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Angiographic Changes in Uterine Cervical Cancer during the Course of Transarterial Infusion Chemotherapy

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Purpose: To assess the correlation between angiographic findings, tumor stage, tumor size, histological type, and the effect of transcatheter arterial infusion (TAI) chemotherapy in patients with uterine cervical cancer.

Materials and Methods: Thirty-three patients with untreated cervical cancer underwent two cycles of TAI. Changes in angiographic findings and other clinical and imaging data were assessed using the χ^2 test, multivariate analysis, and the two-sample t-test.

Results: The group with parametric involvement included more patients with hypervascular tumors (21/24) than the group with no parametric involvement (0/5) ($p<0.001$). Multivariate analysis revealed no correlation between initial tumor size, histology, or angiographic pattern and the effect of TAI.

Conclusion: The angiographic patterns seen in cervical cancer correlated with tumor stage. However, neither angiographic findings nor other clinical features predicted the effect of TAI.

Key words: uterine cervical cancer, angiography, neoadjuvant chemotherapy

Introduction

Although radiologists are involved in carrying out both adjuvant and neoadjuvant transcatheter arterial infusion (TAI) chemotherapy for uterine cervical cancer and in assessing angiograms of this disease, there are very few references in the literature on which to base descriptions of individual disease and selection of the most effective drug delivery option according to angiographic findings, tumor stage, and histological type, or to predict the likely effect of TAI. In this retrospective study, we analyzed the relationship between angiographic patterns and the pathological features of cervical carcinoma, and investigated whether the effects of TAI varied according to these angiographic patterns and pathological characteristics.

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Clinical Materials and Methods

Between 1994 and 1997, 33 patients with uterine cervical cancer underwent our evaluation and treatment protocol. This involved magnetic resonance imaging (MRI), TAI, MRI, TAI, operation and/or irradiation, performed in this order. The interval between the first and second TAI was about one month (26-35 days). Using this protocol, it was possible to compare the angiographic findings from the first TAI with those from the second TAI in all patients, which was a vital factor in making objective retrospective angiographic evaluations. The mean age of the patients was 55 years, and ranged from 32 to 73 years. The FIGO classification was used to stage the cervical cancers, and the World Health Organization (WHO) classification for histological typing (Table 1). A few patients with very early disease (stage 0 or Ia) or those who did not complete the protocol were not included in this study.

In all patients, angiography and TAI were carried out using a 5 Fr Kohno No. 3-type catheter (Hanako-Medical, Japan) via a 5 Fr sheath placed in the femoral artery. Both the right and left proximal internal iliac arteries were used for contrast medium injection and anti-cancer drug infusion. The dose of the anti-cancer drug

Table 1. Subjects: 33 patients with cervical cancer

FIGO stage	
1b	3
2a	2
2b	13
3a	1
3b	11
4a	2
4b	1

WHO classification	
Squamous cell carcinoma:	
Keratinizing	5
Large cell non-keratinizing	14
Small cell non-keratinizing	5
Adenocarcinoma	4
Mixed type	3
Undifferentiated carcinoma	2

Table 2. FIGO stage and angiographic pattern

	1b	2a	2b	3a	3b	4a	4b
Ha type	0	0	8 (7)	0	7 (5)	2 (2)	0
Hb type	0	0	3 (3)	0	3 (3)	0	0
L type	3 (1)	2 (2)	2 (1)	1 (0)	1 (0)	0	1 (0)

Note: ( ) indicates squamous cell carcinoma only; Ha, Hb, and L type indicate early and dense stain with visible neovascularity, early and dense stain without visible neovascularity, and no or delayed stain, respectively.

was divided proportionally between these arteries. The contrast medium, iohexol (Omnipaque, 300 mg/mL; Daiichi-seiyaku, Tokyo, Japan), was injected through an automatic power injector at rates varying from 12 mL/4 s to 15 mL/5 s, depending on the size of patient's artery. In each patient, angiograms were obtained under the same conditions at both the first and the second TAI. The combination chemotherapy for all TAIs consisted of cisplatin 70 mg/m^2, Adriamycin 40 mg/m^2, mitomycin 15mg/m^2, and 5-fluorouracil 500 mg/patient.

The angiographic findings were evaluated by a doctor who was not informed of the patients' clinical details, except that the diagnosis was cervical cancer. Positive findings associated with cancer, such as tumor staining, neovascularity, and mass effect, were deemed to be justified when they had subsided or disappeared at the time of the second angiography, due to the effect of the first TAI on the tumor. When no significant change between the first and second angiograms was observed, an explanation, such as hypovascularity of the tumor, the tumor being too small to allow angiographic recognition, or lack of effect of the first TAI, was sought by comparing the MRIs obtained before and after the first TAI.

The angiographic manifestations of cervical cancer were classified into three categories: obvious tumor-background contrast after the arterial phase, with visible neovascularity (Ha type, Fig. 1); obvious tumor-background contrast after the arterial phase, without visible neovascularity (Hb type, Fig. 2); and no obvious tumor-background contrast during the arterial phase with slight to some contrast after the capillary phase (L type, Fig. 3).

The effect of the first TAI was measured by MRI and defined as follows: complete response (CR): disappearance of the tumor mass; partial response (PR): at least a 50% decrease in the sum of the largest perpendicular diameters of the tumor; minor response (MR): shrinkage of the tumor by less than 50%; stable disease (SD): no change in the tumor size.

Statistical analyses of any correlations between the angiographic pattern and the FIGO stage, histological type, or effect of TAI, and between the histological type and the effect of TAI, were performed using the χ^2 test, multivariate analysis, and the two-sample t-test.

RESULTS

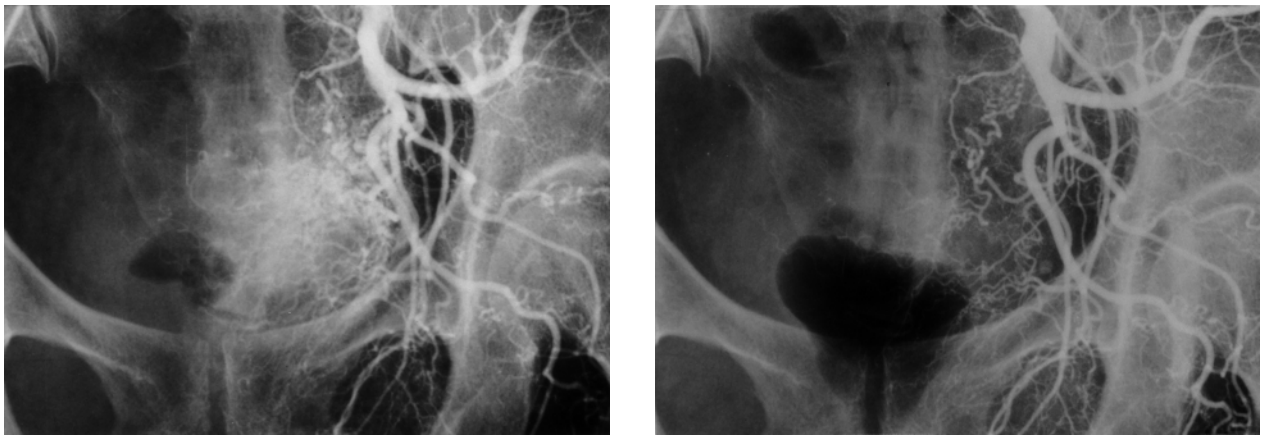
Normal myometrium and incidental coexistent fibroids showed delayed, slight to mild staining similar to L-type tumors, however, the angiogram at the second TAI and MRI measurements enabled the two to be differentiated.

The incidences of Ha-type, Hb-type and L-type tumors were 17/33 (51.5%), 6/33 (18.2%), and 10/33 (30.3%), respectively.

The FIGO staging distribution of these three types is shown in Table 2. There were 21 Ha- and Hb-type tumors in patients at stages with positive parametric involvement (stage 2b+3b, N=24), compared with none in patients at stages without parametric involvement (stage 1b+2a, N=5). This difference was significant ($p<0.001$). Likewise, there were 18 Ha- and Hb-type tumors in patients with squamous cell carcinoma (SCC) at stages with positive parametric involvement (stage 2b+3b, N=19), compared with none in patients with SCC at stages without parametric involvement (stage 1b+2a, N=3). This difference was also significant ($p=0.0041$). However, the angiographic pattern was not significantly correlated with tumor size measured on initial MRI in either of these patient groups.

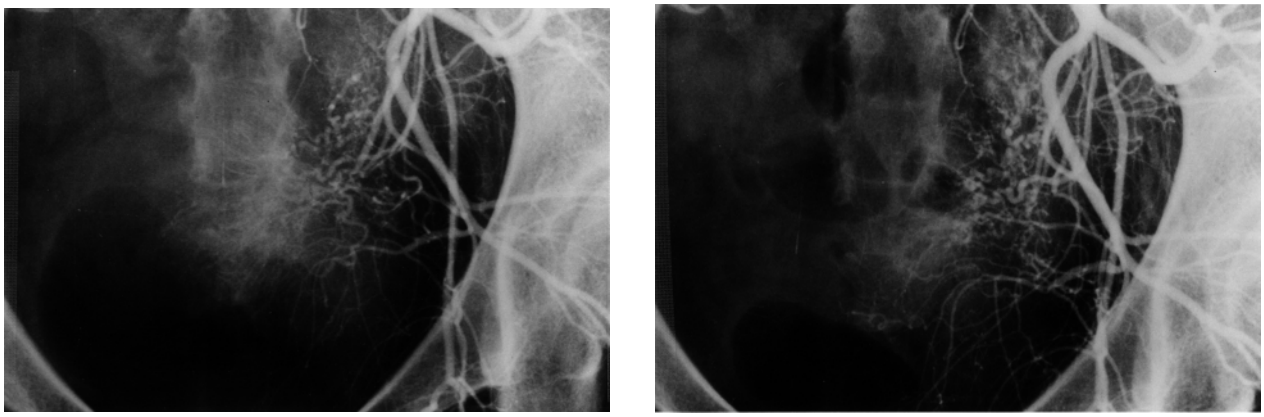
The relationship between angiographic pattern and histological type is shown in Table 3. Although there were nine patients with Ha-type tumors in the group with large cell non-keratinizing carcinoma (a subtype of SCC), all were in stages with parametric involvement, and therefore no statistically significant correlations could be identified.

The relationship between angiographic pattern and the effect of TAI is shown in Table 4. No significant correlation between these factors was apparent. Furthermore, multivariate analysis revealed no



a b

Fig. 1. A Ha-type tumor from a 62-year-old woman with FIGO 2b squamous cell carcinoma. During the arterial phase, a left internal iliac angiogram showed dense tumor staining with prominent neovascularity (a), which could be distinguished from the normal cervicovaginal branches by comparison with a second angiogram obtained one month after the first TAI (b).



a b

Fig. 2. A Hb-type tumor from a 38-year-old woman with FIGO 3b squamous cell carcinoma. During the arterial phase, a left internal iliac angiogram showed moderate tumor staining with slight neovascularity (a). One month after the first TAI, tumor staining decreased but the uterine artery and its branches appeared no remarkable change (b).

a b

Fig. 3. An L-type tumor from a 55-year-old woman with FIGO 3a mixed adenocarcinoma and squamous cell carcinoma. During the arterial phase, a right internal iliac arteriogram showed stretched uterine branches or a huge mass effect (a). The marked effect of the first TAI was evident on a second angiogram obtained one month later (b). Comparison of the two angiograms confirmed that the initial disease had very little tumor staining due to neovascularity.

Table 3. Histological type and angiographic pattern

	SCC, K	SCC, SNK	SCC, LNK	Aden.	Mixed	Undiff.
Ha type	3	2	9	3	0	0
Hb type	1	2	3	0	0	0
L type	1	1	2	1	3	2

Note: SCC, K, SNK, and LNK indicate squamous cell carcinoma, keratinizing, small cell non-keratinizing, and large cell non-keratinizing, respectively; Aden., Mixed, and Undiff. indicate adenocarcinomas, mixed type of adenocarcinoma and squamous cell carcinoma, and undifferentiated carcinoma, respectively; for Ha, Hb, and L, see the legend for Table 2.

Table 4. Angiographic pattern and effects of TAI

	CR	PR	MR	SD
Ha type	2 (2)	6 (5)	8 (6)	1 (1)
Hb type	1 (1)	3 (3)	2 (2)	0
L type	4 (2)	4 (1)	2 (1)	0

Note: CR, PR, MR, and SD indicate complete response, partial response, minor response, and stable disease, respectively; for Ha, Hb, and L, see the legend for Table 2; ( ) indicates squamous cell carcinoma only.

correlation between initial tumor size, histology, or angiographic pattern and the effect of TAI.

Discussion

Neoadjuvant chemotherapy for cervical cancer is preferable to adjuvant chemotherapy because it renders the tumor more amenable to conservative surgery and may significantly enhance curability by radiation.[1-4] The TAI technique has often been used to make this type of therapy more effective by increasing the drug concentration in the target organ.[5-7] It would be useful to be able to predict the likely effect of TAI from pre-TAI angiographic findings combined with other information. However, very few previous reports have dealt with this matter, probably because angiographic decisions tend to be based on individual experience, and therefore often become subjective. In this study, although it is retrospective, it must be emphasized that the first and second angiographies, TAIs, and MRIs were carried out under the same protocol for all patients, and the initial angiographic findings, on which correlations were based, were selected with care by comparison with a subsequent angiogram. Thus, every effort was made to reduce subjectivity.

From the results, two important issues were identified.

Firstly, parametric involvement seemed to be a more important factor in the development of tumor neovascularity than tumor size. In other words, even if the tumor mass was small, parametric involvement would enhance tumor staining on the angiogram due to hypervascularity. This is consistent with the fact that the parametric region includes the vascular-rich broad ligament. Therefore, when laterality of the vascular supply to the tumor is evident on an angiogram, it is important to use the internal iliac artery on each side and to divide the carcinostatic infusions proportionally, as we did in this study.

Secondly, since no significant correlation was observed between initial tumor size, histology, or angiographic pattern and the effect of TAI, it was not possible to identify patients for whom TAI would be either particularly useful or unhelpful based on clinical or imaging characteristics. However, it is worthy of special mention that 4/10 (40%) patients with L-type tumors had a complete response and a further 4/10 (40%) had a partial response. These good responses among patients with hypovascular tumors, despite the probability of lower local delivery of carcinostatics than in patients with hypervascular tumors, may be due to a relatively low clearance rate in the target organ and/or a systemic effect of the carcinostatics caused by re-circulation.

Conclusions

In this study, it was shown that cervical cancers with parametric involvement tended to appear hypervascular on angiography and that pre-treatment factors including tumor size, histology and angiographic pattern did not correlate with the effect of TAI.

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