Review

Thermoradiotherapy in Advanced Cervical Cancer: Clinical Experiments and Molecular Research

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Abstract

Background

For many years, the standard treatment of advanced cervical carcinoma has been radiotherapy (RT). However, locoregional failure rates of RT for Stage III or Stage IV cervical carcinoma are high. To clarify the role of thermoradiotherapy (TRT; radiotherapy plus hyperthermia) for FIGO Stage IIIB cervical carcinomas, we investigated both the clinical response and survival of patients treated with radio- or thermoradiotherapy. On the other hand, to identify a set of genes related to thermoradiosensitivity of cervical carcinoma, we compared the expression profiles of thermoradiosensitive and thermoradioresistant tumors using a cDNA microarray analysis.

A randomized clinical trials in our study and published trials

In our randomized trials, forty patients with Stage IIIB uterine cervix carcinoma were divided randomly into the following two groups: the RT group of 20 patients who underwent RT alone, and the TRT group of 20 patients who underwent three sessions of hyperthermia in addition to RT. A complete response was achieved in 50% in the RT group versus 80% in the TRT group ($P=0.048$). Both the 5-year overall survival and disease-free survival of the patients who were treated with TRT (58.2% and 63.6 %) were better than those of the patients treated with RT (48.1% and 45%), but these differences were not significant. The 5-year local relapse-free survival of the patients who were treated with TRT (79.7%) was significantly better than that of the patients treated with RT (48.5%) ($P=0.048$).

Six randomized trials comparing the results of RT alone with TRT have been published, of which four showed significant better complete response, locoregional tumor control and/or disease-free survival rates. One trial showed a trend of better locoregional tumor control and one did not show any benefit.

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Prediction of advanced cervical carcinoma after thermoradiotherapy using microarray analysis in our previous study

A total of 19 patients with Stage III-IV cervical cancer who underwent definitive thermoradiotherapy were included in this study. We compared the expression profiles of 8 thermoradiosensitive and 11 thermoradioresistant tumors obtained by punch biopsy before treatment using a cDNA microarray. We selected 35 genes on the basis of a clustering analysis, and confirmed the validity of these genes with a cross validation test. Some of these genes were already known to be associated with apoptosis (*BIK, TEGT*), hypoxia-inducible gene (*HIF1A*), and tumor cell invasion and metastasis (*PLAU*). These results may eventually lead to the achievement of "personalized therapy" for this disease.

Key Words : cervical cancer, gene expression profiles, prediction, radiotherapy, thermoradiotherapy

1. Introduction

Worldwide, cervical cancer is the second most common malignant disease among women, both in incidence and mortality[1], and approximately 5,000 women die of this disease each year in Japan. Radiotherapy (RT) remains the most important non-surgical treatment for cervical carcinoma. The ability of RT to cure locally cervical cancer is limited by the size of the tumor, because the doses required to treat large tumors exceed the limit of toxicity in normal tissue. Efforts to overcome this problem have included the concurrent use of chemotherapy (CT)[2] or hyperthermia (HT)[3][4]. Thermoradiotherapy (TRT ; RT plus HT) has been reported to yield higher complete and durable responses compared to radiotherapy alone in both superficial and deep-seated tumors[5][6], and it is believed to be another promising treatment modality for management of advanced cervical cancer[3][4].

On the other hand, several molecular markers of thermoradiosensitivity, for example, *p53*[7], *Bax*[8], and *HSP 70/27*[9], have been reported. However, although the molecular mechanisms for thermoradiosensitivity of such molecules have been partially clarified, the whole picture remains unknown. To identify a set of genes related to thermoradiosensitivity of cervical carcinoma, we compared the expression profiles of thermoradiosensitive and thermoradioresistant tumors obtained by punch biopsy before treatment using a cDNA microarray consisting of 23,040 human genes.

This report demonstrated that the clinical results and molecular research in patients with advanced cervical carcinoma treated with thermoradiotherapy in our previous study[3]. In addition, this report summarized that six randomized trials[3][4][10-13] comparing the results of RT alone with TRT have been published.

2. A Randomized Clinical Trial in Patients with Stage IIIB Cervical Carcinoma

2.1. Materials and Methods

Between October 1994 and February 1999, 40 patients with FIGO Stage IIIB carcinoma of the uterine cervix were enrolled in this study at Kansai Medical University. The patient eligibility criteria for entry into the study were as follows : (1) histologically proven cervical carcinoma at International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB, (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, (3) no prior chemotherapy, radiotherapy, or surgery, (4) adequate bone

marrow, liver, and renal function, (5) no concomitant malignancies, and (6) informed consent.

The patients were divided into two groups : the RT group of 20 patients who received radiotherapy alone, and the TRT group of 20 patients treated with RT and hyperthermia once a week for a total of three sessions of up to 30.6 Gy radiation.

All patients entered in the protocol were treated with external pelvic RT using a 6 MV linear accelerator. A total of 30.6 Gy was targeted to the whole pelvis, with an additional dose to the parametria with central shielding for a total of 52.2 Gy. The fractions were 1.8 Gy daily, given 5 days/week. In addition, iridium 192 high-dose-rate brachytherapy was given in fractions of 7.5 Gy once per week for a total of 30 Gy to point A.

Hyperthermia was delivered via a radiofrequency capacitive heating device (Thermotron RF-8, Yamamoto Vinita Co., Osaka, Japan), which uses 8 MHz radiofrequency electromagnetic waves as a source of heat. Hyperthermia was usually applied within 30 min after external radiotherapy for a total of 60 min dependless on the pattern of temperature elevation once a week for a total of 3 sessions.

2.2. Results

All randomized patients were evaluated for clinical response and survival. There was no significant difference in the patients' demographics or in the tumor characteristics between the two groups.

The number of patients with CR was significantly larger in the TRT (16 of 20 patients, or 80%) than in the RT group (10 of 20 patients, or 50%) ($P=0.048$, Fisher's exact test). The respective number of patients who had a partial response (PR) or no response to treatment (NC) was 25% (5 of 20) and 25% (5 of 20) in the RT group versus 15% (3 of 20) and 5% (1 of 20) in the TRT group ($P=0.3$ and $P=0.09$, Fisher's exact test).

The 3-year overall survival and disease-free survival of patients treated with TRT (58.2% and 63.6%) were better than those of patients treated with RT (48.1% and 45%), but the difference was not significant (log-rank test). The 3-year local relapse-free survival of patients treated with TRT (79.7%) was significantly better than that of patients treated with RT (48.5%) ($P=0.048$, log-rank test).

3. Published Randomized Trials

Six randomized trials[3)4)10-13)] investigating TRT in patients with advanced cervical carcinoma have been published (Table I). The majority of the patients in these studies had Stage IIIB tumors. Four studies[3)4)10)12)] report significantly better results following TRT compared to RT alone. In one study[11)],

Table I. Results of randomized trials comparing RT with TRT in advanced stages of cervical cancer

Author's name	Numbers of patients	Complete Response		Pelvic control		Disease-free survival		Overall survival	
(number of references)	(FIGO stage)	RT	TRT	RT	TRT	RT	TRT	RT	TRT
Harima (3)	40 (IIIB 40)	50	80*	49	80*(3 years)	45	64	48	58 (3 years)
Van derZee (4)	114 (IIB 22, III 81, IV 11)	57	83*	41	61*(3 years)			27	51*(3 years)
Datta (10)	64 (IIIB 64)	58	74	46	67 (2 years)	27	59* (2 years)	73	81 (2 years)
Sharma (11)	50 (II 7, III 43)			50	70 (1.5 years)				
Hong-Wei (12)	120 (IIB 28, IIIB 92)	48	72*						
Vasanthan (13)	110 (IIB 56, III 51, IV 3)			80	70 (3 years)			73	73 (3 years)

RT=radiotherapy, TRT=Thermoradiotherapy, *=significantly better than RT alone with $P<0.05$

the 1.5-year pelvic control tended to be higher in the TRT group. In the study by Vasanthan et al.[13], no beneficial effect from TRT was found.

4. Prediction of Advanced Cervical Carcinoma after Thermoradiotherapy according to Expression Profiles Selected by Microarray Analysis

4.1. Materials and Methods

We selected 19 (1 Stage IIIA, 11 Stage IIIB, 5 Stage IVA, and 2 Stage IVB) of these patients to identify a set of genes related to thermoradiosensitivity or thermoradioresistancy between May 1995 and August 2001. Cervical carcinoma tissues were obtained from 19 patients who underwent biopsy prior to TRT, and were snap-frozen at −80°C.

All 19 patients were treated with TRT according to same protocol after sampling. Details have been described in our previous report[14].

Eight patients are alive and well (NED, no evidence of disease) from 54.9 months to 136.9 months after completion of treatment, and 11 patients have died from recurrent disease (CD, cancer-caused death) between 3.2 months and 22.9 months after completion of treatment. When we divided the patients into an NED group and a CD group, the former were classified as the thermoradiosensitive group and the latter as the thermoradioresistant group.

We have already reported the further information of methods of cDNA microarray analysis including RNA extraction, microarray design, hybridization, data analysis, permutation test, and hierarchical clustering in our previous report[14]. Here, we summarized the methods and results of cDNA microarray analysis comparing with an NED group and a CD group.

4.2. Results

Identification of genes responding to thermoradiotherapy

Thermoradiosensitive group survived significantly longer than thermoradioresistant one ($P < 0.001$, Student's t-test). By means of the Mann-Whitney test ($P < 0.05$) and subsequent procedures, we identified a total of 156 genes that were differently expressed between NED and CD groups. Of those 156 genes, 76 revealed increased expression, and 80 showed decreased expression, in carcinomas belonging to the NED group as compared to the CD group.

Permutation Test, Hierarchical Clustering and Cross-Validation Test

To evaluate the validity of the 156 genes selected as thermoradiosensitivity-related genes, permutation testing was performed. Expression levels of each of the 19 samples in both groups for each gene were permuted (randomly scrambled) 10,000 times. After the 10,000 times permutation, the probabilities of the genes being correlated to both NED and CD group distinction were estimated. As a result, all of the selected 35 genes showed P value < 0.05 without exception. To confirm whether the expression patterns of these 156 genes could allow discrimination between the two groups, we performed a hierarchical cluster analysis. This procedure clearly separated the two groups from each other. Genes that were already known to be associated with apoptosis were significantly up-regulated in the NED group compared to the CD group ; the former included *Bcl-2*-interacting killer (apoptosis-inducing) (*BIK* ; Table II). The latter included testis enhanced gene transcript (*BAX* inhibitor 1) (*TEGT* ; Table

Table II. Genes showing relatively higher expression carcinoma cells in the NED group than those in the CD group

Gene Symbol	Gene Name
BIK	BCL2-interacting killer (apoptosis-inducing)
SSI-3	STAT induced STAT inhibitor 3
TMSB4X	thymosin, beta 4, X chromosome
SCSDL	sterol-C5-desaturase (fungal ERG3, delta-5-desaturase)-like
ALY	transcriptional coactivator
CKB	creatine kinase, brain
LIV	LIV protein, estrogen regulated
SNW1	SKI-INTERACTING PROTEIN
UQCRC1	ubiquinol-cytochrome c reductase core protein I
MLLT4	myeloid/lymphoid or mixed-lineage leukemia (trithorax (Drosophila) homolog)

Table III. Genes showing relatively higher expression carcinoma cells in the CD group than those in the NED group

Gene Symbol	Gene Name
TEGT	testis enhanced gene transcript (BAX inhibitor 1)
HIF1A	hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)
PLAU	plasminogen activator, urokinase
CA12	carbonic anhydrase XII
CD44	CD44 antigen (homing function and Indian blood group system)
P63	transmembrane protein (63kD), endoplasmic reticulum/Golgi intermediate compartment
USP6	ubiquitin specific protease 6 (Tre-2 oncogene)
CTSB	cathepsin B
CTSL	cathepsin L
RPL37A	ribosomal protein L37a
FLJ22833	hypothetical protein FLJ22833
RRBP1	ribosome binding protein 1 (dog 180kD homolog)
D1SI55E	NRAS-related gene
SLC31A2	solute carrier family 31 (copper transporters), member 2
FLJ10422	hypothetical protein FLJ10422
NRBF-2	nuclear receptor binding factor-2
ORC3L	origin recognition complex, subunit 3 (yeast homolog)-like
PBEF	pre-B-cell colony-enhancing factor
VPS33B	vacuolar protein sorting 33B (yeast homolog)
FLJ12287	hypothetical protein FLJ12287 similar to semaphorins
	ESTs
	ESTs

III), and Hypoxia-inducible gene, hypoxia-inducible factor 1 (*HIF1A*) were up-regulated in the CD group relative to the NED group (Table III). In addition, genes that are considered to be associated with tumor cell invasion and metastasis, including plasminogen activator, urokinase (*PLAU, uPA*) was up-regulated in the CD group relative to the NED group (Table III).

Cross-validation testing was performed to examine whether the 35 genes were crucial in classifying the NED and CD groups.

5. Discussion

Our study[3] clearly demonstrates that the addition of HT to conventional RT can result in beneficial effects for complete response ($P=0.048$) and/or local relapse-free survival ($P=0.048$). The Dutch study[4] shows a significant improvement in overall survival in the TRT group compared with RT alone. The study by Datta et al.[10] and our study[3] show a trend of better overall survival of patients treated with TRT compared with RT alone, however, the difference was not significant. The publication of Hong-Wei et al.[12] is in Chinese, which makes most of the data inaccessible. They randomized patients to four treatment groups: RT alone, RT plus HT, RT plus CT (cisplatin, 5 FU and vincristin) and RT plus HT plus CT. The lack of benefit from TRT in the study by Vasanthan et al.[13] may be partly explained by an imbalance in tumor volume over the two treatment arms, the median tumor volume in the TRT arm was 60.3 cc whereas in the RT arm it was 49.5 cc. Probably more important problem in their study is that the treatment application method has been inadequate[15]. They have used a capacitive heating technique, with which it is principally possible to achieve therapeutic heating in depth, provided that the limitations of this technique are taken into account. The one centre that treated half of the patients, and possibly other centre as well, report to have used an intra-vaginal electrode. This results in a high energy level and high temperatures in a small volume around the intra-vaginal electrode with much lower temperatures in the periphery of the tumor. In our study[3], using a radiofrequency capacitive heating device which uses 8 MHz radiofrequency electromagnetic waves, the average temperature was 40.6 ± 1°C being in the radiosensitizing range. The mechanism of tumor response to TRT at this range of temperature seems to involve the development of apoptosis through the activation of one of the *bax* pathways that we reported previously[8].

In our current research, we profiled the gene expression patterns of cervical cancer cells using a cDNA microarray system containing 23,040 genes. We identified 35 genes that were differentially expressed among patients who showed good response as opposed to poor response to TRT.

A gene, involved in apoptosis, *BIK*, one of the pro-apoptotic members of the *Bcl-2* family[16], was significantly up-regulated in the NED group compared to the CD group. In contrast, a gene involved in suppression of apoptosis, *TEGT* (testis enhanced gene transcript, *BAX* inhibitor 1), in the tumor cells was significantly up-regulated in the CD group compared to the NED group. The mechanism of tumor response to TRT seems to involve the development of apoptosis through the activation of a pathway of one of the *Bcl-2* family genes, Bax, that we reported previously[8]. In contrast, as it was shown by others, *Bax* inhibitor-1 (*TEGT*) showed significantly higher expression in the CD group that might compensate for *Bcl-2* downregulation and thus promote cell survival by counteracting Bax functions[17]. Therefore, it is probable that an additive or synergistic anti-tumor effect of TRT, which was shown to occur through

induction of apoptosis, was likely to be involved in one of the pathways with the pro-apoptotic members of the *Bcl-2* family and to inhibit by *TEGT.*

Hypoxia-inducible factors (HIFs) (*HIF1A, HIF1α)* are key proteins regulating the response of a variety of genes to hypoxic stimuli. Because hypoxia has been recognized as a major cause of failure of radiotherapy[18], *HIF* expression may potentially be a potent predictive marker of response to radiation. Several studies also suggest that increased *HIF1A* is related to poor outcome in the patients with cervical cancer after radiotherapy[19)20].

Among the key players in the proteolytic cascade leading to tumor invasion and metastasis are factors of the plasminogen activation system, such as the serine protease urokinase-type plasminogen activator (*PLAU, uPA*)[21] and its type-1 inhibitor PAI-1. *PLAU* also plays an important role in tumor invasion and metastases by initially catalyzing the conversion of plasminogen to plasmin[22)23]. *PLAU* is a key step in various cancer metastases including cervical cancer[24], urinary bladder[25], and breast cancer[26].

Conclusion

The main conclusion of the hyperthermia trials is the patients with advanced cervical cancer, both pelvic tumor control and survival can be improved by the addition of hyperthermia to standard radiotherapy. Our data provided the first evidence that gene-expression profiles can predict sensitivity to TRT for advanced cervical carcinoma, and may eventually lead to the achievement of "personalized therapy" for this disease.

Acknowledgment

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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子宮頸癌温熱放射線治療：臨床と基礎

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要　　旨：我々は IIIB 期子宮頸癌に対して温熱放射線治療は放射線治療単独よりも局所制御生存率が良好であると報告した．進行期子宮頸癌の温熱放射線治療群と放射線治療単独群について我々の結果を含めて 6 無作為臨床試験が報告されている．そのうち 4 試験において温熱放射線治療は放射線治療単独よりも CR 率，局所制御生存率，無再発生存率が良好であった．1 試験は温熱放射線治療群の骨盤内制御が良好ではあったが有意差を認めなかった．しかし，他の 1 試験では温熱放射線治療は放射線治療単独よりも有益ではなかった．本稿ではこれらの臨床試験を紹介し，問題点について言及した．一方，我々は温熱放射線治療抵抗性に関与する遺伝子について，臨床検体を用いてマイクロアレイによる遺伝子発現プロファイルを観察した．35 個の遺伝子が抽出され，これらの遺伝子群には腫瘍の浸潤や転移に関わる低酸素誘導遺伝子である HIF1A 遺伝子，血管新生に関与する PLAU 遺伝子が含まれていた．温熱放射線治療抵抗性に関与する遺伝子を標的として研究することで，進行期子宮頸癌の治療効果を向上させる可能性があると考えられた．