified using a built-in data extraction tool *via* the electronic medical record. Patients were excluded if they underwent hysterectomy, received chemotherapy prior to definitive chemoradiation, had a concurrent malignancy, had unconfirmed pathology or did not complete their primary treatment plan.

2.2 Data collection

Demographic and clinical variables were retrospectively abstracted from the electronic medical record. Radiation therapy data and chemotherapy data, including dosages, were obtained. Time to first post-treatment PETCT scan was calculated from the last day of either brachytherapy or radiation fraction. The official PETCT scan results in the chart were used to abstract the FDG avidity as well as its location and change over time, which was then correlated with further testing and treatment as documented in the chart. Recurrence-free survival (RFS) was measured from the date of diagnosis to the date of recurrence, last follow-up, or death from another cause. Overall survival (OS) was measured from the date of diagnosis to the date of death from any cause or last follow up. Patients who survived were censored at the date of their last contact.

2.3 Statistical methods

The software packages STATA (version 17, StataCorp, College Station, TX, USA) and Prism (version 9, Graphpad, Boston, MA, USA) were used for statistical analysis and modeling. Descriptive statistics with *t*-tests and chi-squared tests were used to summarize and compare clinical variables. Univariable and multivariable analyses were performed using simple and multiple logistic regression models, respectively. Survival analysis was performed on a Kaplan-Meier estimator using the log-rank method. Statistical significance was set at $p = 0.05$.

3. Results

Our cohort included 145 patients with LACC who underwent definitive chemoradiation follow by PETCT during our study time frame, of which 79 (55%) patients were identified as having post-treatment FDG avidity in the cervix. The median age was 47 years, most patients self-identified identified as Hispanic, and the most common stage at diagnosis was stage III (Table 1). Sixty-four patients (81%) had squamous cell carcinoma (SCC), and 65 patients (82%) completed 5 cycles of radiosensitizing cisplatin during chemoradiation. All patients received external beam radiation with a median treatment dose of external beam radiation therapy of 51.75 Gy. Seventy-four (94%) patients received brachytherapy with either interstitial brachytherapy or tandem and ovoids. The remaining 5 (6%) received stereotactic body radiotherapy (SBRT) due to inability to tolerate or receive brachytherapy. The median time to completion of all treatments was 52 days (range 37–91). The median time to PETCT from treatment completion was 93 days (range 33–191 days). There was no significant difference in the timing of PETCT from treatment completion in the 79 patients with persistent FDG avidity in the cervix when compared to the 66 patients who completed definitive chemoradiation without persistent FDG cervical avidity.

The median residual cervical SUV measurement was 5 (range 2–33). The work up management of these 79 patients with residual FDG cervical avidity varied including biopsy, repeat imaging, or placement on surveillance (Table 2). One patient had stable cervical FDG avidity with post treatment SUV of 21.9 that confirmed persistent disease. Two patients had new metastatic disease on PETCT, with or without lack of change in cervical SUV, confirming progression. Eighteen patients underwent biopsy of the cervix, with or without further imaging after PETCT, and 3 confirmed persistent cancer. Additionally, 4 patients underwent biopsy of extra-cervical avid lesion(s). Cervical biopsy was deferred in favor of only repeat imaging in 32 patients. Seventeen patients were placed on surveillance due to decrease in PETCT avidity on the post treatment PETCT scan compared to pretreatment scan. The remaining 5 patients were placed on surveillance based on decrease in tumor size on pre and post treatment imaging.

Sixteen (20.5%) patients in the cohort who had cervical PETCT avidity at the first post-treatment PETCT ultimately were diagnosed with persistent or progressive disease (Table 3). Of the 18 cervical biopsies, 3 (16.5%) were positive for persistent disease. These 3 patients with positive biopsies had residual SUV in the cervix of 8.1 to 8.5. No patients with SUV <5 (n = 39, 49%) had persistent cervical disease either on biopsy or subsequent PETCT. Of the patients with SUV ≥ 5 who did not undergo biopsy, 6/28 (21.4%) had persistent cervical disease on repeat PETCT. Additionally, there were 4 patients with residual cervical FDG avidity and avidity outside the cervix with biopsy proven persistent or progressive disease at extra cervical locations. One patient without persistent cervical avidity had biopsy-proven persistent extra-cervical disease.

We had an average follow up of 19.1 months (range 11–41 months). Overall, 18 patients had a cervical cancer recurrence that included the cervix; median RFS was 9.1 months (range 4.8 to 17 months) and median OS was 19 months (range 11 to 40.6 months). There were only 3 that were cervical confined and candidates for surgical management, 2 of which occurred in the cohort of residual avidity <5 and the remaining 1 patient was in the cohort with no residual FDG avidity in the cervix.

4. Discussion

PETCT is commonly used in locally advanced cervical cancer for treatment planning and to assess treatment response after definitive chemoradiation [3]. In the post-treatment period, a negative PETCT scan in 3–6 months has been shown to be associated with an improved 2-year overall survival [6]. While negative scans are reassuring, our data suggest there is

TABLE 1. Demographics, tumor and treatment information.

	All patients identified as receiving chemoradiation for LACC (N = 145)	Patients with persistent cervical avidity on post-treatment PETCT (N = 79)
Age (med, range)	48 (28–82)	47 (28–82)
Race (#, %)		
Hispanic	97 (66.9%)	54 (68.3%)
Black	25 (17.2%)	13 (16.5%)
White, non-hispanic	14 (9.6%)	7 (8.9%)
Other	9 (6.3%)	5 (6.3%)
Tumor presentation:		
Stage (#, %)		
IB1	2 (1.4%)	0
IB2	5 (3.5%)	3 (3.8%)
IB3	12 (8.2%)	7 (8.9%)
IIA	5 (3.5%)	3 (3.8%)
IIB	30 (20.7%)	11 (13.9%)
IIIA	2 (1.4%)	1 (1.2%)
IIIB	13 (9.0%)	9 (11.4%)
IIIC1	53 (36.6%)	29 (36.7%)
IIIC2	16 (11.0%)	11 (13.9%)
IVA	7 (4.8%)	5 (6.3%)
Median pretreatment tumor size (cm) (range)	5.6 (0.8–11.5)	5.8 (2.1–11.5)
Histology		
Squamous	120 (82.8%)	64 (81.0%)
Adenocarcinoma	17 (11.7%)	11 (13.9%)
Other	8 (5.5%)	4 (5.1%)
Patient treatments		
Chemoradiation	145 (100%)	79 (100%)
≥5 cycles cisplatin	112 (77.2%)	65 (82.3%)
Radiation treatment		
Median EBRT dose (Gy)	51.75	51.75
Tandem and Ovoid	94 (64.8%)	49 (62.0%)
Syed	41 (28.3%)	25 (31.6%)
SBRT	10 (6.9%)	5 (6.3%)
Median time to finish EBRT (d)	40	38
Median time to finish all treatments (range) (d)	51 (36–91)	52 (37–91)
Median time to PETCT (d)	94	93
Complete metabolic response to treatment in the cervix	66	0
Median persistent SUV avidity (range)	0	5 (2–33)

LACC: Locally advanced cervical cancer; PETCT: positron emission tomography with computed tomography; EBRT: external beam radiotherapy; SBRT: stereotactic body radiotherapy; SUV: standardized uptake value.

TABLE 2. Management of patients with FDG cervical avidity on post-treatment PETCT (N = 79).

Number of patients (N = 79)	Clinical management after initial post-treatment cervical FDG-avidity
1	Confirmed persistent disease by unchanged cervical SUV from prior to treatment
2	Confirmed progressive disease with new metastatic disease +/− stable cervical SUV
18	Cervical biopsy +/− repeat PETCT
4	Extra-cervical biopsy confirmed persistent/progressive disease
32	Repeat routine asymptomatic PETCT only
17	Placed on surveillance due to decrease in avidity between pre and post treatment PETCT
5	Placed on surveillance due to decrease in tumor size between pre and post treatment imaging

FDG: fluorodeoxyglucose; SUV: standardized uptake value; PETCT: positron emission tomography with computed tomography.

TABLE 3. Outcome of work up for FDG cervical avidity on post-treatment PETCT.

	Neg FDG cervical avidity (n = 66)	SUV <5 (n = 39)	SUV ≥5 (n = 40)
Diagnosed with progressive or persistent disease at first PETCT	1	3	13
Biopsy with persistent cervical disease	0	0	3
Lack of SUV change confirmed persistent disease	0	0	1
Repeat asymptomatic PETCT with persistent cervical disease	0	0	6
Placed on surveillance	65	36	27

FDG: fluorodeoxyglucose; SUV: standardized uptake value; PETCT: positron emission tomography with computed tomography.

a high rate of patients treated with definitive chemoradiation who have persistent cervical avidity on post treatment PETCT.

Our data is in line with the paucity of data available on the use of PETCT for the management of LACC. In a retrospective review of PET scans at least 6 months after treatment for cervical cancer, Peters *et al.* [7] found that almost 10% were due to previous ambiguous findings, suggesting that close follow up of these abnormal findings is common practice. RFS was similar in this study to our data (around 11–15 months), and patients with diagnosis after an asymptomatic PETCT had longer OS. Unfortunately, they did not look at the chance of recurrence related to SUV-avidity.

Another retrospective review focused on the prognostic ability of PETCT parameters before and after chemoradiation [8]. SUV avidity of the cervix pretreatment was not prognostic, but the avidity 7 months after treatment was associated with OS. Interestingly, the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were more predictive. These PETCT scans occurred later than the PETCT in our data, and we did not look at advanced PETCT parameters such as MTV and TLG.

A meta-analysis from 2019 shows that post-treatment PETCT SUV avidity is a strong prognostic factor for OS in cervical cancer patients [9]. These studies however looked at complete *vs.* partial metabolic response versus progressive disease, without mention of actual FDG avidity and levels that are more likely to be associated with ongoing remission and should be approached thoughtfully. Our data suggest that even in patients with persistent cervical FDG avidity, an initial remission is achieved for the majority of patients after definitive chemoradiation. Our data also suggests, in addition to no residual FDG avidity, residual PET avidity of SUV <5 in the cervix may be reassuring and biopsies can be avoided unless there is a high clinical suspicion for persistent cancer. Conversely, our data suggest when there is an SUV ≥5, persistent disease occurs at a higher rate and further work up should be considered. A prior retrospective chart review showed that OS was similar for cervical cancer patients treated with chemoradiation who had complete response at initial post-treatment PETCT (3 months) and those who took another 3 months for complete response on a PETCT at 6 months after treatment [10]. While our patients had a lower rate of complete metabolic response, our patient population was overall more advanced that this study. These findings again support that watchful waiting may be a safe option in certain situations.

Our data suggest that in the setting of persistent SUV avidity consistent with persistent disease, isolated central cervical disease is rare. Most recurrences for our patients with LACC treated with definitive chemoradiation in our study were not limited to the cervix. In the previously referenced retrospective review, 34% of patients had pelvic recurrences, but they do not differentiate isolated to the cervix [7]. Furthermore, the majority of recurrences do not occur until after the typical timing of post treatment response PETCT assessment, making ongoing surveillance crucial.

The main limitation of this study is its retrospective nature, collecting patients in a time period before the addition of immunotherapy or induction chemotherapy to cervical cancer treatment protocols. It is also important to note that central persistence of disease and FDG-avidity were our primary focus.

5. Conclusions

Persistent FDG avidity on post treatment PETCT scan after definitive chemoradiation in the treatment of LACC is common. Residual SUV levels should be considered when determining the concern for persistent disease and work up. To triage further work up, our data suggests that patients with SUV <5 are unlikely to have persistent cervical disease and can be considered for repeat imaging alone. Those with cervical SUV 5 or higher could consider repeat biopsy or exam under anesthesia based on physical exam, versus close follow-up with repeat imaging. The average time to recurrence of almost 1 year makes close surveillance for the two years after treatment crucial.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article. Additional data are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

CH and YGZ—performed the initial literature review and wrote the IRB. CH and TRH—provided expert consultation including data analysis and manuscript composition. TRH—initiated the concept for this paper and supervised this project in its entirety. CH, YGZ, TRH, ST and DCM—contributed to data collection and editing of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This was a retrospective review of all patients diagnosed with locally advanced cervical cancer between 2015–2021 in a safety-net county health system approved by the institutional review board (IRB) (Harris Health System IRB, protocol number: 21-10-2741). A waiver of consent was approved.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[2] Raut A, Chopra S, Mittal P, Patil G, Mahantshetty U, Gurram L, *et al*. FIGO classification 2018: validation study in patients with locally advanced cervix cancer treated with chemoradiation. International Journal of Radiation Oncology, Biology, Physics. 2020; 108: 1248–1256.

[3] National Comprehensive Cancer Network. Cervical cancer 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (Accessed: 16 April 2023).

[4] Rosenbaum SJ, Lind T, Antoch G, Bockisch A. False-positive FDG PET uptake—the role of PET/CT. European Radiology. 2006; 16: 1054–1065.

[5] Chung HH, Jo H, Kang WJ, Kim JW, Park NH, Song YS, *et al*. Clinical impact of integrated PET/CT on the management of suspected cervical cancer recurrence. Gynecologic Oncology. 2007; 104: 529–534.

[6] Gandy N, Arshad MA, Park WE, Rockall AG, Barwick TD. FDG-PET imaging in cervical cancer. Seminars in Nuclear Medicine. 2019; 49: 461–470.

[7] Peters PN, Pierson WE, Chen LM, Westphalen AC, Chapman JS, Hsu IC. PET-detected asymptomatic recurrence is associated with improved survival in recurrent cervical cancer. Abdominal Radiology. 2021; 46: 341–350.

[8] Markus M, Sartor H, Bjurberg M, Trägårdh E. Metabolic parameters of [^{18}F]FDG PET-CT before and after radiotherapy may predict survival and recurrence in cervical cancer. Acta Oncologica. 2023; 62: 180–188.

[9] Kim YJ, Han S, Kim YS, Nam JH. Prognostic value of post-treatment ^{18}F-fluorodeoxyglucose positron emission tomography in uterine cervical cancer patients treated with radiotherapy: a systematic review and meta-analysis. Journal of Gynecologic Oncology. 2019; 30: e66.

[10] Michaan N, Wenkert A, Even-Sapir E, Kerzhner K, Rabin T, Safra T, *et al.* Prognostic significance of delayed complete metabolic response on PET/CT after primary chemoradiation treatment of cervical cancer. International Journal of Gynecologic Cancer. 2023; 33: 1695–1701.

How to cite this article: Claire Hoppenot, Yingao Zhang, Sarah Tounsi, Daniela C Marcano, Tracilyn R Hall. Management of persistent post-treatment cervical FDG-avidity after definitive chemoradiation for locally advanced cervical cancer. European Journal of Gynaecological Oncology. 2024; 45(6): 67-71. doi: 10.22514/ejgo.2024.117.