Post-radiation Pap smear for Chinese patients with cervical cancer: a ten-year follow-up

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Summary

Background: To study the performance of routine follow-up Pap smears after curative radiotherapy (RT) for Chinese cervical cancer (CC) patients.

Methods: In 1996, 50 patients with non-metastatic CC received curative RT. Forty-six patients had routine follow-up Pap smears and constituted the study group. Details regarding clinical characteristics were retrospectively abstracted. Pap smear results were obtained via national Pap smear database linkage and chart review. The Pap smear results during recurrence-free survival (RFS) were analyzed and compared with clinical outcomes to study the performance characteristics.

Results: After 34 (2~105) months' median follow-up, the clinical outcomes were isolated central recurrence (ICR), other recurrence (OR), and no evidence of disease (NED) for six, 20, and 20 patients, respectively. During 22 months' median RFS (range 2-105), 422 Pap smears (including missing data, n = 33) were performed. Most of the Pap smear results were within normal limits (65.8%) or benign (reactive changes or atrophy with inflammation) (25.2%). Atypical cells, low-grade squamous intraepithelial lesion (LSIL), high-grade intraepithelial lesion (HSIL), and carcinoma were found in ten (2.6%), 11 (2.8%), 11 (2.8%), and three (0.8%) specimens, respectively. Follow-up of the 21 atypical cells/LSIL smears among seven patients revealed five NED with normal/benign smears, one NED with HSIL and one OR with HSIL. Follow-up of the 11 HSIL smears among four patients revealed two ICR, one OR and one NED with HSIL. Follow-up of the three carcinoma smears revealed three ICR (one followed by HSIL in a repeat Pap smear before ICR). The sensitivity for the detection of ICR by carcinoma smears was 50%, with a specificity and positive predictive value (PPV) of 100%.

Conclusion: Few (~3%) of the routine follow-up Pap smears after CC patients receiving curative RT were HSIL/carcinoma, but most (4/6) of these patients turned out to be ICR.

Key words: Cervical cancer; Radiotherapy; Pap smear; Utilization.

Introduction

Cervical cancer (CC) has been the one of the leading female cancers worldwide, being the cause of death for 239,000 females in 2002 [1]. Routine Papanicolaou (Pap) smear screening has been shown to be effective in reducing the incidence and mortality of invasive cervical cancer [2]. However, whether it has also been effective in post-therapy follow-up remains controversial, especially after curative radiotherapy (RT), because only selective patients in good condition with an isolated central recurrence (ICR) have had the chance for successful salvage therapy (mostly exenteration) [3] and previous RT could interfere with the interpretation of the Pap smear [4]. This study aimed to investigate the performance of follow-up Pap smear exams in a cohort of patients with invasive CC treated with curative RT in 1996, which was the first year complete national registry Pap smear data were available.

Materials and Methods

Clinical characteristics:

According to the cancer registry of our department and institute (a 1500-bed tertiary medical center), medical records of patients with pathologically proven non-metastatic cervical cancer being treated with curative radiotherapy in 1996 were identified. Their medical histories were reviewed and patient-related (age, pre-RT hemoglobulin (Hgb)), disease-related (histology, FIGO stage), treatment-related factors (treatment setting, operation, RT technique and dosage, chemotherapy), and clinical follow-up outcomes were retrospectively retrieved. Recurrence was coded as isolated central recurrence (ICR), lateral pelvis only (LPO), both pelvis and distant metastasis (BPDM), and distant metastasis (DM) only. Other recurrence (OR) was defined as either one of LPO, BPDM, or DM. Recurrence-free survival (RFS) was coded from the end of RT to the first day of clinically suspected recurrence or death or final clinical follow-up with no evidence of disease (NED). Overall survival after recurrence (OSAR) was coded from the day of recurrence to death or last contact according to the cancer registry or clinical follow-up.

This database was then linked to the Pap Smear Screening Registry System, Republic of China, and complemented with hospital records. Those treated with curative intent and with follow-up Pap smear data constitute our study group.

Pap smear: results and performance

Pap smears performed during RFS were studied since most recurrences cannot be salvaged successfully and there was no need of further screening in that situation [3]. The relationship between recurrent status and the most recent Pap smear was recorded to evaluate the clinical performance of follow-up Pap smears. The log-rank test was used to test the difference of OSAR.

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Results

Clinical characteristics:

Fifty patients with Stage I-III and local recurrent CC received curative RT in 1996 at our institute. Forty-six patients had follow-up Pap smears and constituted the study group. Their patient and disease characteristics are listed in Table 1. The median age was 56 years old (range: 31-82). Most of the histological diagnoses were squamous cell carcinoma (39/46). Median pre-RT Hgb level was 12.4 mg/dl (range: 10.3~14.6) since blood transfusions were usually given to patients presenting with Hgb < 10.

Table 1. — *Disease characteristics of patients.*

	Subtypes or Median	Patients (no.)
Histology	Squamous cell carcinoma	39
	Adenocarcinoma	3
	Adenosquamous carcinoma	1
	Carcinoma in situ	2
	Carcinoma in situ at least	1
Stage	I	17
	IIa	9
	IIb	9
	III	3
	Local recurrence	8
Treatment	Adjuvant (group I)	15
	Definitive (group II)	23
	Salvage (group III)	8

According to treatment strategy, 15 patients (group 1) received adjuvant RT after hysterectomy with risk factors, 23 patients (group 2) received definitive RT alone, and eight patients received salvage RT for cervical stump recurrence after hysterectomy (7 patients) or radical RT (one patient). RT techniques included a combination of pelvic external beam RT (EBRT) and intracavitary brachytherapy (ICBRT) for all except one patient in group 1 who received ICBRT alone and one patient in group 3 who received EBRT alone. For ICBRT, the dose specificity was at either point-A (for group 2) or the mucosal surface (for group 1, 3). No patient received extended field RT or chemotherapy. The median (range) EBRT dose, BRT dose, and RT duration were 50 Gy (40-60), 20 Gy (15-40), and 52 days (41-69), respectively.

Clinical outcomes:

The clinical outcomes are shown in Table 2. Generally speaking, recurrence was usually found two years after treatment, so the NED status was further divided into NED with follow-up < 2 years and NED with follow-up > 2 years [5]. After 34 (2~105) months' median clinical follow-up duration at our institute, 17 pelvic recurrences and 13 distant metastases were noted. Ten patients were diagnosed by histology, while the others were diagnosed by imaging (13 patients) or clinically (three patients). All the patients with recurrence had clinically progressive disease and were dead except for two patients, even though salvage treatment was done in 12 of them. For the six patients with ICR, curative therapy was planned for four of them (hysterectomy for one, RT for one, local chemotherapy for one, and radical excision for one but she refused). All six patients had died of disease with the exception of one patient with recurrence of CIS who was still alive after local 5FU chemotherapy then lost to follow-up (OSAR: 84 months according to the cancer registry). Another living recurrent patient was diagnosed with bone metastasis and received palliative RT, and was then lost to follow-up (OSAR: 54 months by cancer registry).

Table 2. — *Clinical outcome characteristics.*

Status	Subtype	Number
Disease status (n = 46)	No evidence of recurrence, (clinical follow up < 2 years)	6
	No evidence of recurrence, (clinical follow up > 2 years)	14
	Isolated central pelvic recurrence	6
	Pelvis only with lateral pelvis involved	7
	Both pelvic and distant recurrence	4
	Distant recurrence only	9

Pap smear results:

During a median RFS of 22 months (range 2~105), the median follow-up Pap smear number was five times (range 1~45). These Pap smear results (n = 389) are shown in Table 3 after exclusion of missing data (n = 33) for the total 1,622 RFS months. Most of the Pap smear results were within normal limits (65.8%) or benign (reactive changes or atrophy with inflammation) (25.2%). Atypical cells, low-grade squamous intraepithelial lesion (LSIL), high-grade intraepithelial lesion (HSIL), and carcinoma were found in ten (2.6%), 11 (2.8%), 11 (2.8%), and three (0.8%) specimens, respectively.

Table 3. — *Pap smear results (n = 389).*

Category	Cytological diagnosis	Number (%)
Normal	Within normal limits	256 (65.8)
Benign lesions	Reactive changes or atrophy with inflammation	98 (25.2)
Atypical cells	Atypical squamous cells (ASC-US) or Atypical glandular cells	10 (2.6)
LSIL	High-grade squamous intraepithelial lesion	11 (2.8)
HSIL	Low-grade squamous intraepithelial lesion	11 (2.8)
Carcinoma	–	3 (0.8)

Pap smear results vs clinical outcomes: point of view of Pap smears results:

The association between abnormal Pap smear results during RFS and clinical outcomes is shown in Table 4. Follow-up of the 21 atypical cells/LSIL smears among seven patients revealed five NED with normal/benign smears, one NED with HSIL and one OR with HSIL. Follow-up of the 11 HSIL smears among four patients revealed two ICR, one OR and one NED with HSIL. Follow-up of the three carcinoma smears revealed three ICRs (one followed by HSIL in a repeat Pap smear before ICR).

Table 4. — *Clinical outcomes and Pap smear results.*

Clinical outcomes (final Pap smear results)	Abnormal Pap smears(s)/patient number(n) during RFS*		
	Atypical cells or LSIL (s/n = 21/7)	HSIL (s/n = 11/4)	Carcinoma (s/n = 3/3)
NED (normal/benign)	5	0	0
NED (HSIL)	1	1	0
ICR	0	2	3
OR (HSIL)	1	1	0

*: not exclusive since patients may have several different Pap smear results during follow-up; HSIL: high-grade squamous intraepithelial lesion; ICR: isolated central recurrence; LSIL: low-grade squamous intraepithelial lesion; NED: no evidence of disease; OR: other recurrence; RFS: recurrence-free survival.

Pap smear results vs clinical outcomes: point of view of recurrence pattern:

The location of recurrence and the most significant Pap smear results within three months before recurrence are detailed in Table 5 [6]. Sensitivity for the detection of ICR by carcinoma smears was 50%, with a specificity and positive predictive value (PPV) of 100%. The intervals between Pap smear and recurrence for the four positive carcinoma/HSIL cases were one, three, eight and 11 weeks, respectively. After clinical diagnosis of recurrence, 13 of the 26 patients still had follow-up Pap smears, which led to a further diagnosis of local recurrence in two patients. For the other 20 patients without clinical diagnoses of recurrence, five were found to have further follow-up Pap smear data (not performed at our institute), which were all negative.

Table 5. — . *Most severe Pap smear results three months before recurrence or last clinical follow-up.*

1st failure site	Central pelvis	Lateral pelvis	Both pelvis and metastasis	Metastasis of disease	No evidence
Carcinoma	3	0	0	0	0
HSIL	1	0	0	1	1
Negative Pap smear*	0	1	2	0	0
Negative Pap smear	2	6	2	8	19

* Interval between pelvic recurrence with most recent Pap smear more than three months (5, 8, 8 months) for these three patients; HSIL: high-grade squamous intraepithelial lesion.

Overall survival after recurrence (OSAR):

Although none of recurrent patients were definitively successfully salvaged, the OSAR was slightly better for the four positive carcinoma/HSIL smear cases when compared with Pap undetected recurrences with borderline statistical significance (median (range) survival: 21 (15~84) vs eight (0-54), p = 0.07).

Discussion

Although a routine follow-up Pap smear has generally been recommended after curative RT for CC patients [6], the previous RT would interfere with the interpretation of the Pap smear. Irradiation induced atypia can interfere with cytological analysis and thus detection of a local recurrence, or simulate malignant atypia and cause unnecessary suspicion of recurrence [4]. Therefore, whether or not it was effective in the early detection of recurrence is controversial [7-11], and none of these reports was based on Chinese patients.

In the present study, the sensitivity for the detection of ICR by carcinoma smears was 50%, with a specificity and PPV of 100%, which is similar to earlier reports [8, 9] and a recent liquid-based cytology report [12]. Although our patient number was not as large as previous studies, there were 26 recurrences noted as these patients had been followed for up to ten years, which may be comparable to recent studies (such as 9 recurrences in Wright *et al.* and 45 recurrences in Morice *et al.*) [11, 12].

Most (4/6) ICR had positive/suspicious routine Pap smears before the clinical diagnosis of ICR in the present study. Half (2/4) of the patients with HSIL Pap smears and all (3/3) of the patients with carcinoma Pap smears turned out to be ICR. It seems that a routine follow-up Pap smear was a reliable indicator of recurrence in most cases and was a valuable tool for the detection of local recurrence in Chinese cervical carcinoma patients after primary radiotherapy.

Methods to improve the accuracy may also influence this result, such as HPV testing [13]. However, controversy exists, and it was documented as "promising" only in a recent U.S. National Cancer Institute Recommendation [14].

Although some studies have questioned the value of routine post-RT Pap smear surveillance for asymptomatic patients, we felt that it was difficult to make this conclusion for retrospective studies [10, 11]. Our data showed that this strategy was a valuable tool for the detection of local recurrence with good sensitivity and high specificity. Prospective trials may be needed to see whether this strategy will find asymptomatic recurrences and whether this strategy will impact survival.

On the other hand, central recurrence was not the dominant failure pattern. In our study, central recurrence accounted for 23% (6/26) of recurrences, which was similar to other studies (such as 28% in Bodurka-Bevers *et al.*) [10]. As a systemic exam, positron emission tomography (PET) may be predictive of tumor recurrence [15]. In a recent report, 80% sensitivity and 100% specificity for asymptomatic patients was reported [16]. However, PET was much more expensive compared to Pap smears and its impact on survival needs to be validated since there is no effective treatment for systemic recurrence [3].

Conclusion

Few (~3%) of the routine follow-up Pap smears from Chinese cervical cancer patients receiving curative RT were HSIL/carcinoma, but most (4/6) of these patients turned out to have an isolated central recurrence. A follow-up Pap smear was a reliable indicator of recurrence in most cases and was a valuable tool for the detection of local recurrence.

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