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Detection of distant metastatic disease by positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) at initial staging of cervical carcinoma

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Abstract

Objective—The detection of distant metastatic disease in cervical cancer patients at diagnosis is critical in accurate prognostication and directing treatment strategies. This study describes the frequency and sites of distant metastatic disease at diagnosis in patients with cervical cancer as detected by positron emission tomography with ¹⁸F-fluorodeoxyglucose (FDG-PET).

Methods—Patients with newly diagnosed cervical cancer underwent pre-treatment whole-body FDG-PET starting in 1997 at an academic institution. Patients with evidence of distant FDG-avid disease, defined as disease outside of typical sites of lymphatic spread, were included for analyses. Patients were not surgically-staged, but biopsy to confirm metastatic disease was attempted at the discretion of the treating physicians. Overall survival was calculated using Kaplan-Meier analysis.

Results—From 1997–2017, 72 (6.2%) of 1158 consecutively evaluated cervical cancer patients exhibited FDG-avid distant disease at diagnosis; 27 (38%) of these had biopsy confirmation of distant disease. Only 35 (49%) of FDG-detected metastases were clinically apparent. The sites of distant disease were lung (35%), multiple sites (25%), omentum (16.5%), bone (16.5%) and liver (7%). There were 12 (17%) patients with distant disease who did not display FDG-avid lymph nodes. Median overall survival amongst patients with distant FDG-avid disease was 7.0 months (95% CI; 4.3–9.7). Patients with multiple sites of distant disease demonstrated the worst overall survival.

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Conclusions—Distant metastatic disease detected by FDG-PET is found in 6.2% of patients with cervical cancer at the time of initial diagnosis and the most common site of disease is the lung. Further prospective investigation is warranted to delineate best treatment practices for cervical cancer patients presenting with distant metastases.

Keywords

Cervical cancer; FDG-PET; distant metastasis; omental; peritoneal

Introduction

Cervical cancer accounted for 311,000 deaths worldwide in 2018 and is the fourth leading cause of cancer death in women.¹ The presence of distant metastatic disease portends poor clinical outcomes, with median overall survival of 8 to 13 months.² The patterns of spread of metastatic cervical cancers have been described in a number of autopsy studies. These reports highlight distant involvement most commonly within the lung, liver, and bone.^{3–6} Accurate knowledge of the relative frequency of disease involvement in each distant site has led to national guidelines on appropriate pre-treatment imaging.⁷

Whole-body positron emission tomography with ¹⁸F-fluorodeoxyglucose (FDG-PET) has demonstrated marked utility in management of uterine cervix carcinoma.⁸ FDG-PET allows evaluation of metabolic tumor volume at diagnosis and identifies lymph node involvement and distant metastatic disease.^{9–11} Metabolic tumor response has been associated with patterns of failure.¹² Clinically occult FDG-avid lymph node and distant involvement have also been shown to be independent predictors of poor survival after treatment.¹³ Further identifying the distribution of FDG-avid distant metastasis in these patients may lend insight on the natural progression of cervical cancer, which may help physicians delineate best treatment practices.^{14–16} Our institution has routinely used FDG-PET for staging of cervical cancer since 1997. In this study, we report the site-frequency of FDG-avid distant disease and report survival based on sites of disease.

Methods

Patients

This study reviewed patients with newly diagnosed cervical cancer treated at Washington University in St. Louis from 1997 to 2017. All patients underwent a history and physical examination, examination under anesthesia, cervical tumor biopsy, pelvic computed tomography (CT) or magnetic resonance imaging (MRI), and FDG-PET. Our institution transitioned from PET to PET/CT in 2002; 27 patients who were on a study received PET/MRI from 2011–2017. Except for the change in scanners over time, with expected improvement in resolution, there was no significant change in patient preparation, FDG dosage, and time from injection to imaging over the course of this study, as previously described.¹⁷ Foley catheterization and furosemide administration was routinely performed in patients undergoing PET for cervical cancer until approximately 2015. It was employed primarily to improve discrimination of activity in the bladder from uptake of FDG in the primary cervical tumor; its elimination would be expected to have no effect on the detection

of distant metastases. Each FDG-PET scan was interpreted by board-certified nuclear medicine physicians over the study period. We included patients with evidence of FDG-avid distant organ disease, defined as sites of disease beyond pelvic, inguinal, para-aortic and supraclavicular nodes. Patients were not surgically staged, but biopsy-confirmation of cancer was done at the discretion of the treating physicians. The International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system, which does not allow PET, CT or MRI findings, was used to define clinically apparent metastatic disease. This retrospective analysis was approved by our institutional review board with waiver of informed consent (IRB# 201809029).

Treatment and Follow up

There were 14 (19%) of 72 patients who did not receive any external pelvic irradiation. Palliative ring brachytherapy for cervical tumor bleeding was administered to 4 (29%) of these patients and chemotherapy was administered to 3 (21%) of these 14 patients. Of the 58 (81%) of 72 patients receiving external pelvic radiation, the median dose delivered was 50 Gy (range; 1.8–70); 51 (88%) of 58 patients received a brachytherapy boost to the cervix and 47 (81%) of 58 patients were administered concurrent weekly cisplatin. The para-aortic and supraclavicular nodal regions and sites of FDG-avid distant disease were not routinely included in the irradiated volume. Further systemic therapy, typically 6 cycles of a platinum and taxane combination, was given following radiation.

Patients were followed with clinical examinations approximately every 2 months for the first 6 months, every 3 months for the next 2 years, and then every 6 months. FDG-PET was performed 3 months after completion of treatment in most patients and then as indicated by clinical examination or symptoms. Overall survival was measured from the date of the first FDG-PET scan.

Statistical Analyses

Descriptive statistics were done to categorize the sites of FDG-avid distant disease. Kaplan-Meier survival analyses were performed, with statistical significance calculated by log-rank test. Final significance was defined as $p < 0.05$, and all tests were two-tailed. Statistical analyses were done in Statistical Package for the Social Science (SPSS), version 23 (IBM, Armonk, NY).

Results

Sites and frequency of FDG-avid distant disease

From 1997–2017, 113 (9.5%) out of 1185 cervical cancer patients who underwent FDG-PET had FDG-avid supraclavicular nodes and/or distant non-nodal metastatic disease at diagnosis. Outcomes of cervical cancer patients with isolated supraclavicular lymph nodes were previously described¹⁸. There were 72 (6.1%) of 1185 patients with FDG-avid distant non-nodal metastatic disease, and 27 (38%) of these 72 patients underwent biopsy, confirming metastasis. The frequency of distant metastasis detection in patients undergoing PET was 6.6% (15/226), versus 5.8% (54/928) for PET/CT and 11.1% (3/27) for PET/MRI. These frequencies did not differ significantly. Clinical examination and selected imaging

allowed by FIGO staging identified distant metastasis in 35 (49%) of these 72 patients. (Table 1) The most common sites of distant metastasis were lung 35%, omentum/peritoneum 16.5%, bone 16.5%, and liver 7%; and 25% of patients had multiple sites of distant disease. (Figure 1) Metastasis was biopsy proven in 9 of 25 patients (36%) in lung, 8 of 12 patients (67%) in omentum/peritoneum, 4 of 12 patients (33%) in bone, 1 of 5 patients (25%) in liver, and in 5 of 18 patients (28%) in multiple sites of FDG-avid distant disease.

Lymph nodes detected by sites of FDG-avid distant disease

FDG-avid lymph nodes were also detected in 60 (83%) of 72 patients. All patients with FDG-avid para-aortic lymph nodes also had FDG-avid pelvic lymph nodes; all patients with FDG-avid supraclavicular lymph nodes also had FDG-avid pelvic and para-aortic nodes. However, 12 (17%) of 72 patients with distant metastases did not have coexisting FDG-avid lymph nodes (Figure 2); 9/12 (75%) were squamous histology, 1 (8.3%) was adenosquamous, 1 (8.3%) was adenocarcinoma, and 1 (8.3%) was poorly differentiated. The most common distant metastasis sites in patients without coexisting FDG-avid lymph nodes were the liver (2/5 patients, 40%) and omentum/peritoneum (3/12 patients, 25%). (Table 2)

Patient Survival

With a median follow-up of 7 months (0.5–120), the overall mortality rate was 66 (92%) of 72 patients, and median overall survival was 7 months. Three patients died within one month of their PET scan. At the time of this analysis, 6 of the 72 patients were still alive for intervals ranging from 5 to 92 months. Four patients lived longer than 5 years. Two were patients with squamous-histology, bone-only metastasis (not biopsy proven), one alive with disease at 70 months and one dead of other causes at 122 months. One patient with squamous-histology, omentum-only metastasis (biopsy proven) had no evidence of disease at 92 months. One adenocarcinoma patient with initial FDG-avid disease in bone and lung (not biopsy proven) was alive with disease at 62 months. Survival stratified by site of initial FDG-avid distant disease is shown in Figure 3. Patients with multiple sites of distant FDG-avid disease had the worst median overall survival (3 months, 95% CI 0.9–5.1), though this was not statistically significant. Patients selected by the treating physician to receive palliative external irradiation to the pelvis survived a median of 9 months (95% confidence interval 5.4–13); patients receiving either no radiation or only palliative ring brachytherapy survived a median of 1 month (95% confidence interval 0.4–1.6, $p < 0.001$).

Discussion

Distant organ metastasis was found in only 6.2% of cervical cancer patients at initial diagnosis. Notably, 51% of FDG-avid distant disease was clinically occult. As others have reported, the lungs were the most common site of metastasis.^{4,5,11,14–16,19–22} In contrast to surgical series, omental/peritoneal metastases were discovered in 19% of patients with FDG-PET, suggesting that this pattern of intra-abdominal spread may be more common than previously thought.^{23,24} Our results are congruent with those of Gee et al., who found that 7 of 15 patients (46%) with biopsy-proven FDG-avid distant organ metastasis at diagnosis of cervical cancer had peritoneal metastasis.¹¹ There was no statistical difference in survival based on site of distant metastasis.

Studies describing the distribution of distant metastases at diagnosis are limited. One 45-patient study of patients from Nigeria reported the sites of distant metastases at presentation to be 47.4% lung, 16.9% nodes, 11.9% liver, 10.2% bone, 6.8% gastrointestinal tract and 6.8% cutaneous using only FIGO staging criteria²⁰ A recent secondary analysis of a multi-center prospective trial of cervical cancer patients staged with FDG-PET and confirmed with biopsy or surgical dissection found 15 (9.8%) of 153 patients with distant organ metastases.¹¹ Of this group, the distribution was 53% lung, 46% peritoneal, and less than 1% bone. Our analysis of 72 patients confirms that lung, omentum/peritoneum and bone are frequent sites of metastasis. A number of case reports in the literature describe rare sites of metastatic disease in cervical cancer patients, including breast, brain, intestine and pericardium, though these metastatic sites were not detected in our study.^{25–28}

Comparison of findings from our study to reported distributions in the literature is complicated by the fact that most reports describe distant metastasis at tumor recurrence or combine patients with distant metastatic disease found at diagnosis and at recurrence. In 1968, Badib et al.⁶ proposed that treatment procedures might impact the patterns of spread of cervical cancer. The autopsy study by Henricksen of 420 patients described patterns of distant metastases in untreated versus treated patients.³ While liver metastases were present in 24.5% of untreated cases, this proportion dropped to 16.4% in the treated cases. Other sites exhibited little variation. In another study, lung metastases were present in 47% of patients with metastases at diagnosis, but only 22% of patients developed failure at this site during follow-up.²⁰ Therefore, future studies will require distinction between treated and untreated cases in order to define the natural history of metastasis accurately.

Lymphatic dissemination is the major route of spread for metastatic cervical carcinoma, typically proceeding in an orderly fashion from pelvic nodes to para-aortic nodes and then to supraclavicular nodes before spreading to distant sites. However, 17% of our patients with distant FDG-avid disease did not exhibit FDG-avid lymph nodes, a finding corroborated by others. Badib et al. found at autopsy that 36 of 163 patients (22%) with distant metastases did not have pelvic nodal disease.⁶ In a more recent study, FDG-PET/CT follow-up of cervical cancer patients who underwent primary or post-operative definitive radiation therapy detected 122 patients with distant recurrence. Of this cohort, 13 (11%) patients exhibited pulmonary metastasis at recurrence with negative nodal status.¹⁴ However, these studies are limited by studying a previously-treated patient population and may be interpreted as durable treatment response in the pelvis. Microscopic disease not detected by PET or detailed pathological examination of lymph nodes also cannot be excluded. In the present study, the omentum/peritoneum and liver were most frequently found to harbor metastatic disease without coexisting nodal disease, suggesting that dissemination to these sites may alternatively include hematogenous dissemination or direct invasion of the peritoneum.^{29,30} Notably, our data demonstrates that the absence of detectable lymph node metastases does not preclude the possibility of distant disease, although still a rare phenomenon.

Patient survival when presenting with a single site of FDG-avid distant metastasis is not described in the literature. Many series have reported the dichotomy of overall survival with distant organ versus lymphatic metastasis, without further specifying survival based on

distant metastatic sites.^{16,22,29} Patients exhibiting multiple sites of metastases in our study displayed the worst outcome (median overall survival of 3 months), a finding seen in phase I clinical trials.³¹ There is a growing body of evidence suggesting that aggressive treatment with curative intent may confer improved survival for cervical cancer patients with oligometastatic disease.^{32–36} A prior report from our institution found clinical stage IVB cervical cancer patients treated with high-dose chemoradiotherapy had a 3 year overall survival of 44%.¹⁹ A recent report from Kim et al.¹⁴ found patients who developed metastatic disease in the lungs alone or distant lymph nodes alone after initial treatment had a 44.8% 5-year survival rate from the time of recurrence. Most (83%) of these patients received aggressive salvage therapy, defined as chemotherapy combined with surgical resection or irradiation of the metastatic site. A recent National Cancer Database analysis of 3169 patients with metastatic cervical cancer found the addition of pelvic radiation to chemotherapy alone was associated with improved overall survival from 10.6 months to 14.4 months ($p<0.001$), and patients who also received a brachytherapy boost had a median overall survival of 30 months ($p<0.001$).³⁴⁼

A large selection bias is inherent in these retrospective studies and limits any firm conclusions associating treatment paradigm and survival. Also, as noted, many studies of outcomes in metastatic cervical cancer have combined both patients with metastatic disease at diagnosis and those with recurrent cervical cancer in the analyses. This combination neglects differences in disease characteristics and treatment sensitivity, which is likely necessitated by limited numbers of patients presenting with metastatic cervical cancer at any single institution. Future studies assessing optimal treatment strategies should distinguish between initially metastatic and recurrent cervical cancer.

Our study has a number of limitations and these include: only 6.2% of cervical cancer patients in this 20-year period demonstrated distant metastasis on PET scan at diagnosis, limiting the sample size. Over the course of this retrospective analysis the technology improved from PET alone to several different generations of PET/CT and PET/MRI. Thus, our estimate of the frequency of detection of distant metastasis might be lower than it would have been if all studies had been done with current technology. The distant disease was proven by biopsy in only 38% of our patients with FDG-avid distant disease, including 1 (25%) of 4 of the long-term survivors. However, the distribution and frequency of distant organ metastases mirror a smaller prospective study where all FDG-avid metastases were biopsied.¹¹ Our patients also had a median overall survival of 7.0 months, indicating that the majority of FDG-avid distant metastasis represented true disease.

In summary, our data corroborate previous descriptions of disease spread and suggest that omental metastases as a site of first metastasis are not uncommon. Given their prolonged survival, patients with one site of distant organ disease at our institution now typically receive definitive chemoradiation to all sites of disease followed by chemotherapy. Future prospective studies are needed to validate the best treatment approach in patients with oligometastatic disease.

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References

1. Bray F, Ferlay J, Soerjomataram I. Global cancer statistics 2018 : GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2018;394–424. doi:10.3322/caac.21492.
2. Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol. 2016. doi:10.3802/jgo.2016.27.e43.
3. Henriksen E The lymphatic spread of carcinoma of the cervix and of the body of the uterus. A study of 420 necropsies. Am J Obstet Gynecol. 1949. doi:10.1016/0002-9378(49)90200-8.
4. Carlson V, Delclos L, Fletcher G. Distant metastases IN squamous-cell carcinoma OF THE uterine cervix. Radiology. 1967;88(5):961–966. [PubMed: 6025051]
5. French SW, DiSibio G. Metastatic patterns of cancers. Arch Pathol Lab Med. 2008;132(6).
6. Badib AO, Kurohara SS, Webster JH, Pickren JW. Metastasis to organs in carcinoma of the uterine cervix: Influence of treatment on incidence and distribution. Cancer. 1968. doi: 10.1002/1097-0142(196803)21:3<434::AID-CNCR2820210312>3.0.CO;2-3.
7. Crispens MA, Frederick P. NCCN clinical practice in oncology : cervical cancer. Natl Compr Cancer Netw. 2017.
8. Grigsby PW. PET/CT imaging to guide cervical cancer therapy. Future Oncol. 2009. doi:10.2217/fon.09.70.
9. Mittra E, El-Maghraby T, Rodriguez C a., et al. Efficacy of ¹⁸F-FDG PET/CT in the evaluation of patients with recurrent cervical carcinoma. Eur J Nucl Med Mol Imaging. 2009. doi:10.1007/s00259-009-1206-x.
10. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. J Clin Oncol. 2001;19(17):3745–3749. <http://jco.ascopubs.org/content/19/17/3745.short>. [PubMed: 11533097]
11. Gee MS, Atri M, Bandos AI, Mannel RS, Gold MA, Lee SI. Identification of Distant Metastatic Disease in Uterine Cervical and Endometrial Cancers with FDG PET/CT: Analysis from the ACRIN 6671/GOG 0233 multicenter trial. Radiology. 2018. doi:10.1148/radiol.2017170963.
12. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Metabolic response on post-therapy FDG-PET predicts patterns of failure after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2012;83(1):185–190. doi:10.1016/j.ijrobp.2011.05.053. [PubMed: 22014958]
13. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: Relationship to prognosis. J Clin Oncol. 2010;28(12):2108–2113. doi:10.1200/JCO.2009.25.4151. [PubMed: 20308664]
14. Kim TH, Kim M-H, Kim B-J, Park S-I, Ryu S-Y, Cho C-K. Prognostic Importance of the Site of Recurrence in Patients With Metastatic Recurrent Cervical Cancer. Int J Radiat Oncol. 2017. doi: 10.1016/j.ijrobp.2017.03.029.
15. Fagundes H, Perez CA, Grigsby PW, Lockett MA. Distant metastases after irradiation alone in carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1992.
16. Im JH, Yoon HI, Kim S, et al. Tailored radiotherapeutic strategies for disseminated uterine cervical cancer patients. Radiat Oncol. 2015. doi:10.1186/s13014-015-0373-0.
17. Wright JD, Dehdashti F, Herzog TJ, et al. Preoperative lymph node staging of early-stage cervical carcinoma by [18F]-fluoro-2-deoxy-D-glucose-positron emission tomography. Cancer. 2005;104(11):2484–2491. doi:10.1002/cncr.21527. [PubMed: 16270319]
18. Ioffe YJ, Massad LS, Powell MA, et al. Survival of cervical cancer patients presenting with occult supraclavicular metastases detected by FDG-Positron Emission Tomography/CT: Impact of disease extent and treatment. Gynecol Obs Invest. 2018;83:83–89.

19. Zigelboim I, Taylor NP, Powell MA, et al. Outcomes in 24 selected patients with stage IVB cervical cancer and excellent performance status treated with radiotherapy and chemotherapy. *Radiat Med - Med Imaging Radiat Oncol*. 2006;24(9):625–630. doi:10.1007/s11604-006-0082-6.
20. Elumelu T, Jatto J. Distant metastases in uterine cervical cancer patients. *JSM Clin Oncol Res*. 2015;3(1):1044.
21. Schmid MP, Franckena M, Kirchheiner K, et al. Distant metastasis in patients with cervical cancer after primary radiotherapy with or without chemotherapy and image guided adaptive brachytherapy. *Gynecol Oncol*. 2014. doi:10.1016/j.ygyno.2014.02.004.
22. Usami T, Takahashi A, Matoda M, et al. Review of treatment and prognosis of stage IVB cervical carcinoma. *Int J Gynecol Cancer*. 2016. doi:10.1097/IGC.0000000000000771.
23. Fulcher A S, O'Sullivan SG, Segreti EM, Kavanagh BD. Recurrent cervical carcinoma: typical and atypical manifestations. *Radiographics*. 1999. doi:10.1148/radiographics.19.suppl_1.g99oc19s103.
24. Spottswood SE, Lopatina OA, Fey GL, Boardman CH. Peritoneal carcinomatosis from cervical cancer detected by F-18 FDG positron emission tomography. *Clin Nucl Med*. 2005;30(1):56–59. doi:10.1097/00003072-200501000-00022. [PubMed: 15604978]
25. Piura E, Piura B. Brain metastases from cervical carcinoma: Overview of pertinent literature. *Eur J Gynaecol Oncol*. 2012.
26. Mangla A, Agarwal N, Saei Hamedani F, Liu J, Gupta S, Mullane MR. Metastasis of cervical cancer to breast: A case report and review of literature. *Gynecol Oncol Reports*. 2017. doi: 10.1016/j.gore.2017.06.009.
27. Yu X, Wang Z, Zhang Z, Liu Y, Huang J. Postoperation of cervical cancer with intestine metastasis: A case report and literature review. *World J Surg Oncol*. 2016. doi:10.1186/s12957-015-0759-3.
28. Kim HS, Park NH, Kang SB. Rare metastases of recurrent cervical cancer to the pericardium and abdominal muscle. *Arch Gynecol Obstet*. 2008. doi:10.1007/s00404-008-0602-y.
29. Park KJ, Braschi-Amirfarzan M, DiPiro PJ, et al. Multimodality imaging of locally recurrent and metastatic cervical cancer: emphasis on histology, prognosis, and management. *Abdom Radiol*. 2016. doi:10.1007/s00261-016-0825-5.
30. Aziz SW, Aziz MH. Chapter 5 - Cervical Cancer Metastasis. In: Ahmad ABT-I to CM, ed. Academic Press; 2017:77–94. doi:10.1016/B978-0-12-804003-4.00005-0.
31. Hou MM, Liu X, Wheler J, et al. Outcomes of patients with metastatic cervical cancer in a phase I clinical trials program. *Anticancer Res*. 2014.
32. Kim JY, Kim JY, Kim JH, Yoon MS, Kim J, Kim YS. Curative chemoradiotherapy in patients with stage IVB cervical cancer presenting with paraortic and left supraclavicular lymph node metastases. *Int J Radiat Oncol Biol Phys*. 2012. doi:10.1016/j.ijrobp.2012.01.070.
33. Kim HS, Kim T, Lee ES, et al. Impact of chemoradiation on prognosis in stage IVB cervical cancer with distant lymphatic metastasis. *Cancer Res Treat*. 2013. doi:10.4143/crt.2013.45.3.193.
34. Wang Y, Farmer M, EW I, et al. Association of definitive pelvic radiation therapy with survival among patients with newly diagnosed metastatic cervical cancer. *JAMA Oncol*. 2018;4(9):1288–1291. [PubMed: 30054609]
35. Ioffe Y, Massad L, Powell M, et al. Survival of cervical cancer patients presenting with occult supraclavicular metastases detected by FDG-positron emission tomography/CT: impact of disease extent and treatment. *Gynecol Obs Invest*. 2018;83(1):83–89.
36. Ning MS, Ahobila V, Jhingran A, et al. Outcomes and patterns of relapse after definitive radiation therapy for oligometastatic cervical cancer. *Gynecol Oncol*. 2018;148(1):132–138. doi:10.1016/j.ygyno.2017.10.017. [PubMed: 29089122]

A.

B. **Figure 1:**

A) Frequency distribution of FDG-avid distant metastases in cervical cancer patients at initial diagnosis. B) Frequency of FDG-avid metastases of a subset of patients only having one initial site of distant disease.

Figure 2:
Frequency of FDG-avid lymph nodes in cervical cancer patients with FDG-avid distant disease at initial diagnosis.

Figure 3:

Kaplan-Meier estimates of overall survival for all patients with FDG-avid distant disease at diagnosis stratified by site(s) of metastases.

Table 1:

Patient and tumor characteristics

	Number of patients (%)
Median age (years)	53 (26–93)
<u>Race</u>	
White	45 (63%)
Black	24 (33%)
Other	3 (4%)
<u>Histology</u>	
Squamous	56 (78%)
Adenocarcinoma	9 (12%)
Adenosquamous	3 (4%)
Small cell carcinoma	2 (3%)
Poorly differentiated	2 (3%)
<u>FIGO stage</u>	
IB1	1 (1.3%)
IB2	3 (4%)
IIA	2 (3%)
IIB	8 (11%)
IIIA	1 (1.3%)
IIIB	21 (29%)
IVA	1 (1.3%)
IVB	35 (49%)

Table 2:

FDG-avid lymph node distribution by site of initial distant metastasis in patients with single sites of distant metastasis

Total N=53	Lung N=24	Bone N=12	Omentum N=12	Liver N=5
None (N=9; 17%)	3 (12%)	1 (8%)	3 (25%)	2 (40%)
Pelvic (N=9; 17%)	4 (17%)	4 (33%)	1 (8%)	0 (0%)
Pelvic + Para-aortic (N=17; 32%)	7 (29%)	5 (42%)	5 (42%)	0 (0%)
Pelvic + Para-aortic + Supraclavicular (N=18; 36%)	10 (42%)	2 (17%)	3 (25%)	3 (60%)