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BRIEF REPORT

Relevance of routine pathology review in cervical carcinoma

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Abstract

To determine the impact of pathology review on the management of patients with cervical carcinoma, 264 reports of pathology review from 230 patients referred to Erasmus MC (2010–2012) were studied retrospectively. Discrepancies between pathologic diagnoses were classified as 'major' if they led to changes in treatment, and as 'minor' where there was no change. Patient and tumor characteristics were analyzed to identify the factors influencing these discrepancies. Fifty-eight (25.2%) discrepancies were identified; 28 (12.2%) were major, these resulted frequently from missing essential information, or discordant assessment of tumor invasion. Pathology review prevented under-treatment of 3.5%, over-treatment of 1.3%, treatment for incorrect malignancy of 1.3%, and enabled definitive treatment of 6.1% of patients. This highlights the importance of pathology review for appropriate management. Major discrepancies were rare (1%) for patients with macroscopic tumor and histologic diagnosis of squamous cell carcinoma ($n = 100$). For these patients, yield of pathology review may be limited.

Keywords Pathology review · Cervical carcinoma · Over-treatment · Under-treatment · Discrepancies

Introduction

Routine review of pathology slides from referred patients with gynecologic malignances is a standard practice across tertiary care centers, including in The Netherlands [1]. Pathology review improves the quality of healthcare and helps avoid diagnostic errors and consequent medical litigations [2–4]. However, pathology review also increases the workload of the pathologist, administrative burden, and health-care costs. Treatment of the patient can also be delayed by the pathology review, which may lead to disease-related complications, or cause distress to the patient [5].

For cervical carcinoma, accurate histologic typing and staging is crucial to determine the appropriate surgical and adjuvant treatment. This retrospective study was therefore conducted to determine the impact of pathology review on the management of cervical carcinoma and to identify the factors influencing the discrepancies in pathology review.

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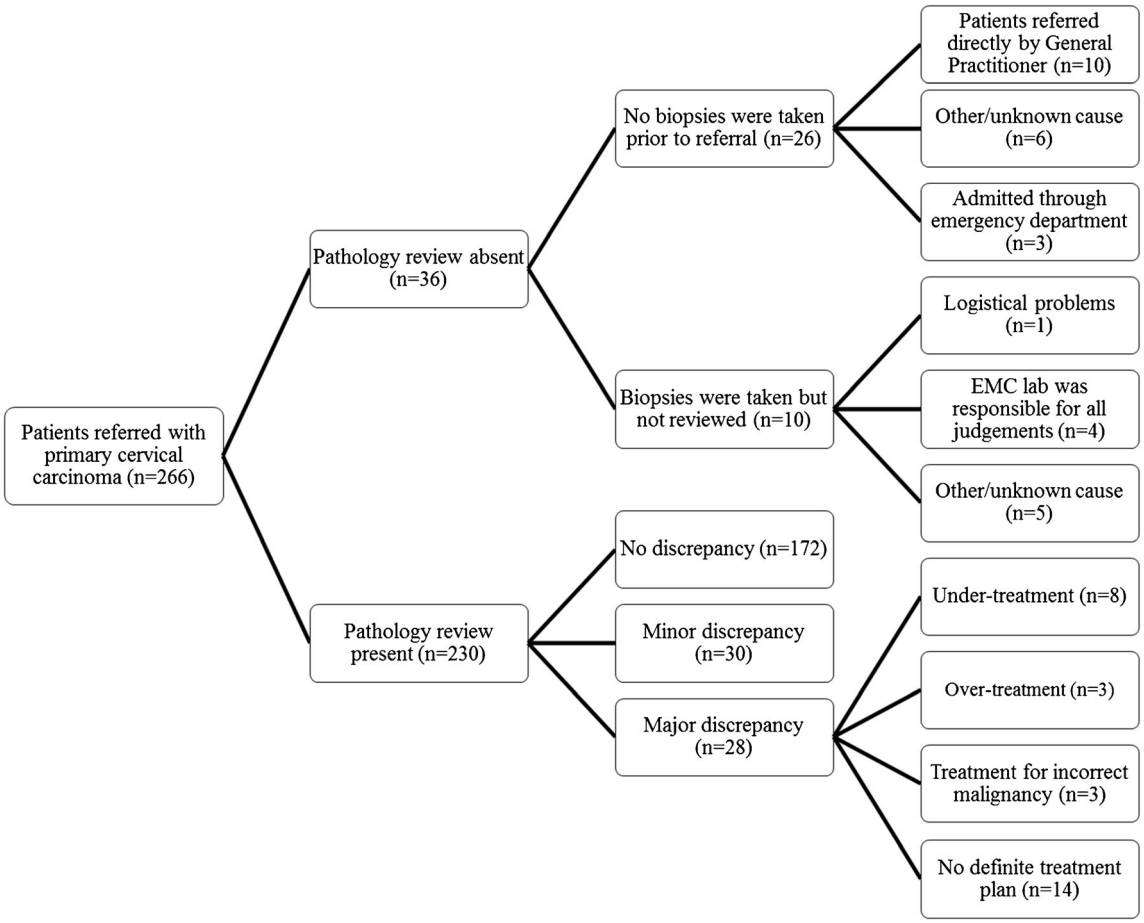

Fig. 1 Flowchart of all patients referred with primary cervical carcinoma to Erasmus MC Cancer Institute from 2010 till 2012

Material and methods

The Erasmus MC Cancer Institute is the tertiary referral center for gynecological malignancies for South-West Netherlands. Patients of all ages referred between January 1st, 2010 and December 31st, 2012, for the treatment of primary cervical carcinoma, were included.

Patient characteristics and treatment details were obtained from hospital records. Clinical descriptions of the tumor by the referring, as well as the reviewing, gynecologist were abstracted from case notes. Tumors described as having a 'malignant appearance' on inspection by the referral gynecologist were categorized as macroscopic. Tumors with any other descriptions, e.g., impression of cervical intraepithelial neoplasia (CIN) or atypical blood vessel pattern on colposcopy, were classified as non-visible.

Pathology slides from all included patients had been reviewed by an experienced gynecologic pathologist, occasionally in consultation with a second gynecologic pathologist. For this study, data were extracted from both the original and the review pathology reports. The extracted data included the type of specimen and tumor characteristics: size, site of origin, histologic type, depth of invasion, horizontal extension, margin status, presence of lymphovascular space involvement (LVSI), and differentiation grade. Tumor stage before and after the pathology review was assigned on the basis of reports using the TNM-Classification. The final tumor stage was determined by taking into consideration the radiology reports, through discussions at the Multidisciplinary Tumor-Board meetings.

All discordant histologic parameters in the original and review pathology reports were recorded, and thereafter independently reviewed by two gynecologic oncologists (HvB and HvD). In case of disagreement, consensus was reached through discussion, and consultation of a third gynecologic oncologist. If parameter(s) essential for treatment planning were missing in the original pathology report, e.g., depth of invasion in a stage T1a carcinoma, this was recorded as missing essential information.

Reports were not considered to be discrepant if the original and review diagnoses were essentially in agreement, with or without slight differences in diagnostic terminology, e.g., severe dysplasia and CINIII. Differences in tumor differentiation grade were also not considered as discrepancies, as this has no well-defined diagnostic criteria.

Discrepancies in parameters, e.g., LVSI-status, or tumor stage, which did not alter the treatment, were categorized as minor, and discrepancies which altered the treatment, e.g., change in tumor site or histologic type, were categorized as major.

For cases with a major discrepancy, the treatment that the patient would have received based on the original diagnosis was categorized as under-treatment, over-treatment, treatment for incorrect malignancy, and no definitive treatment, as described below.

Under-treatment: Treatment for carcinoma of a lower stage.

Over-treatment: Treatment for carcinoma of a higher stage.

Treatment for incorrect malignancy: Treatment for carcinoma of a different anatomic site or histologic type.

No definitive treatment: Treatment plan could not be formulated.

To identify the factors influencing the discrepancies, characteristics of the discrepant cases were compared, which included specimen type, presence of macroscopic tumor, invasive-status, and histologic type of tumor (as reported by the referring pathologist).

Data were analyzed using SPSS version 20.0 (IBM SPSS Statistics, Chicago, IL). Chi-squared tests or Fisher's exact tests were used to identify any significant differences; $p < 0.05$ was considered significant. Mantel-Haenszel test was used to analyze any systematic pattern in discrepancies.

Table 1 Patient characteristics ($n = 230$)

Characteristics	Value
Age in years (± 95% confidence interval)	51.0 (± 15.0)
Type of specimen *n* (%)	
Biopsy	133 (57.8)
LEEP-specimen	59 (25.7)
Cone biopsy	21 (9.1)
Hysterectomy	8 (3.5)
Endocervical curettage	7 (3.0)
Endometrial curettage	2 (0.9)
Further sampling needed *n* (%)	36 (15.7)
Macroscopic tumor *n* (%)	
Yes	135 (58.7%)
No	95 (41.3%)
Invasive-status *n* (%)	
Invasive	215 (93.5%)
Inconclusive	15 (6.5%)
TNM-staging $n = 221$[a,b] *n* (%)	
Tx	5 (2.2%)
Premalignant	2 (0.9%)
T1a1	15 (6.5%)
T1a2	5 (2.2%)
T1b1	88 (38.3%)
T1b2	11 (4.8%)
T2a1	7 (3.0%)
T2a2	1 (0.4%)
T2b	65 (28.3%)
T3a	5 (2.2%)
T3b	10 (4.3%)
T4	7 (3.0%)
Histological type $n = 221$[b] *n* (%)	
Squamous cell carcinoma	163 (70.9%)
Adenocarcinoma	57 (24.8%)
Neuroendocrine tumor	6 (2.6%)
Adenosquamous	2 (0.9%)
Undifferentiated	2 (0.9%)

[a] In nine patients, there was no cervical carcinoma, but endometrial cancer ($n = 6$), colon carcinoma ($n = 1$), ovarian cancer (n = 1), or vaginal cancer ($n = 1$)

[b] Definitive stage or histologic type

LEEP loop electrosurgical excision procedure

Results

Of 266 referred patients, 36 were excluded as they had no pathology review (Fig. 1). From the 230 included patients, there were 264 pathology specimens. These included biopsies (57.8%), loop electrosurgical excision procedure (LEEP) specimens (25.7%), cone biopsies (9.1%), total hysterectomies (3.5%), endocervical curettage (3%), and endometrial curettage (0.9%).

For nine patients, the diagnosis of cervical carcinoma was ruled out based on clinical features, or pathology review. The diagnosed carcinomas ($n = 221$) included squamous cell carcinoma (SCC) (70.9%), adenocarcinoma (24.8%), neuroendocrine carcinoma (2.6%), adenosquamous carcinoma (0.9%), and undifferentiated carcinoma (0.9%) (Table 1). Two patients had both SCC and adenocarcinoma. For both, the diagnosis of

Table 2 Classification of discrepancies

Discrepant parameters	Major ($n = 28$)[a]	Minor ($n = 30$)[b]
Missing essential information	10	7
Invasive-status	7	6
Site of origin of tumor	3	2
Histologic type	3	11
LVSI-status	4	2
Tumor size	7	6
Tumor margin status	2	2

LVSI lymphovascular space invasion

[a] In eight patients, there was more than one major discrepancy

[b] In six patients, there was more than one minor discrepancy

Table 3 Overview of all major discrepancies

#	Age (y)	Specimen	Original diagnosis	Review diagnosis	Discrepant parameters	Changes in treatment	Classification
1	45	Biopsy	Cervical adenocarcinoma	Endometrial carcinoma	Site of origin of tumor	Treatment for endometrial carcinoma	Incorrect malignancy
2	66	Biopsy	Cervical adenocarcinoma	Endometrial/ovarian carcinoma	Site of origin of tumor	Treatment for endometrial carcinoma	Incorrect malignancy
3	72	Endocervical curettage	Cervical adenocarcinoma	Endometrial carcinoma	Site of origin of tumor	Treatment for endometrial carcinoma	Incorrect malignancy
4	45	LEEP	Cervical SCC, tumor margins dubious	Cervical SCC, tumor margins negative	Tumor margin status	Re-conization canceled, simple hysterectomy done	No definitive treatment plan
5	37	LEEP	Cervical SCC (stage Tx), no LVSI	Cervical SCC (stage T1a2), LVSI present	Missing essential information (depth of invasion), LVSI-status	Indecisive situation changed to simple hysterectomy	No definitive treatment plan
6	37	Cone biopsy	Cervical SCC (stage Tx)	Cervical SCC (stage T1b1)	Missing essential information (horizontal extension)	Indecisive situation changed to radical hysterectomy	No definitive treatment plan
7	75	Biopsy	CIN III	Cervical SCC	Invasive-status	Extra biopsy canceled, treated with radiotherapy	No definitive treatment plan
8	44	Biopsy	Cervical SCC (stage Tx)	Cervical SCC (stage T1b1)	Tumor size, missing essential information (horizontal extension)	Indecisive situation changed to radical hysterectomy	No definitive treatment plan
9	45	LEEP	Cervical SCC (stage Tx), tumor margins dubious	Cervical SCC (stage T1b1), tumor margins negative	Tumor size, tumor margin status	Cone biopsy canceled, radical hysterectomy done	No definitive treatment plan
10	39	LEEP	Cervical SCC, (stage Tx), LVSI dubious	Cervical SCC (stage T1b1), no LVSI	Tumor size, LVSI-status	Indecisive situation changed to radical hysterectomy	No definitive treatment plan
11	45	LEEP	Cervical SCC (stage Tx)	Cervical SCC (stage T1b1)	Tumor size, missing essential information (horizontal extension)	Indecisive situation changed to radical hysterectomy	No definitive treatment plan
12	61	Cone biopsy	Cervical SCC (stage T1a2)	Cervical SCC (stage T1b1)	Tumor size, missing essential information (horizontal extension)	Cone biopsy canceled, radical hysterectomy done	No definitive treatment plan
13	46	LEEP	Cervical SCC (stage Tx)	Cervical SCC (stage T1b1)	Missing essential information (horizontal extension)	Cone biopsy canceled, radical hysterectomy done	No definitive treatment plan
14	31	Cone biopsy	AIS	Cervical adenocarcinoma	Invasive-status	Indecisive situation changed to re-conization	No definitive treatment plan
15	47	LEEP	Cervical SCC (stage Tx)	Cervical SCC (stage T1b1)	Tumor size, missing essential information (horizontal extension)	Indecisive situation changed to radical hysterectomy	No definitive treatment plan
16	45	Biopsy	Cervical SCC (stage Tx)	Cervical SCC (stage T1a2)	Missing essential information (horizontal extension)	Indecisive situation changed to radical hysterectomy[a]	No definitive treatment plan
17	40	Biopsy	Cervical SCC (stage Tx)	Cervical SCC (stage T1a1)	Tumor size	Indecisive situation changed to cone biopsy	No definitive treatment plan
18	31	Biopsy	Basaloid SCC	Adenoid cystic carcinoma	Histologic type	Chemotherapy canceled, treated with radiotherapy	Over-treatment
19	60	Biopsy	Cervical adenocarcinoma	AIS	Invasive-status	Cone biopsy performed	Over-treatment
20	87	LEEP	Cervical SCC	CIN III	Invasive-status	Chemo-radiotherapy canceled	Over-treatment
21	39	Biopsy	Cervical villoglandular carcinoma	Cervical adenocarcinoma, usual type	Histologic type	Radical instead of simple hysterectomy	Under-treatment
22	59	Biopsy	Cervical villoglandular carcinoma	Cervical adenocarcinoma, usual type	Histologic type	Radical instead of simple hysterectomy	Under-treatment
23	36	LEEP	AIS	Cervical adenocarcinoma	Invasive-status	Reconization canceled, radical hysterectomy done	Under-treatment
24	35	Cone biopsy	AIS	Cervical adenocarcinoma	Invasive-status	Hysterectomy instead of reconization	Under-treatment
25	44	Cone biopsy	AIS	Cervical adenocarcinoma	Invasive-status	Reconization canceled	Under-treatment

Table 3 (continued)

#	Age (y)	Specimen	Original diagnosis	Review diagnosis	Discrepant parameters	Changes in treatment	Classification
26	50	LEEP	Cervical SCC (stage Tx), no LVSI	Cervical SCC (stage T1b1), LVSI present	Missing essential information (horizontal extension), LVSI-status	Radical hysterectomy instead of simple hysterectomy	Under-treatment
27	58	Hysterectomy	Cervical SCC (stage T1a1), no LVSI	Cervical SCC stage T1a1, LVSI present	LVSI-status	Subsequent lymph node dissection	Under-treatment
28	29	Biopsy	Cervical SCC (stage T1a)[b] LVSI not described	Cervical SCC (stage T1a), LVSI present	Missing essential information (LVSI)	Subsequent lymph node dissection	Under-treatment

y years, *LEEP* loop electrosurgical excision procedure, *CIN* cervical intraepithelial neoplasia, *SCC* squamous cell carcinoma, *AIS* adenocarcinoma in situ, *LVSI* lymphovascular space involvement

[a] Cone biopsy was performed. Tumor stage was determined based on both cone biopsy specimen and biopsy

[b] Differentiation between T1a1 and T1a2 could not be made because there were multiple tumors

SCC was decisive for further treatment planning and was therefore used for the analysis.

Fifty-eight (25.2%) discrepancies were identified; 28 (12.2%) were major, and 30 (13%) were minor. Discrepancies arose from missing essential information, or discordant assessment of histologic parameters, i.e., invasive-status, site of tumor, histologic type, LVSI-status, tumor size, and margin status (Table 2). More than one factor was operative in eight cases of major, and six cases of minor discrepancies. Missing essential information caused 27.8% of major and 19.4% of minor discrepancies. For cases with minor discrepancies, these items were horizontal extension and margin status of the tumor. For cases with major discrepancies, these were depth of invasion, horizontal extension, and LVSI status. Changes in histologic type of tumor caused 30.5% of minor discrepancies.

Pathology review prevented under-treatment of eight patients (3.5%) and over-treatment of three patients (1.3%). For three patients (1.3%), treatment for incorrect malignancy could be avoided, and for 14 (6.1%) patients, definitive treatment plan could be formulated. Following the pathology review, chemo-radiotherapy was canceled for two patients, and additional cone biopsy was omitted for nine patients. For five patients, invasive carcinoma was discovered on pathology review, while for two patients, the diagnosis of invasive carcinoma was changed to carcinoma in situ (Table 3).

On comparing the characteristics of discrepant cases through Chi-squared test, major discrepancies were found to be significantly less frequent for patients with macroscopic tumor and histologic diagnosis of conventional SCC. However, on stratified Mantel-Haenszel analysis, macroscopic tumor was found to be a confounder, and only histologic diagnosis of SCC retained statistical significance ($p = 0.001$). For patients with a macroscopic tumor and histologic diagnosis of conventional SCC ($n = 100$), only one major discrepancy was found (1.0%, 95% CI 0.0–3.0%). No other factors significantly influenced the chances of a discrepancy (Supplementary Table 1).

Discussion

Major discrepancies were identified on pathology review for 12.2% of our cases. Major discrepancy rates varying between 0.6 and 13.5% have been previously reported for gynecologic oncology [2, 5–12]. Missing essential information, such as horizontal extension, depth of invasion, and LVSI status, was the most common cause of major discrepancies. We therefore recommend implementing synoptic templates, which ensures standardization of pathology reporting, and usage of uniform terminology [13–16]. Khalifa et al. hypothesized that incomplete reporting results from the lack of awareness of the peripheral pathologist of the clinical relevance of the prognostic

and predictive parameters [2]. Workgroup meetings at tertiary centers and discussion of the discrepant cases with the referring pathologist can prove beneficial in this context.

Discordant assessment of invasive-status and size of the tumor also led to major discrepancies. Proper presentation of cone biopsies in separate, well-labeled containers, pinned up to improve orientation, can facilitate assessment for both referring and reviewing pathologists [17]. For complicated diagnoses, we recommend requesting additional consultation(s).

Pathology review prevented under-treatment of 3.5%, over-treatment of 1.3%, treatment for incorrect malignancy of 1.3%, and enabled definitive treatment of 6.1% of patients. This conclusively elicits the importance of pathology review at tertiary centers for ensuring appropriate management of cervical carcinoma.

Significantly fewer major discrepancies were noted in patients with macroscopic tumors, as was also reported by Chan et al. [7]. On stratified analysis, histologic diagnosis of SCC was identified as the only factor significantly associated with fewer major discrepancies. We noted only one major discrepancy for cases with macroscopic tumor and histologic diagnosis of SCC ($n = 100$). Therefore, for patients with macroscopic tumor and histologic diagnosis of SCC, yield of pathology review appears limited. In health-care settings with limited resources, to reduce the workload and expenditure, omitting mandatory pathology review for these patients may be considered. Eskander et al. reported higher rates of discrepancies for biopsy specimens [5]. This was, however, not reflected in our study, which might be due to the small sizes of our subgroups, or because LEEP/cone biopsies are more frequently performed for non-visible tumors.

Minor discrepancies were noted in 13% of our cohort. Similarly to Minig et al., the majority of these arose from discordant assessment of histologic type [12].

This study suffers from the limitation characteristic of retrospective chart review, such as unrecorded information and inconsistent quality of information. Since this is a single-center study, our results may not be generalizable. The pathology review was not blinded, and thus, some bias cannot be ruled out. Moreover, blinded studies have demonstrated that the reviewed diagnoses may not necessarily be correct [7, 15, 18]. Nevertheless, the findings from a relatively large cohort are presented, who were treated within a short time span, during which the diagnosis or treatment did not change.

Conclusion

Pathology review reveals discrepancies of relevance for the management of cervical carcinoma. For patients with a macroscopic tumor, and pathologic diagnosis of SCC, yield of mandatory pathology review may be limited, as this rarely leads to treatment modification.

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

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Compliance with ethical standards

The Dutch national guidelines state that no ethical approval is required for the use of anonymous leftover tissue (www.federa.org), and this is also part of a standard treatment agreement with patients at Erasmus MC.

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