表4　局所進行子宮頸部扁平上皮癌に対する術前NACのRCT

報告者	臨床病期，症例数	デザイン	レジメン	結果
Sardiら (1997)	Ib期，205	NAC+S+RT vs S+RT	quick VBP	無病生存率（M=67カ月）は Ib1期で有意差なし Ib2期でNAC群が有意に良好
Sardiら (1998)	IIb期，309	NAC+S vs S+RT	quick VBP	生存率（M=84カ月）は NAC群が有意に良好
Changら (2000)	Ib2，II期，120	NAC+S vs RT	quick VBP	2年，5年生存率ともに 有意差なし
Benedetti-Paniciら (2002)	Ib2～III期，303	NAC+S vs RT	CDDP含む多剤療法	5年生存率は Ib2～IIa期で NAC群で有意に良好
Napolitanoら (2003)	Ib～IIIb期，166	NAC+S±RT vs S±RT	VBP	5年生存率は Ib～IIa期で有意差なし IIb期で有意差なし 5年無病生存率は Ib～IIa期で有意差あり IIb期で有意差なし
NACCCMA* (2003)	872	NAC+S±RT vs RT	様々	ハザード比がNAC群 有意に減少（0.65）

NAC：neoadjuvant chemotherapy，RT：radiation therapy，S：根治術
*：5つのRCTのメタアナリシス

NAC群：56.2％，根治術単独群：57.1％で有意差はなかった．結論として，NACに感受性がある症例は根治術が可能となり，そのことが予後向上につながるとした．

NACCCMA Collaborationの5つのRCT（NAC+根治術群±RTとRT単独群の比較）を集めた872症例における大規模なメタアナリシスによると[5]，ハザード比はNAC群で0.65と有意に減少した（p=0.0004）と報告している．ただし，このメタアナリシスでは5つのRCT間でその治療法，結果が違っているとコメントされている．この報告では，18のRCTによる2074例の放射線治療前NACの有用性についてメインに述べられており，術前NACに関する症例数872例はメタアナリシスとしては些か症例数が少ない（表4）．

以上のRCTでは80％を超えるNACの高い一次奏効率が得られているにもかかわらず，5年生存率では，NAC群がnon-NAC群（RT単独群や根治術+RT群）に比べてやや優れている傾向はあるものの，明らかな有意差が示されているわけではない．ここで興味深いことは，Sardiらが腫瘍サイズの大きい進行例ほどNAC+根治術の有効性が高いとしているのに対し，Benedetti-Paniciらと Napolitanoらは腫瘍サイズの小さい早期例に対するほど有効性が高いという相反する結果となっていることである．Sardiらだけが NAC+根治術群の全症例に対して補助放射線療法を行っている点がその原因となっているかは判然としない．果たしてNACがどのような臨床進行期や腫瘍サイズの頸癌に対して有効であるかは，もっとも重要な今後の検討課題である．

7．本邦での多施設共同研究の現状

本邦でも婦人科がん化学療法共同研究部会

(JGOG) において1991～1997年までの頸部扁平上皮癌II期に対して，NAC（NAC＋根治術）群（34例）と根治術単独群（22例）の間で封筒法によるpilot studyが行われた．NAC群ではBOMP療法2コース後，広汎子宮全摘術が施行された．両群ともに病理学的リスク因子陽性の症例に対しては放射線療法が追加されている．その結果，NACの奏効率は61％（CR：9％）であり，間質浸潤と傍結合織浸潤はNAC群で有意に低率であった．リンパ節転移率には有意差は認めなかった．ところが5年生存率を見ると，根治術単独群：90％に対してNAC群：67％と有意に低率となった．このように期待を裏切る結果となった理由で，症例の割付を封筒法としたために，より重篤な症例が主治医により恣意的にNAC群に割付された可能性が高い．とはいえ，この術前NAC療法に大きな予後改善は望めぬと判断され臨床治験は中止された．

現在，JGOGにより，子宮頸部扁平上皮癌I期（bulky）／II期に対して，術前NAC（BOMP）群と根治術群との間でRCT（JGOG 0102）が進行中である．両群とも術後補助療法として放射線治療が追加されるプロトコールである．世界でも少ない術前NACのrandomized studyであり，より多くの症例登録が期待される．

米国GOGではNACのrandomized studyは行われていない．米国では局所進行頸癌に対しては放射線療法が主たる治療となっている．本邦と米国の体格や肥満度の違いも背景にあると思われるが，折しも公表されたconcurrent chemoradiotherapy（CCRT）の良好な成績から，これがNCIアナウンスメントにより推奨されるに及んで，術前NACに関する臨床試験は進んでいない．

おわりに

子宮頸部扁平上皮癌に対するNACは非常に高い一次効果を有することは上述の通りである．しかし，術前NACに投げかけられている疑問は，どのようなレジメンが有効か（一次効果があるか）ということではなく，術前NAC自体が長期予後を改善するかということである．これまでのRCT報告を見てみると，術前NACは，症例を選択すれば長期予後を飛躍的ではないものの改善させる可能性は十分にあると思われる．本稿のタイトルでもある「Ib2，IIb期の子宮頸部扁平上皮癌」に対する術前NACは，もっともその効果が期待される．III期症例はconcurrent chemoradiotherapy（CCRT）が標準治療となっており，術前NAC（down staging）＋根治術は，あまり長期予後改善は期待できないとする欧米の流れがある．また，扁平上皮癌に比較して化学療法の感受性が低いとされる頸部腺癌が除かれていることも，上述のように術前NACの感受性が低い症例は予後不良であることがわかっているからである．化学療法の感受性があり，手術の完遂度の向上が期待できる症例に限定すれば，術前NACの長期予後を含めた有効性は明らかにされると思われる．まず，JGOG 1020のような，NACの感受性がある症例を限定したRCTによって，術前NACの有効性が証明されることを祈りたい．今後，術前NACを行うにあたっては，化学療法に対して不応性の症例をどれだけ除外できるかが課題となるであろう．

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R E V I E W

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Postoperative Radiation Therapy for Carcinoma of the Uterine Cervix

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Postoperative radiation therapy (PORT) for cervical cancer has been empirically performed for patients with pathologic risk factors for recurrence after surgery. The efficacy of PORT is mainly supported by retrospective studies. Despite convincing evidence demonstrating a reduction in pelvic recurrence rates when PORT is employed, there is no evidence that it eventually improves patient survival. Local recurrence, such as vaginal stump recurrence, is not always fatal if diagnosed earlier. Some patients, unfortunately, may develop distant metastases even after PORT. The positive effects of PORT also may be counterbalanced by increased toxicities that result from combining local therapies. These factors obscure the efficacy of PORT for cervical cancer patients. There has been no consensus on the predictive value of risk factors for recurrence, which renders indication of PORT for early-stage cervical cancer quite variable among institutions. Today, efforts have been made to divide patients into three risk groups based on the combination of risk factors present after radical hysterectomy. In Europe/USA and Japan, however, a fundamental difference exists in the indications for radical surgery, highlighting differences in the concept of PORT; "adjuvant pelvic irradiation for stage IB-IIA patients after complete resection" in Europe/USA and "pelvic irradiation after surgery irrespective of initial clinical stage and surgical margin status" in Japan. Thus, it is questionable whether scientific evidence established in Europe/USA is applicable to Japanese clinical practice. The purpose of this article is to review the role of PORT by interpreting the results of clinical studies.

Key words: cervical cancer, risk factor, postoperative radiation therapy, adjuvant

Introduction

Radical hysterectomy and pelvic lymphadenectomy is a well-established therapy for early-stage carcinoma of the uterine cervix. However, 10-20% of patients die of recurrent disease, with most of the failures being pelvic recurrences with or without distant metastases.[1,2] Postoperative radiation therapy (PORT) for cervical cancer has been performed for those with pathologic risk factors after surgery, such as positive pelvic lymph nodes, large tumor size, deep stromal invasion, lymphatic-vascular invasion, adenocarcinoma histology, and positive or close surgical margin. However, there has been no consensus as to the predictive value of these factors for recurrence, and thus indications for PORT differ between institutions. PORT has been performed empirically, and its efficacy is mainly supported by retrospective studies. Most of these studies have shown improved pelvic control rates, however, it is still unknown whether PORT eventually improves patient survival. In this article, we review the role of PORT for carcinoma of the uterine cervix by interpreting results of large retrospective studies and two recent prospective studies with a special emphasis on the difference in the concept of PORT between Europe/USA and Japan.

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Concept of PORT: Difference between Japan and Western Countries

In Europe/USA and Japan, the treatment strategy is quite different for patients with cervical cancer, especially for FIGO IIB lesions. In Europe/USA, indication of radical surgery is limited to stage IB to IIA lesions, and patients

with stage IIB cervical cancer are considered as having locally advanced lesions. The concept of PORT is "adjuvant pelvic irradiation for stage IB-IIA patients who underwent complete resection and have some pathologic risk factors for recurrence".[3] Because a combination of two local therapies, surgery and radiation therapy, increases the probability of late toxicities such as leg edema when compared with definitive radiation therapy or chemoradiation, surgery is not indicated for clinical IIB or more advanced lesions in Europe/USA.

In contrast, FIGO IIB or even more advanced lesions can be subjected to surgery in Japanese clinical practice, where PORT simply means "pelvic irradiation after surgery irrespective of initial clinical stage and surgical margin status." Recent reports from Japan include patients with IIB lesions.[4-8] Clinical IIB or more advanced lesions generally have one or more risk factors for recurrence; thus patients receive PORT with or without chemotherapy if initial radical surgery is selected. Therefore, in Europe/USA, the role of PORT has been evaluated in patients with early stage disease (IB-IIA) as an adjuvant therapy after complete surgery. Because the differences in treatment strategies for patients with IIB lesions in Europe/USA versus Japan are crucial, this review focuses only on PORT for IB-IIA lesions. Results of PORT for IIB or more advanced lesions are beyond the scope of this review.

Risk Factors for Recurrence

Risk factors for recurrence of cervical cancer have been determined in large retrospective studies by carefully examining the relationship between clinical/pathological findings and relapse patterns.[9-11] Known factors include positive pelvic lymph node, number and location of lymph nodes, size of primary tumor, deep stromal invasion, lymphatic-vascular invasion, tumor histology, and positive or close surgical margins. However, there is an intrinsic relationship between these risk factors, such as nodal status and tumor size or depth of stromal invasion,[12-16] that limits statistical analyses. No systemic analysis has examined various combinations of prognostic factors to precisely define associated levels of risk and patterns of relapse. Thus, there has been no consensus as to the priority of risk factors.

Thomas and Dembo compiled data from retrospective studies that addressed the overall patterns of failure according to risk factors, and concluded that node-negative patients relapse more commonly at locoregional sites, whereas node-positive patients exhibit a greater proportion of distant failure.[17] PORT reduces the risk of pelvic relapse and improves the relapse-free survival but has no apparent impact on overall survival in the entire group of patients selected for treatment. This lack of survival benefit may relate to the choice of patients with positive pelvic nodes. Irrespective of the probability of pelvic failure, most of these patients likely have predominant patterns of distant failure. Patients with primary tumor-related risk factors but negative nodes may be more likely to show a benefit of adjuvant pelvic irradiation since their disease is in an earlier stage than those with positive pelvic nodes. In contrast, the FIGO staging system does not take the pelvic node status into account. The FIGO system takes into consideration the tumor size, which is generally considered one of the most important prognostic factors.[18] Tumor size also predicts distant metastases in patients who have undergone radiation therapy.[19] Thus, the relevance of the postulation proposed by Thomas and Dembo, that the recurrence pattern is primarily determined by lymph node status alone, is questionable and should be confirmed prospectively.

Many surgical studies, however, have reported that the most important prognostic factor is positive pelvic nodes.[9,11,12,20] Despite receiving PORT, 5-year survival rates for stage IB cervical cancer decrease from 85%-90% to 50% when positive pelvic nodes are diagnosed.[21-23] Therefore, although the concept is supported solely by retrospective studies, it is now widely accepted that positive pelvic lymph nodes after complete resection are a major predictor of recurrence outside the pelvis. These patients are currently eligible for a combination of PORT and chemotherapy. Pathologic tumor cut-through mandates PORT in clinical practice; however, the prognostic significance of positive surgical margins should be discussed separately because these cases are outside the concept of adjuvant therapy after complete surgery. Reports from studies, especially those that include positive surgical margin as a prognostic factor, should be interpreted carefully.[24]

Indication of PORT: Recent Concept

Indications for PORT should be carefully determined by evaluating the above-mentioned risk factors in each case. Recently, efforts have been made to divide patients into three risk groups based on a combination of risk factors: low-risk patients for whom no adjuvant therapy is necessary, intermediate-risk patients for whom PORT may increase pelvic control rate and therefore improve patient survival (Table 1), and high-risk patients for whom systemic chemotherapy should be incorporated.

Patients at low risk after complete surgery who would not be expected to benefit from PORT are those with negative pelvic nodes, and with tumors less than 4 cm in diameter, no lymphatic-vascular invasion, and stromal invasion of less than one-third. The risk of positive pelvic

Table 1. Intermediate-risk group by Gynecologic Oncology Group (GOG)

Lymphatic-vascular invasion	Stromal invasion	Tumor diameter
Positive	Outer third	All
Positive	Middle third	≥2 cm
Positive	Inner third	≥5 cm
Negative	Outer-middle third	≥4 cm

Table 2. Clinical significance and intrinsic problems in Gynecologic Oncology Group study 92 (GOG 92)

Significance	
	Prospectively demonstrated PORT significantly reduces recurrence in intermediate-risk group
Problems	
	Survival benefit was unknown due to shorter follow-up
	Use of clinically determined tumor diameter
	Lower compliance of PORT
	Still higher pelvic recurrence rate in PORT group
	Lack of evaluation of late toxicities such as leg edema

PORT, postoperative radiation therapy.

nodes after surgery in these patients is less than 15%.[1,9,25-28] Patients at intermediate risk include those with lymphatic-vascular invasion and at least one of the following characteristics: outer third stromal invasion, middle third stromal invasion with a tumor size of 2 cm or greater, or superficial third penetration with a tumor diameter of 5 cm or greater. Alternatively, patients with tumor diameters of 4 cm or greater with outer or middle third stromal invasion who have no lymphatic-vascular invasion are allocated to the intermediate-risk group.[10]

The Gynecologic Oncology Group (GOG) conducted a randomized trial examining the role of PORT for an intermediate-risk group (GOG 92). The results indicated a statistically significant (47%) reduction in risk of recurrence in the PORT group, with 2-year recurrence-free rates of 88% for the PORT group versus 79% for the group with no further treatment.[29] This study showed that PORT significantly reduces recurrence in patients at intermediate risk after hysterectomy. However, several intrinsic problems existed in the trial: follow-up was too short to report patients' survival; tumor size was determined preoperatively by clinical examination despite surgical series; compliance of PORT was insufficient; and a pelvic recurrence rate of 13% in the PORT group was still higher than that in many reported series. In addition, late toxicities are important in evaluating the role of PORT, and this report lacks discussion of late adverse effects such as gastrointestinal toxicities and leg edema. Thus, evidence supporting the role of PORT in patients with intermediate risk after hysterectomy is still insufficient. The clinical significance and intrinsic problems in interpreting the GOG 92 report are listed in Table 2.

Microscopic involvement of the pelvic nodes is a strong predictor of survival in early-stage cervical cancer. In spite of receiving PORT, survival in these patients is apparently lower than in those with negative pelvic nodes (Table 3).[30-34] In the United States, a large intergroup phase III trial was conducted for post-hysterectomy high-risk IA2-IIA cases where PORT alone was compared with PORT combined with concurrent CDDP and 5-FU (intergroup study by Southwest Oncology Group, GOG, and Radiation Therapy Oncology Group). Results of the study were published in the form of a rapid publication.[35] Although 85% of the study subjects had positive pelvic nodes, this trial included patients with risk factors other than positive pelvic nodes. Progression-free and overall survival were significantly improved in the patients receiving concurrent chemotherapy. The hazard ratios for progression-free survival and overall survival in the PORT alone arm versus the PORT with concurrent chemotherapy arm were 2.01 (p=0.003) and 1.96 (p=0.007), respectively. Progression-free survival at 4 years was 63% with PORT and 80% with PORT combined with concurrent chemotherapy. The overall survival rate at 4 years was 71% for the PORT alone group versus 81% for the PORT with concurrent chemotherapy group. This is the first prospective clinical study that showed how a difference in the postoperative treatment strategy significantly

Table 3. Results of postoperative radiation therapy for stage IB-IIA cervical cancer according to pelvic nodal status

Author (year)	Pelvic node metastases	Number of patients	5 year overall survival
Gonzalez (1989)[30]	Negative	43	85%
	Positive	89	60%
Frigerio (1994)[31]	Negative	98	88%
	Positive	39	44%
Garipagaoglu (1999)[32]	Negative	67	95%
	Positive	33	65%
Yeh (1999)[33]	Negative	113	81%
	Positive	66	53%
Tsai (1999)[34]	Negative	150	87%*
	Positive	72	71%*

*Disease-free survival.

Table 4. Clinical significance and intrinsic problems in the intergroup study

Significance	
	Prospectively demonstrated that difference in the postoperative treatment strategy significantly influences overall survival in patients with cervical cancer
	Prospectively demonstrated that patients with positive nodes benefit from chemotherapy
Problems	
	Unknown role of PORT in both groups
	Suboptimal fractionation schedule in PORT
	Lower photon energy in PORT was accepted
	Eligibility also included risk factors other than positive pelvic node
	Patients with positive surgical margin were included

PORT, postoperative radiation therapy.

affects overall survival in patients with cervical cancer. The results of the study surely influenced subsequent clinical practices. Several pitfalls, however, exist in this study. First, both the control arm and the experimental arm included PORT — the role of which in patients with positive pelvic nodes is still unknown. Second, prolonged overall treatment time with PORT utilized a suboptimal dose/fractionation schedule (1.7 Gy per day for pelvic irradiation, 1.5 Gy per day for pelvic and paraaortic irradiation). Third, treatment with inappropriately lower photon energy (4 MV) was accepted. Fourth, 15% of patients had negative pelvic nodes, which are not included in the criteria for high-risk patients described by Thomas and Dembo. This inclusion resulted in a group of relatively heterogenic study subjects. Finally, eligibility included patients with positive surgical margins, despite the study's intention to examine the role of "adjuvant" treatment. Thus, from this context, it is questionable whether concurrent chemoradiation was necessary for all study subjects in the intergroup trial; for some patients, concurrent chemoradiation might have been overtreatment. Patients with parametric invasion without pelvic lymph node metastases could have achieved a good clinical course with PORT alone.[36] A separate analysis with a longer follow-up of the intergroup study performed by Monk *et al.* revealed that patients with only one positive pelvic node did not benefit from concurrent chemotherapy.[37] It is not surprising that the most important prognostic factor determined by multivariate analyses in the intergroup study was not positive pelvic nodes but tumor diameter. The clinical significance and intrinsic problems in interpreting the intergroup phase III clinical trial results are summarized in Table 4.

Because reports of clinical trials tend to insufficiently publish late adverse effects of radiation therapy, long-term follow-up with careful monitoring of each participant is crucial, especially for those receiving concurrent chemoradiation. In the experimental arm of the ongoing European Organization for Research and Treatment of Cancer clinical trial for IB2, large IIA, or IIB cervical cancer, neoadjuvant chemotherapy followed by radical

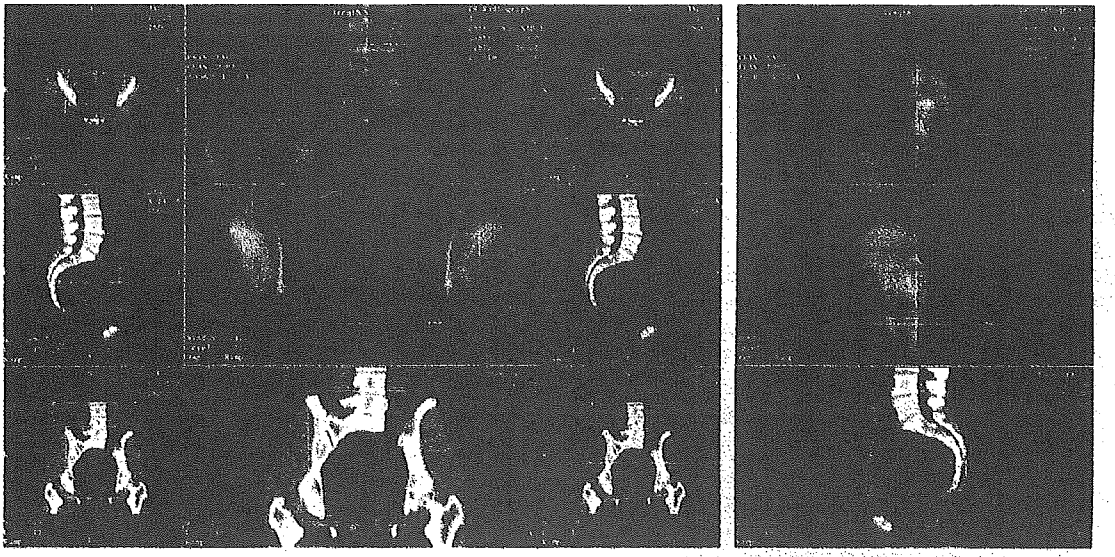

Fig. 1. A four-field technique consisting of the anterior-posterior (A) and two opposed lateral fields (B) determined three-dimensionally by using CT-simulator.

A | B

hysterectomy with tailored PORT is being compared with a standard definitive chemoradiation. Initial radical hysterectomy followed by PORT with concurrent chemotherapy is now not a treatment of choice in this setting. This practice underlines that, to reduce toxicities, surgery and PORT should not be combined if possible.

Technical Concerns of PORT

Once indicated, PORT should be performed using the proper radiation therapy technique. A conventional opposed anterior-posterior field technique using bony landmarks is inadequate and now out of date. To reduce the dose to normal tissues such as the small intestine, pelvic irradiation should be given with the four-field technique consisting of the anterior, posterior, and two opposed lateral fields using 10 MV or higher photon energies (Fig. 1). Treatment machines should be equipped with a multi-leaf collimator to shape each port automatically. By using the four-field technique, the incidence of late complications can be reduced.[38] In general, a fractional daily dose of 1.8-2.0 Gy, 5 times per week, up to a total dose of 45-50 Gy, is prescribed at the beam intersection point. Because bony landmarks are suboptimal to cover clinical target volumes such as tumor bed and lymph node area, care must be taken to cover them adequately when lateral fields are added.[39,40] A modern three-dimensional treatment plan using a CT-simulator is required to decrease the potential geographic miss when PORT is given using the four-field technique.

Conclusion

Efficacy of PORT is mainly supported by retrospective studies. There is no conclusive evidence that PORT eventually improves patient survival. Based on the results of large surgical series, patients are now divided into three risk-groups by combining risk factors: low-risk patients for whom no adjuvant therapy is necessary, intermediate-risk patients for whom PORT increases pelvic control rate and therefore may improve patient survival, and high-risk patients for whom systemic chemotherapy should be incorporated. Recent prospective clinical studies have demonstrated the efficacy of PORT for the intermediate-risk group as well as survival benefit of PORT with concurrent chemotherapy for the high-risk group. However, care should be taken in interpreting these results to evaluate the role of PORT. Difference in the concept of PORT in Europe/USA and Japan should also be of concern.

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Germline polymorphism of *p53* codon 72 in gynecological cancer

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Abstract

Objective. To investigate the biological significance of single nucleotide polymorphism at codon 72 of the *p53* gene in the development of gynecological cancer.

Methods. *p53* codon 72 polymorphism was examined in a total of 354 blood samples from 95 normal, 83 cervical, 108 endometrial and 68 ovarian cancer cases using polymerase chain reaction and restriction fragment length polymorphism techniques.

Results. When *p53* codon 72 genotype was classified into two subgroups of Arg/Arg and Arg/Pro+Pro/Pro, the Arg/Arg genotype was associated with an increased risk for the development of endometrial cancer (OR = 1.86, 95% CI = 1.06 to 3.26) compared with the Arg/Pro+Pro/Pro genotype ($P = 0.0301$). The Arg allele also increased the risk of endometrial cancer (OR = 1.42, 95% CI = 0.93 to 1.52) compared with the Pro allele, but no statistical difference was found ($P = 0.1031$). There was no significant difference in the genotype or allele prevalence between control subjects and cervical or ovarian cancer patients.

Conclusion. Homozygous Arg at codon 72 of the *p53* gene may be a risk factor for developing endometrial cancer in a Japanese population.

Keywords: *p53*; Polymorphism; Gynecological cancer

Introduction

p53 is a tumor suppressor gene involved in multiple pathways including apoptosis, cellular transcriptional control, and cell cycle regulation [1,2]. A large number of human tumors, including smoke-induced lung cancer, show mutations and deletions of the *p53* gene that result in loss of tumor suppression function and cell cycle deregulation [3]. The *p53* gene shows a polymorphism at codon 72 with a single-base change that causes an amino acid replacement in the transactivation domain of the protein of Arg (CGC) by Pro (CCC) [4]. Single nucleotide polymorphism (SNP) at codon 72 of the *p53* gene has been associated in the last decade with the risk of developing various neoplasms such as lung [5–7], esophageal [8], and cervical cancer [9]. An influence of this polymorphism on endometrial and ovarian cancer has been recently suggested [10–13]. However, the correlation between this SNP and gynecological cancer susceptibility has not been extensively studied, and previous experimental results are controversial. In the present study, we investigated germline polymorphism at codon 72 of the *p53* gene in human cervical, endometrial, and ovarian cancer patients and reevaluated the role of this SNP in the development of these gynecological malignancies in a Japanese population.

Materials and methods

Sample collection

We conducted genotype analysis of *p53* codon 72 in a total of 354 blood samples from normal healthy women and gynecological cancer patients. They consist of 95 normal controls and 83 cervical, 108 endometrial and 68 ovarian cancer patients with invasive diseases. All subjects were Japanese women who visited Osaka Medical College in the past 3 years. The non-cancer controls had no history of gynecological disease and for whom there was no present evidence of gynecological cancer. Women with any malignant disease or other systemic problems such as chronic liver diseases were excluded from the control group. Final histologic diagnosis was confirmed by biopsy or surgical specimens from each cancer patient. Table 1 shows the clinical characteristics of cancer patients examined in this study. For 108 endometrial cancer patients, putative risk factors, such as body mass index (BMI), a history of hypertension or diabetes, and family history, were also obtained by reviewing the medical

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Table 1
Clinical characteristics of gynecological cancer patients

Variable	Cervical cancer (n = 83)	Endometrial cancer (n = 108)	Ovarian cancer (n = 68)
Age distribution (years)			
≤30	4 (4.8%)	3 (2.8%)	3 (4.4%)
31–50	39 (47.0%)	26 (24.1%)	20 (29.4%)
51–70	35 (42.2%)	68 (62.9%)	41 (60.3%)
>70	5 (6.0%)	11 (10.2%)	4 (5.9%)
Menstrual status			
Premenopause	45 (54.2%)	34 (31.5%)	25 (36.8%)
Postmenopause	38 (45.8%)	74 (68.5%)	43 (63.2%)
Stage (FIGO)			
I	37 (44.6%)	84 (77.8%)	26 (38.2%)
II	31 (37.3%)	4 (3.7%)	7 (10.3%)
III	15 (18.1%)	19 (17.6%)	32 (47.1%)
IV	0 (0%)	1 (0.9%)	3 (4.4%)
Histologic type	Squamous	Endometrioid	Serous
	59 (71.1%)	97 (89.8%)	34 (50.0%)
	Non-squamous	Non-endometrioid	Non-serous
	24 (28.9%)	11 (10.2%)	34 (50.0%)

records. No statistically significant differences were found between control subjects and cancer patients in each group in terms of age distribution, smoking, and menstrual status. The protocol of this study was approved by our institutional review board, and all samples were obtained with informed consent. Genomic DNA was extracted from peripheral blood lymphocytes using the standard method of proteinase K treatment and phenol/chloroform extraction.

Genotyping of p53 codon 72

Polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) analysis of codon 72 of the *p53* gene, modified from a technique described by Ara et al. [4], was conducted to identify p53 genotypes with the primers, 5′-TTGCCGTCCCAAGCAATG-GATGA-3′ and 5′-TCTGGGAAGGGACAGAAGATGAC-3′. 100 ng of the DNA template from each sample was amplified by PCR in a final volume of 50 μl reaction containing 10 mM Tris–HCl (pH 8.3), 50 mM KCl, 2 mM $MgCl_2$, 0.01% (w/v) gelatin, 200 μM dNTP, 0.5 μM each primer, and 1.25 units Taq polymerase (Applied Biosystems, Branchburg, NJ) as previously described [14]. After an initial denaturation at 96°C for 3 min, 40 cycles of denaturation (94°C for 1 min), annealing (60°C for 1 min), and extension (72°C for 2 min) were carried out on a Perkin-Elmer GeneAmp PCR System 9700. The final extension was performed at 72°C for 10 min. After confirmation of an amplified fragment of the expected size (199 bp) on a 1.5% agarose gel, 17 μl of each PCR product was digested with 10 units of restriction enzyme *Bst*UI (New England Biolabs, ME) at 60°C for 3 h. DNA fragments were visualized on a 3.0% agarose gel with ethidium bromide. As shown in Fig. 1, the Arg allele is cleaved by *Bst*UI and yields two small fragments (113 and 86 bp). The Pro allele is not cleaved by *Bst*UI and has a single 199 bp band. The heterozygote contains three bands (199, 113, and 86 bp). We have previously demonstrated that these experimental procedures are quite useful to minimize the misclassification of *p53* codon 72 genotype [15,16].

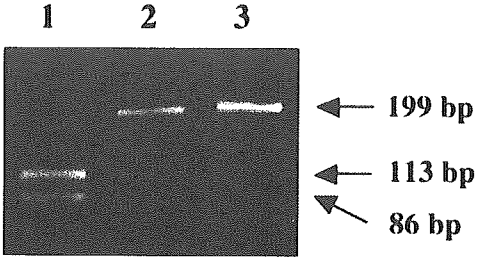

Fig. 1. Genotyping of *p53* codon 72 by PCR-RFLP. Lane 1, Arg/Arg homozygote. Lane 2, Arg/Pro heterozygote. Lane 3, Pro/Pro homozygote. The fragment of 199 bp is the nondigested PCR product from the Pro allele. Fragments of 113 and 86 bp result from *Bst*UI digestion of the Arg allele.

Statistical analysis

To compare the polymorphic features of *p53* codon 72 between control subjects and cancer patients, Pearson's chi-square test was used. A level of $P < 0.05$ was accepted as statistically significant.

Results

Table 2 shows the genotype and allele frequencies of *p53* codon 72 in 354 samples examined. There was no significant difference in the genotype or allele prevalence between control subjects and cervical, endometrial, or ovarian cancer patients. However, when *p53* codon 72 genotype was classified into two subgroups of Arg/Arg and Arg/Pro+Pro/Pro, the Arg/Arg genotype was associated with an increased risk for the development of endometrial cancer (OR = 1.86, 95% CI = 1.06 to 3.26) compared with the Arg/Pro+Pro/Pro genotype (P = 0.0301) as shown in Table 3. The Arg allele also increased the risk of endometrial cancer (OR = 1.42, 95% CI = 0.93 to 1.52) compared with the Pro allele, but there was no significant difference (P = 0.1031). Thus, homozygous Arg genotype of *p53* codon 72 was found to be a risk factor for endometrial cancer.

We further examined the correlation between genotypic and allelic frequencies of *p53* codon 72 and epidemiological factors including putative risk factors for endometrial cancer, such as BMI, a history of hypertension or diabetes, and family history. 108 endometrial cancer patients were also classified into two groups of type I and type II. Type I cancer is related to hyperestrogenism by association with endometrial hyperplasia, whereas type II cancer is unrelated to estrogen, associated with atrophic endometrium. Histologically, non-endometrioid carcinomas, such as serous and clear cell carcinomas, are considered

Table 2
Genotypic and allelic frequencies of *p53* codon 72 in control subjects and cancer patients

Samples	Genotype frequency			Allele frequency	
	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro
Normal (n = 95)	34 (35.8%)	54 (56.8%)	7 (7.4%)	122 (64.2%)	68 (35.8%)
Cervical cancer (n = 83)	28 (33.7%)	46 (55.4%)	9 (10.8%)	102 (61.4%)	64 (38.6%)
Endometrial cancer (n = 108)	55 (50.9%)	45 (41.7%)	8 (7.4%)	155 (71.8%)	61 (28.2%)
Ovarian cancer (n = 68)	21 (30.9%)	41 (60.3%)	6 (8.8%)	83 (61.0%)	53 (39.0%)

as type II cancer. There was no significant difference in the genotype or allele prevalence among these epidemiological factors as shown in Table 4.

Discussion

There is an expanding body of literature suggesting that host factors, including genetic polymorphisms, may explain some of the individual differences in cancer occurrence. A large number of previous studies have been conducted on the correlation between germline polymorphisms of cancer susceptibility genes and the higher risk of human malignant tumors.

Codon 72 of exon 4 was the first polymorphism detected in the *p53* gene, and it was suggested that the two alleles of codon 72 might have different oncogenic properties [17]. Previous studies have failed to find the correlation between the genetic polymorphism of *p53* codon 72 and the risk of endometrial cancer [18,19]. In a recent study published in this journal, Roh et al. [10] reported that SNP at codon 72 of the *p53* gene is associated with the development of endometrial cancer in Korean population. They stated that the *p53* genotype containing the Pro allele statistically increased the risk of endometrial cancer compared with homozygous Arg genotype. In contrast, our present results on germline polymorphism of *p53* codon 72 demonstrated that homozygous Arg genotype increased the risk of endometrial cancer compared with Arg/Pro+Pro/Pro genotype. Very recently, Agorastos et al. [11] reported that there was no significant difference in the genotype prevalence of *p53* codon 72 between control subjects and endometrial cancer patients in Greek women. However, they also found a positive linear trend of Arg/Arg towards poor differentiation in endometrial malignancies. These discrepancies may be due to the differences of sample size and the ethnic variation of genotype frequency of *p53* codon 72 in different geographical regions. Allelic differences of *p53* polymorphisms were observed in various ethnic groups [20]. The frequency of Arg/Arg homozygote in normal controls of Japanese population was reported to be 30–40% [20–22], which was consistent with our present results. Roh et al. [10] reported that homozygous Arg was observed in 58.3% of normal healthy women. The higher Arg/Arg genotype prevalence in Korean population may affect our discrepant results.

Currently, two different pathways are distinguished for tumorigenesis of sporadic endometrial cancer, one estrogen-related and another unrelated to estrogen [23]. The majority of sporadic endometrial cancers (at least approximately 70–80%), designated as type I cancers, follow the estrogen-related pathway. About 10–20% of endometrial cancers, designated as type II cancers, follow the estrogen-unrelated pathway and arise in the background of atrophic endometrium. These two types of tumors may have different genetic pathways, especially regarding *p53* mutations. However, there was no significant difference in the genotype or allele prevalence of *p53* codon 72 between type I and type II cancers in our series. Moreover, this SNP was not correlated with putative risk factors for endometrial cancer. The associations of germline polymorphism of *p53* codon 72 with these epidemiological factors should be further elucidated in a larger sample size of Japanese population.

Several mechanisms have been proposed to explain the role of the Arg allele in cancer development. The Arg allele is found to be more susceptible to degradation by the human papillomavirus E6 protein than the Pro allele [24]. In addition, the Arg allele may enhance mutant *p53* binding to *p73*, thus neutralizing *p73*-induced apoptosis independently of human papillomavirus-related mechanisms [25,26]. Moreover, several studies have examined the role of the codon 72 polymorphism in mutation of the *p53* gene in cancer. Langerod et al. [27] identified *p53* mutations more commonly in breast cancer from Arg/Arg homozygotes (28.5%) than among Arg/Pro heterozygotes (21%) or Pro/Pro homozygotes (4%). They have also suggested that the codon 72 Arg allele is preferentially mutated and retained in Arg/Pro heterozygotes [27,28]. These authors indicated that the codon 72 Arg containing mutants may have a

Table 3
Risk of endometrial cancer associated with *p53* codon 72 genotypes and alleles

p53 codon 72 polymorphism	Control subjects	Cancer patients	OR (95% CI)	P value
Genotype				
Arg/Pro+Pro/Pro	61 (64.2%)	53 (49.1%)	1.00 (referent)	
Arg/Arg	34 (35.8%)	55 (50.9%)	1.86 (1.06 to 3.26)	0.0301
Allele				
Pro	68 (35.8%)	61 (28.2%)	1.00 (referent)	
Arg	122 (64.2%)	155 (71.8%)	1.42 (0.93 to 1.52)	0.1031

Table 4
Correlation between genotypic and allelic frequencies of *p53* codon 72 and epidemiological factors in endometrial cancer patients

Variable	Genotype frequency			Allele frequency	
	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro
Menstrual status					
Premenopause	17 (50.0%)	13 (38.2%)	4 (11.8%)	47 (69.1%)	21 (30.9%)
Postmenopause	38 (51.4%)	32 (43.2%)	4 (5.4%)	108 (73.0%)	40 (27.0%)
Obesity (BMI)					
>25 kg/m^2	22 (44.0%)	25 (50.0%)	3 (6.0%)	69 (69.0%)	31 (31.0%)
≤25 kg/m^2	33 (56.9%)	20 (34.5%)	5 (8.6%)	86 (74.1%)	30 (25.9%)
Hypertension history					
Yes	8 (50.0%)	7 (43.7%)	1 (6.3%)	23 (71.9%)	9 (28.1%)
No	47 (51.1%)	38 (41.3%)	7 (7.6%)	132 (71.7%)	52 (28.3%)
Diabetes history					
Yes	7 (58.3%)	4 (33.3%)	1 (8.3%)	18 (75.0%)	6 (25.0%)
No	48 (50.0%)	41 (42.7%)	7 (7.3%)	137 (71.4%)	55 (28.6%)
Family history					
Yes	4 (57.1%)	3 (42.9%)	0 (0%)	11 (78.6%)	3 (21.4%)
No	51 (50.5%)	42 (41.6%)	8 (7.9%)	144 (71.3%)	58 (28.7%)
Histologic type					
Endometrioid	50 (51.5%)	39 (40.2%)	8 (8.2%)	139 (71.6%)	55 (28.4%)
Non-endometrioid	5 (45.5%)	6 (54.5%)	0 (0%)	16 (72.7%)	6 (27.3%)
Cancer type					
Type I	45 (53.6%)	33 (39.3%)	6 (7.1%)	123 (73.2%)	45 (26.8%)
Type II	10 (41.7%)	12 (50.0%)	2 (8.3%)	32 (66.7%)	16 (33.3%)

selective growth advantage influencing the ratio of Arg and Pro containing mutants in tumors. However, previous reports have demonstrated that the incidence of mutations of the *p53* gene in endometrial cancer ranges from 4.8 to 20%, which is relatively infrequent compared with other malignancies [29–31]. Further studies are needed to clarify the molecular interaction between *p53* codon 72 polymorphism and mutation of the *p53* gene involving the development of human endometrial malignancies.

Our present results revealed that the differences in the polymorphic frequency of *p53* Arg/Arg, Arg/Pro and Pro/Pro genotypes between control subjects and cervical cancer patients were statistically not significant. Some previous studies have reported no correlation between germline polymorphisms of the *p53* codon 72 and increased risk of cervical cancer [32–35]. The recent study reported by Nishikawa et al. [36] using cervical condyloma, dysplasia, and cancer tissue samples demonstrated that no statistically significant differences in the distribution of *p53* genotypes were found among the patients with these diseases, regardless of HPV status. We have also reported the similar results in a recent issue of this journal using cytologic materials from abnormal cervix [16]. These data suggest that *p53* codon 72 polymorphism does not correlate with the development of cervical neoplasms in a Japanese population.

In the present study, we found no association between *p53* codon 72 polymorphism and the risk of ovarian cancer. However, Agorastos et al. [11] and Pegoraro et al. [12] reported that women with ovarian neoplasias had the Arg/Arg genotype or Arg allele more often than healthy controls. In contrast, Wang et al. [13] demonstrated that analyses of this SNP in tumor DNA of ovarian cancer patients gave a higher frequency of homozygosity or heterozygosity for the Pro allele, which was closely associated with higher frequency of *p53* sequence variants and poorer prognosis. Resistance to chemotherapy remains a complex problem in ovarian cancer which is one of the reasons for its poor prognosis. *p53* functional status may be a critical determinant for the success of systemic chemotherapy with drug that can induce *p53*-dependent apoptosis [37]. Previous studies have reported that wild-type *p53* of the Arg allele may be more efficient in suppression of the multiple drug resistance gene MDR1 or induction of the proapoptotic oncogene BAX, while wild-type *p53* of the Pro allele is more efficient at promoting cell cycle arrest and DNA repair via its induction of *p21*-Waf and GADD45 [38,39]. Recently, ovarian cancers were also divided into two broad categories designated as type I and type II cancers, which correspond to two main pathways of tumorigenesis [40]. Type I cancers tend to be low-grade neoplasms that arise in stepwise manner from borderline tumors, whereas type II cancers are high-grade neoplasms for which a morphologically recognizable precursor lesion has not been identified, so-called de novo development. These two types of ovarian cancer may have different genetic alterations including *p53* mutations. Although these designations only refer to pathways of tumorigenesis and are not specific histopathological terms, it would be of interest

to examine the correlation between genotypic and allelic frequencies of *p53* codon 72 and ovarian cancer types. Further studies on the functional differences of two variants of *p53* codon 72 and their biological correlation to apoptosis, cell cycle regulation, chemosensitivity, and genetic backgrounds would contribute to the better understanding for pathogenesis and clinical management of ovarian cancer.

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Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type

The Significance of Radiotherapeutic Parameters

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BACKGROUND. The objective of this study was to investigate the correlation between local recurrence and radiotherapeutic parameters, including dose and RT radiotherapy (RT) field.

METHODS. The current study included 35 patients who were diagnosed with immunohistochemically confirmed nasal natural killer (NK)/T-cell lymphoma between 1976 and 2004. There were 21 males and 14 females, and they ranged in age from 18 years to 76 years (median, 51 yrs). The primary tumor originated in the nasal cavity in 28 patients, and 32 patients had Stage I disease. Seventeen patients received treatment solely with RT, and the remaining 18 patients received a combination of chemotherapy and RT. The median tumor dose was 50 grays (Gy) (range, 22–60 Gy). Twenty-seven patients received RT to include all macroscopic lesions, all paranasal sinuses, the palate, and the nasopharynx. Eight patients received RT to all macroscopic lesions with generous margins.

RESULTS. A complete remission (CR) or a CR/unconfirmed was achieved in 28 patients (80%). The 5-year overall survival (OAS) rate, disease-free survival (DFS) rate, and local control probability (LCP) were 47.3%, 42.9%, and 65.2%, respectively. Patients who received RT only to macroscopic lesions fared less well in terms of LCP (LCP 5 years, 71.9% vs. 41.7%; $P = 0.007$). The difference in RT field also affected both the OAS rate and the DFS rate. Patients who received RT doses ≥ 50 Gy tended to achieve favorable local control.

CONCLUSIONS. In the management of nasal NK/T-cell lymphoma, the RT field affected treatment outcomes. RT doses ≥ 50 Gy resulted in favorable local control. *Cancer* **2006;106:609–15.** © *2005 American Cancer Society.*

KEYWORDS: extranodal natural killer/T-cell lymphoma, angiocentric lymphoma, radiotherapy field, radiotherapy dose, chemotherapy.

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (formerly known as midline lethal granuloma, polymorphic reticulosis, or angiocentric immunoproliferative lesions) recently was recognized as a distinct entity of malignant lymphoma.[1–4] Because this type of lymphoma often shows an angiocentric and angiodestructive growth pattern, together with a broad cytologic spectrum of atypical cells and a zonal necrosis, it was categorized as angiocentric lymphoma in the revised European–American lymphoma classification.[5] These lymphomas are uncommon in the U.S. and Europe, but they are prevalent in East Asia and in certain parts of Central and South America. In a recent nationwide study of malignant lymphoma among Japanese, it was reported that NK/T-cell lymphoma accounts for approximately 2.6% of all malignant lymphomas in Japan.[6] Patients with this lymphoma present either with symptoms of nasal

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obstruction or epistaxis due to the presence of a mass lesion or with destruction of midfacial structures. The tumor also extends to adjacent tissues, such as the nasopharynx, paranasal sinuses, orbit, oral cavity, palate, and oropharynx.

The confusing nomenclature and its rarity have prevented investigators from establishing the optimal treatment for patients with extranodal NK/T-cell lymphoma. Furthermore, the finding that much published research not only included patients who did or did not undergo immunohistochemical confirmation of NK/T-cell lymphoma[7–22] but also included patients who had B-cell lymphoma served to complicate the interpretation of that research.[22–30] However, the response to radiotherapy (RT) generally is so rapid and dramatic that the delivery of RT has been accepted as the preferred treatment of choice for localized disease. Several investigators have advocated the combination of chemotherapy and RT[9,18,26,30]; however, whether the addition of chemotherapy to RT offers any survival benefits to patients is questionable in most series.[11,12,14–17,19–22,24,25,27–29] Patients with nasal NK/T-cell lymphoma experience recurrence at various anatomic sites, including the lymph nodes, skin, liver, spleen, and bone marrow; however, local failure remains the predominant pattern of recurrence. Thus, it is indispensable to clarify the role of RT in each clinical setting. The optimal dose required to achieve appropriate local control and the volume to be treated also require clarification.

In the current study, we analyzed the effects of various factors on local control with special reference to RT parameters, such as the dose to be delivered and the fields to be covered. The objectives of this study were to investigate the correlation between RT field and local recurrence and to establish the dose-response relation that influenced the probability of local control in patients with Stage I and II nasal NK/T-cell lymphoma who were treated at our institutions.

MATERIALS AND METHODS

Between July 1976 and May 2004, 38 patients with nasal NK/T-cell lymphomas received RT at Chiba University Hospital and Narita Red Cross Hospital. Of these 38 patients, 3 were excluded from the current analysis for the following reasons: palliative intent for advanced disease (n = 2 patients) and consultation at the time of recurrence (n = 1 patient). The median follow-up was 27 months (range, from 1.5 mos to 28.0 yrs), and the median follow-up of surviving patients was 11.1 years.

Histologic specimens were evaluated by an expert hematopathologist (J. T.). Immunohistochemical examination was undertaken in every patient to exclude B-cell lymphomas. Consequently, all tumors were positive for either CD56 and CD3ϵ or for T-cell markers, such as CD3, CD43, and CD45RO. For staging of their disease, patients underwent a physical examination; complete blood counts; screening blood tests of hepatic and renal function; chest radiograph; gallium scintigraphy; computed tomography (CT) scans of the head and neck, chest, abdomen, and pelvis; examination of the gastrointestinal tract; and bone marrow aspiration and/or biopsy. All patients were staged according to the Ann Arbor criteria.

TABLE 1
Patient Characteristics

Characteristics	No. of patients (%)
Age	
Range	18–76 yrs
Mean ± SD	52 ± 16 yrs
Median	51 yrs
Gender	
Male	21 (60)
Female	14 (40)
Primary site	
Nasal cavity	28 (80)
Paranasal sinus	4 (11)
Pharynx	3 (9)
B symptoms	
Yes	7 (20)
No	28 (80)
Lactate dehydrogenase elevation	
Yes	7 (20)
No	28 (80)
Disease stage	
Stage I	32 (91)
Stage II	3 (9)

SD: standard deviation.

Patient Characteristics

There were 21 males and 14 females, and the patients ranged in age from 18 years to 76 years (median, 51 yrs). The primary tumor originated in the nasal cavity in 28 patients and in the paranasal sinuses in 4 patients, including 2 patients with mesopharynx tumors and 1 patient with a nasopharyngeal tumor. Thirty-two patients had Stage I disease. Systemic B symptoms were present in seven patients, and lactate dehydrogenase (LDH) elevation was found in seven patients (Table 1). Informed consent was provided according to the Declaration of Helsinki.

Treatment

All patients received RT from a cobalt-60 unit or a linear accelerator with 4-megavolt (MV), 6-MV, or 10-MV photons to achieve dose homogeneity. An ap-

TABLE 2
Treatment Characteristics

Characteristic	No. of patients (%)
Treatment	
RT alone	17 (49)
RT and chemotherapy	18 (51)
Anthracycline	
Yes	15 (83)
No	3 (17)
Dose	
Range	22.0–60.0 Gy
Mean ± SD	37.9 ± 9.3 Gy
Median	50.0 Gy
Field	
Primary alone	8 (23)
Others	27 (77)

RT: radiotherapy; SD: standard deviation; Gy: grays.

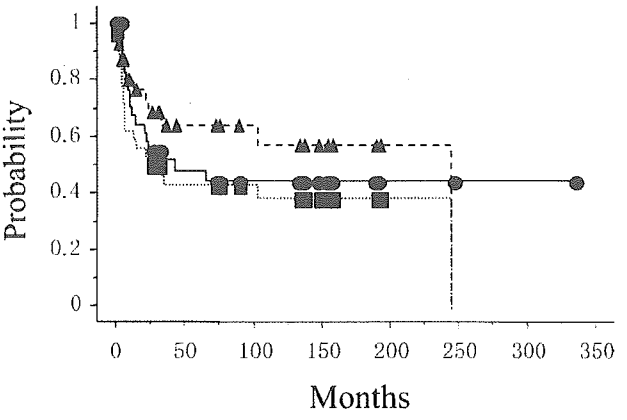

FIGURE 1. This chart illustrates the curves for overall survival (solid line), disease-free survival (dotted line), and local control probability (dashed line).

propriate energy of electron field also was applied to treat the tumor behind the lens block in the photon field. Generally, the planning target volume included all macroscopic lesions, the paranasal sinuses, the nasopharynx, the upper gum, and the palate with adequate margins. Regardless of primary tumor localization, elective cervical lymph node irradiation was not delivered unless the neck was involved clinically. The most common field arrangement was two lateral opposing photon fields with supplementation between the medial canthus by appropriate energy of electron. All patients received RT with a conventional fractionation schedule at a median tumor dose of 50 grays (Gy) (range, 22–60 Gy). Seventeen patients received treatment treated solely with RT, and the remaining 18 patients received a combination of chemotherapy followed by RT. Anthracycline-containing combination chemotherapy was administered to 15 patients (Table 2).

Statistical Analysis

Tumor response was assessed by using standard criteria.[31] Overall survival (OAS), disease-free survival (DFS), and the local control probability (LCP) were calculated using the method of Kaplan and Meier.[32] The log-rank test was used to assess significance in univariate analysis, and the Cox proportional hazards model was used to assess significance in multivariate analysis.[33]

RESULTS

Overall Results

At the time of evaluation, 28 patients achieved complete remission (CR) or CR/unconfirmed (CRu), which resulted in an 80% CR rate (95% confidence interval [95% CI], 66–94%). Of the seven patients who failed to obtain CR or CRu, the primary tumor was controlled well in three patients. The 2-year OAS rate, DFS rate, and LCP were 57.6% (95% CI, 40.7–74.4%), 53.0% (95% CI, 36.2–69.8%), and 73.8% (95% CI, 57.9–89.6%), respectively. The corresponding values at 5 years were 47.3% (95% CI, 29.8–64.7%), 42.9% (95% CI, 25.8–60.0%), and 65.2% (95% CI, 47.3–83.2%), respectively (Fig. 1). The 5-year OAS rate, DFS rate, and LCP for the patients who received RT alone were 43.8% (95% CI, 19.4–68.1%), 43.8% (95% CI, 19.4–68.1%), and 60.2% (95% CI, 35.2–85.2%), respectively. The corresponding values for patients who received both chemotherapy and RT were 51.8% (95% CI, 27.5–76%), 43.2% (95% CI, 19.8–66.6%), and 71.9% (95% CI, 48.2–95.7%), respectively. The administration of chemotherapy did not appear to have an impact on all endpoints.

At the time of the current analysis, 16 patients were alive without evidence of disease, and 14 disease recurrences were observed. Of these 14 patients who developed disease recurrence, 5 patients had locally recurrent disease, 6 patients had distant metastasis, and the remaining 3 patients experienced both local and distant or regional failure. The median time to disease recurrence was 11.6 months. The metastatic sites included the liver, spleen, lymph nodes, subcutaneous soft tissue, skin, intestine, bone marrow, and brain. Two patients who experienced local recurrence were salvaged successfully by a second course of RT. Those 2 patients developed local disease recurrence at 8.5 years and 15.5 years after their initial course of RT. There were 18 deaths during the study period, all of which were due to progressive or recurrent tumors.

RT Field, RT Dose, and Local Control

We also assessed the relation between RT field and the LCP. During the study period, 27 patients received RT