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Research Article

Clinically Significant Discrepancy between Clinical and Pathologic Stage of Early Operable Cervical Cancer

Jennifer McEachron[1*], Victoria Hastings[2], Nikita Malakhov[1], Constantine Gorelick[2], Katherine Economos[2], Yi-Chun Lee[1] and Margaux J. Kanis[2]

[1]*Division of Gynecologic Oncology, SUNY Downstate Medical Center, New York, USA*
[2]*Division of Gynecologic Oncology, New York-Presbyterian Brooklyn Methodist Hospital, New York, USA*

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ABSTRACT

Objectives: The cornerstone of the management of cervical cancer (CC) traditionally relies on clinical examination (CE) of tumor size (TS) and local extension of disease. The goal of this study is to determine the accuracy of CE in comparison to final pathology (FP) in early operable CC.

Methods: This is a multi-center retrospective review of patients with early CC (FIGO 2009 Stage IB1, IIA1). CE of TS, parametrial invasion (PI), and vaginal involvement (VI) were compared to FP.

Results: The final analysis included 135 patients. Overall, there was a significant difference between CE of TS compared to FP; mean error of 1.22 cm ($p<0.0001$). In tumors ≥ 2cm the mean error was 1.28 cm ($p<0.0001$). No significant discrepancy was observed in tumors <2 cm (mean error: 1.10cm; $p=0.5$). CE of TS of endophytic tumors was poor (mean error 1.68cm; $p=0.004$) compared to exophytic tumors (mean error: 1.12 cm; $p=0.693$). There was no significant difference in the identification of VI between CE and FP (3.7% vs. 8.89%; $p=0.067$). 14.07% of patients were found to have PI on FP ($p<0.0001$). There was no difference in the accuracy CE of TS between non-obese (<30 kg/m^2) and obese patients (≥30 kg/m^2) ($p=0.061$). As a result of FP, 55 patients (40.7%) received adjuvant RT and 38 patients (28.14%) were upstaged from IB1 to IB2.

Conclusion: CE of TS and PI is inaccurate, especially in tumors ≥ 2cm and endophytic tumors. This suggests the role of imaging should be further explored to improve outcomes.

Introduction

Cervical cancer is a global health burden with approximately 500,000 new cases diagnosed worldwide annually [1]. Historically, the staging of cervical cancer has been based solely on physical exam and limited use of diagnostic tools. More recently, pathologic and radiologic factors have been added to this system, reflected in the updated FIGO 2018 staging system [2]. Despite this change, the cornerstone of management continues to rely on physical assessment of tumor size (TS) and local extension of the tumor. Bulky tumors (≥ 4 cm) and those with extension to the parametria are triaged to definitive chemoradiation rather than radical hysterectomy (RH) [3-6].

Previous studies demonstrate a wide variation in accuracy and a low sensitivity of physical examination. Concordance between clinical and pathologic stage only occurs in 42 – 66% of cases [7-10]. The most common discrepancy is the failure to identify parametrial invasion (PI), the most clinically important implication of which is the need for adjuvant radiation therapy [7]. Recurrence is much more frequent with PI, and adjuvant chemoradiation is associated with a significant increase in progression-free survival (PFS) and overall survival (OS) as demonstrated in GOG 109 [11].

Similarly, the majority of patients with tumors ≥ 4 cm on final pathology qualify for adjuvant radiation therapy. This is based on the fact that these tumors have a high propensity for parametrial and lymphatic spread [11].

Correspondence to: Jennifer McEachron, Department of Gynecologic Oncology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203, USA; E-mail: Jennifer.McEachron@downstate.edu, ORCID: 0002-3605-1163

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Additionally, those patients without PI or lymph node metastasis (LNM) may qualify for adjuvant radiation based on Sedlis Criteria [12, 13]. Collectively, patients with tumors ≥ 4 cm will require adjuvant radiation in up to 80% of cases [14].

While the addition of adjuvant radiation to RH is associated with improved oncologic outcomes, the rate of complications increases significantly in those who undergo dual therapy [11-15]. The key to avoiding morbidity lies in accurate patient selection, primarily based on initial examination. The goal of this study is to determine the accuracy of physical examination in comparison to the final pathologic report in early operable cervical cancer.

Methods

This is a multi-center retrospective review of patients with early cervical cancer who underwent operative management from 1996-2018. Participating institutions included the University Hospital of Brooklyn – Downstate Medical Center, King's County Hospital Center and New York Presbyterian Brooklyn Methodist Hospital. Institutional Review Board approval was obtained by each site. Tumor board registries from each institution were queried for cases of stage IB1 and IIA1 cervical cancer (2009 FIGO staging system). Demographic data were collected, including age, body mass index (BMI) and race. Clinical examination and pathologic data were obtained for each patient, including assessment of tumor size (TS), vaginal involvement (VI), and parametrial involvement (PI). This data was obtained from the operative report and reflected the impression of the immediate preoperative exam performed by a board-certified gynecologic oncologist.

Pathologic data included: assessment of TS, VI, PI and lymph node metastasis (LNM). Clinical assessment of TS, VI and PI were compared to final pathology. Exclusion criteria included those with final pathologic diagnosis other than cervical cancer, those patients who did not have complete pathologic data available, and patients for whom surgery was aborted without completion of hysterectomy. Paired T-tests were conducted to analyze the mean error between clinical assessment and final pathology. Cohen's Kappa was used to analyze the correlation between PI and LNM. Statistical significance was defined as $P<0.05$. Analyses were performed using SPSS, Version 22.0 (IBM, USA).

Results

For 1996-2018, 191 patients with stage IB1 and IIA1 cervical cancer undergoing primary surgical management were identified. In 31 cases, surgery was aborted before completion of hysterectomy due to intraoperative finding of positive lymph nodes and therefore they were excluded. An additional 25 patients were excluded from the final analysis due to incomplete documentation, particularly of the clinical examination. Final analysis included 135 patients. The majority of patients had squamous cell carcinoma (SCC) (72.6%); the other histologies included adenocarcinoma (18.5%), adenosquamous (3.7%), neuroendocrine (2.9%), clear cell (1.5%) and glassy cell carcinoma (0.7%). The median age of patients was 52.5 years (range 26 – 83 years) and median BMI was 29.1 kg/m^2 (range 18.1 – 50.4 kg/m^2). 55 patients (40.7%) received adjuvant radiation therapy postoperatively (Table 1).

Table 1: Patient characteristics.

Age (years)	52.5 (Range 26 – 83)	n = 135
BMI (kg/m^2)	29.1 (Range 18.1 – 50.4)	n = 135
	n	**%**
Race:		
White	14	10.3
Black	107	78.9
Asian	4	3.2
Other	10	7.6
FIGO Stage*:		
IB1	130	96.3
IIA1	5	3.7
Histology:		
SCC	98	72.6
Adenocarcinoma	25	18.5
Adenosquamous	5	3.7
Neuroendocrine	4	2.9
Clear Cell	2	1.5
Glassy Cell	1	0.8
Adjuvant Radiation:		
Yes	55	40.7
No	80	59.3

BMI: Body mass index; SCC: Squamous cell carcinoma.
*Based on FIGO 2009 staging system.

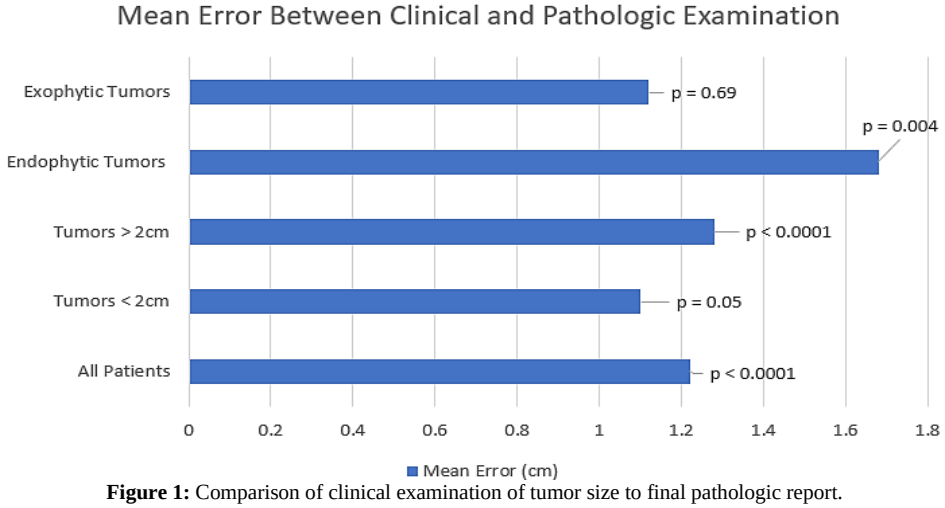

Figure 1: Comparison of clinical examination of tumor size to final pathologic report.

The present study demonstrates a statistically significant difference between clinical examination assessment of TS and final pathology. For the entire cohort, the mean error between clinical and pathologic assessment was 1.22 cm ($p<0.0001$). Subanalysis was conducted based on TS (< 2cm versus ≥ 2cm), endophytic (barrel-shaped) tumors versus exophytic tumors, and BMI (<30 kg/m^2 versus ≥ 30kg/m^2). Significant discrepancy between clinical and pathologic exams was observed in those patients with tumors ≥ 2cm (mean error: 1.28 cm; $p<0.0001$). However, this was not observed in tumors <2 cm (mean error: 1.10 cm; $p=0.5$). Clinical assessment of TS of endophytic tumors was poor (mean error 1.68 cm; $p=0.004$) compared to exophytic tumors (mean error: 1.12 cm; $p=0.693$). There was no difference in the accuracy of clinical assessment of TS between non-obese (<30 kg/m^2) and obese patients (≥30 kg/m^2), mean error 1.13 cm and 1.3 cm, respectively ($p=0.061$) (Figure 1). Clinical assessment of parametrial and vaginal involvement was also analyzed. There was no significant difference in the identification of VI between clinical exam and final pathology (3.7% vs. 8.89%; $p=0.067$). No patients with PI on clinical examination were included in this analysis. However, 14.1% of patients were found to have PI on final pathology ($p<0.0001$).

As this was a multi-center study, it was not the preference of all participating surgeons to perform intra-operative assessment of lymph nodes. Additionally, in some cases in which intraoperative assessment was performed, which resulted as negative for LNM, the final pathology report confirmed positive nodes. Because of these factors, LNM was identified in 17.04% of all patients on final pathology. Importantly, the present study demonstrates the correlation between PI and LNM. In patients with PI, the incidence of LMN increased to 42.1%. The presence of PI on final pathology was a significant risk factor for nodal disease ($p=0.023$).

Discussion

The cornerstone of the management of cervical cancer relies on clinical examination assessment of TS and local extension of disease. Early-stage disease can be managed with RH or definitive chemoradiation. Studies demonstrate that both methods offer equal oncologic outcomes, with OS exceeding 80% at 5-years [16]. The goal of performing RH is to offer a patient cure with surgery alone, avoiding the need for radiation therapy and its associated morbidity. However, patients with intermediate-high risk factors based on final pathology have improved PFS and OS with the use of adjuvant radiation therapy [11, 12]. Patients receiving dual modality therapy experience significantly higher morbidity, most clearly demonstrated by the higher rate of urologic complications in this population [11, 15, 16]. This undoubtedly illustrates that accurate assessment of disease status, specifically TS and PI, are critical for triaging patients to appropriate therapy.

We limited our analysis to clinically visible tumors which were candidates for surgical management, exclusively stage IB1 and IIA1. We excluded stage IA tumors, which by definition, are microscopic, and therefore would render negative clinical examination findings. The present study demonstrates the inaccuracy of clinical examination of TS and PI. For all patients, the average discrepancy of 1.22cm between clinical examination and final pathology assessment was significant. Additionally, 14.1% of patients were found to have parametrial involvement on final pathology, translating to 40.7% of patients requiring adjuvant radiation. Additionally, 38 patients (28.14%) with clinical stage IB1 were upstaged to IB2 on final pathology. Of these patients, 94.7% went on to receive adjuvant radiation therapy (Figure 2).

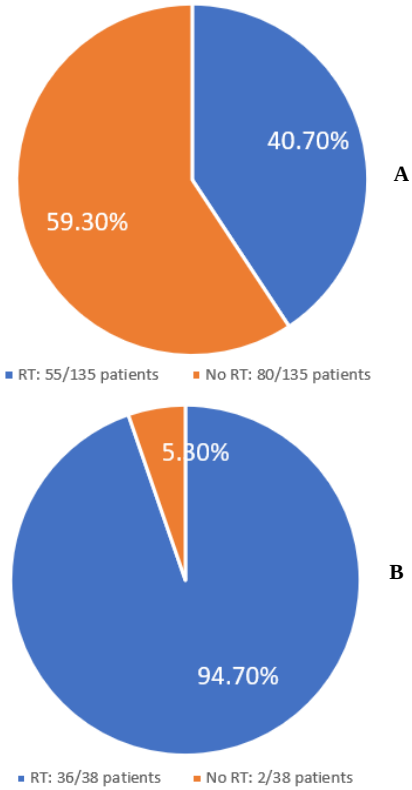

Figure 2: Percentage of patients receiving radiation based on final pathology. **A)** Entire cohort; **B)** Patients upstaged to stage IB2 on final pathology.
RT: Radiation therapy.

The role of imaging in the assessment of cervical tumors has been explored by several authors. Multiple reports demonstrate the superiority of imaging studies assessment of TS compared to physical examination [17-19]. Magnetic resonance imaging (MRI) has proven the most sensitive, with an accuracy of up to 93% for TS and up to 87% for PI [16, 20-22]. Computed tomography (CT) lags behind MRI in sensitivity and specificity and should be reserved for those patients who cannot undergo MRI [17]. More recently, the utility of positron emission tomography (PET) has been explored; however, its primary utility lies in the detection of LNM and distant metastatic disease [23].

Despite the improved accuracy of imaging, it is not standard practice to obtain preoperative imaging for assessment of local disease status in early cervical cancer [6]. The recently updated 2018 FIGO staging system differs from the previous system in that it allows for the use of imaging to define LNM. Patients with nodal disease, whether diagnosed by tissue sampling or imaging, now fall into the newly added category of stage IIIC disease [2]. However, even in this updated system, imaging is not yet utilized in the classification of early-stage disease. Studies in rectal cancer have demonstrated improved accuracy of tumor assessment with imaging studies [24, 25]. This has resulted in the universal adoption of imaging in the staging and pre-treatment workup of rectal cancer.

More specifically, MRI is utilized in the assessment of TS and local disease extension leading to improved treatment strategies in rectal cancer [25, 26]. In the current study, we are not able to draw conclusions regarding the accuracy of imaging compared to physical examination and final pathology as it is not standard practice to obtain preoperative MRI or CT and only a very small number of patients in our cohort had imaging information available. However, based on data supporting the improved assessment of TS and PI with imaging and data extrapolated from rectal cancer, we believe this topic is worthy of further prospective evaluation.

At present, there is limited literature comparing the outcomes of exophytic versus endophytic cervical tumors. A prospective analysis by Trimbos *et al*. demonstrated significantly worse disease-free survival and OS in patients with endophytic versus exophytic tumors [27]. Additionally, investigators at the University of Washington conducted a prospective analysis of barrel-shaped tumors >4 cm treated with external beam radiation, a total of 80 Gy to point A, followed by extrafacial hysterectomy. They found that 61% of patients had persistent disease in the hysterectomy specimen and 73% of patients went on to die of the disease. Based on these findings, they concluded that endophytic tumors carry a worse prognosis compared to their exophytic counterparts, and standard doses of radiation are not adequate for the eradication of these tumors [28]. In the current study, we observed a significantly less accurate clinical assessment of endophytic tumors compared to exophytic tumors. This is likely due to the global distortion of the cervix by these barrel-shaped tumors, making CE challenging even by experienced physicians. As these tumors tend to carry poorer prognosis, accurate staging and triage to appropriate upfront treatment is critical to optimizing patient outcomes. Based on the large discrepancy between CE and final pathology we observed, we strongly suggest considering imaging endophytic tumors preoperatively.

Current cervical cancer literature has focused on the mode of RH – minimally invasive (MIS) versus traditional abdominal approach. A recent prospective trial reported an increase in recurrence rates and a decrease in OS with minimally invasive RH compared to open RH [29]. This data was supported by a large retrospective analysis reporting decreased survival in early-cervical cancer after the adoption of MIS [30]. Following these publications, Margul *et al*. performed a similar comparison but noted inferior oncologic outcomes were limited to patients with tumors ≥ 2 cm in diameter undergoing MIS RH [31]. The present study demonstrates improved accuracy of CE in tumors < 2 cm and exophytic tumors. Based on this data, one could consider foregoing imaging in exophytic tumors < 2 cm. However, with an average error of approximately 1 cm, the authors would suggest there is a role for imaging all tumors clinically judged to be ≥ 1 cm in size to account for the clinical examination error, in addition to all endophytic tumors. This carries particular relevance when counseling patients regarding options for surgical approach, the inherent risks of surgery and risks of adjuvant therapy. Again, emphasizing the importance of accurate clinical assessment of TS to triage patients to the appropriate surgical procedure to achieve the best outcome.

The major limitation of this study is its retrospective nature. Additionally, we were unable to draw conclusions on the accuracy of imaging due to a limited number of patients in our cohort undergoing preoperative imaging. Despite these limitations, the present study demonstrates critical inaccuracy in physical examination and staging of early operable cervical cancer. Incorrect clinical assessment leads to greater use of dual-modality treatment, exposing patients to higher morbidity. The importance of precise clinical assessment cannot be over-emphasized; yet at present, critical management decisions are based on an inaccurate practice.

Conclusion

Clinical assessment of TS and PI is inaccurate, especially in tumors ≥ 2 cm and endophytic tumors, exposing a significant number of patients to surgery and chemoradiation. Although associated with good oncologic outcomes, dual-modality treatment is associated with a significant increase in morbidity when compared to either treatment modality alone. This suggests the role of imaging should be further investigated as a potentially more accurate means of assessment of TS and extent of local disease and additionally supports the use of the updated FIGO 2018 staging system.

Conflicts of Interest

None.

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