厚生労働科学研究費補助金

がん臨床研究事業

日本における子宮頸癌予防 HPV ワクチンの医療経済的評価のための大規模臨床研究

平成 24 年度　総括研究報告書

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平成 25（2013）年 5 月

目次

I. 総括研究報告書 ····· 1

日本における子宮頸癌予防HPVワクチンの医療経済的評価のための
大規模臨床研究

榎本隆之

Ⅱ. 研究成果の刊行に関する一覧表 ····· 11

Ⅲ. 研究成果の刊行物・別刷 ····· 13

別紙３

研究報告書

厚生労働科学研究費補助金（がん臨床研究事業）
総括研究報告書

日本における子宮頸癌予防HPVワクチンの医療経済的評価のための大規模臨床研究

研究代表者　榎本　隆之　新潟大学大学院・医歯学総合研究科・産科学婦人科学　教授

研究要旨
大阪府下で 12-18 歳時に HPV 予防ワクチンを接種した者を登録し、20 歳及び 25 歳時での子宮頸部細胞診異常の発生頻度と HPV 感染状況を解析し、非接種者と比較することにより、若年健常女性における HPV の感染状況および HPV 予防ワクチンの中・長期予防効果を検証する。

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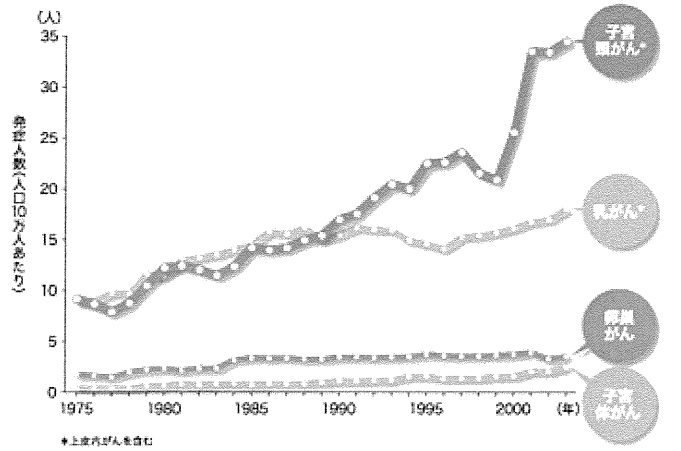
＜緒言＞

日本における子宮頸がんの発症率は10万あたり11.1人で、米国（7.8人）カナダ（8.25人）ドイツ（11.5人）フランス（10.1人）とほぼ同等である。子宮頸がんは子宮頸部の扁平上皮円円柱上皮接合部（Squamo-Columnar-Junction　SCJ）から発生することが知られている。多くは扁平上皮癌であるが、近年腺癌の占める割合の増加が著しく1975年では5%であったのが2006年には23%となっている。また20~30代の発症率の増加が著しく、1975年には10万人あたり10人であったのが2002年には36人となっている（図1）。

図1　20-39歳の女性10万人当たりの各種がんの発症率推移



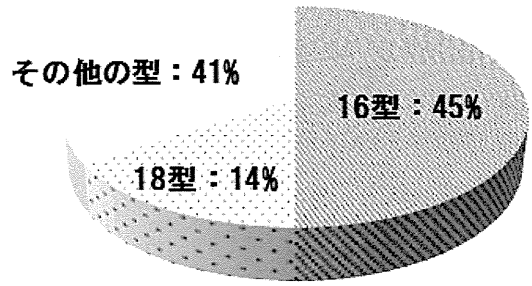
国立がんセンターがん対策情報センター、人口動態統計（厚生労働大臣官房統計情報部）

＜HPVと子宮頸がん＞

子宮頸がんはヒトパイローマウィルス（human papilloma virus　HPV）の感染によっておこることが知られている。HPVはパポバ属に属する約8000塩基対ほどの環状二本鎖DNAウィルスで主要キャプシド（L1）DNA配列の近似性から100種類が同定されて、うち30種類が性的接触によって感染し、15種類（HPV16、18、31、33、35、39、45、51、52、56、58、59、68、73、82）が発がんに関与しているといわれている。発がんに関与しているHPVを高リスク型HPV（あるいは悪性型HPV、発がん性HPV）と呼ぶ。高リスクHPVは子宮頸がん以外にも膣がん、外陰がん、肛門がん、中咽頭がんの発生にも関与していることが知られている。しかし、子宮頸がんではほぼ100%HPVが検出されるのに対し膣・外陰がんでは40%、中咽頭がんでは12%に過ぎない。高リスク型HPVには15 種が含まれるが、16型および18型が特に重要で、多くの国では子宮頸がんの約70%から16型か18型が検出されるが、日本では60%である[1)]（図2）。HPVは1

5~24才の一般女性の30~40%に検出され、20才代の女性の20%から高リスク型HPVが検出されるという報告もある。

図２　日本人の子宮頸がんから検出されるHPVの種類



その他の型：52,58,33,31,35型　etc.

＜HPV ワクチンとその効果＞

1990 年代になってウイルス様粒子（virus-like particle ; VLP）を昆虫細胞や酵母などの真核細胞で生成する技術が開発されるようになり HPV ワクチンが開発されるようになった。子宮頸がん予防ワクチンには２価ワクチン（グラクソ・スミスクライン社）と４価ワクチン（メルク万有社）がありいずれも 16 型及び 18 型の感染を防御することで、16 型 18 型 による CIN2、CIN3、子宮頸がんの発生を予防する。４価ワクチンは 16 型 18 型以外に尖圭コンジローマの原因となる 6 型 11 型の感染を予防できる。いずれのワクチンも初回接種後 3 回（2 価ワクチンは 1, 6 か月後、4 価ワクチンは 2, 6 ヶ月後）投与する。

HPV 感染から子宮頸がんの発生まで 10 年以上かかることと、発がんをエンドポイントとするのは倫理上の問題があるため、ワクチンの有効性を検討する臨床試験は前がん病変（CIN2、CIN3）の発生をエンドポイントとして４価ワクチン（ガーダシル）は 15-26 歳の 12167 人を対象に、2 価ワクチン（サーバリックス）は 15-25 歳の 18644 人を対象に大規模な第三相無作為化二重盲検試験が行われている。　4 価ワクチンは HPV16/18 の未感染女性に対して１回目の接種から 36 ヶ月（平均値）の時点で、ワクチン投与群とプラセボ投与群とを比較して、HPV16/18 による CIN2/3 及び上皮内腺がん（AIS）に対して 97%（95%CI:80-98%）の予防効果が認められた [15]。　また、2 価ワクチンは１回目の接種から 34.9 ヶ月（中央値）の時点で、HPV16/18 による CIN2 以上の病変に対して 93%(95%CI:80-98%)の予防効果が認められた [16]。

＜HPV ワクチンの問題点＞

HPVは感染すると一時増殖を経ずに潜伏・持続感染の状態となるので、ワクチンで誘導された抗体は常に生殖器粘膜に存在して、感染を防がなければならない。従って、ワ

クチンによって誘導された抗HPV抗体のレベルが長期間維持されることが重要である。血清中の抗HPV抗体が生殖器粘膜に滲出することでHPV感染を阻害すると考えられているが、接種から20-30年後の40-50歳代の女性での抗HPV抗体の滲出状態も含めて、感染防御に必要な抗体のレベルは現時点では不明である。

ワクチン接種の長期に渡る効果をフォローアップした報告では、2価ワクチンでは15～25才の436人に対しワクチン接種から平均6.4年の時点でHPV16/18陽性のCIN2以上の病変の予防効果は100%、4価ワクチンは16～23才の552人でHPV16/18陽性のCINの予防効果は100%であったが観察症例が少ないために有意とは言えなかった[17, 18]。これらの成績から、接種から少なくとも5-6.4年後までは、ワクチン型HPVによる子宮頸部前がん病変の発生を予防する効果が持続すると考えられる。

＜日本における子宮頸癌予防HPVワクチンの医療経済的評価のための大規模臨床研究＞

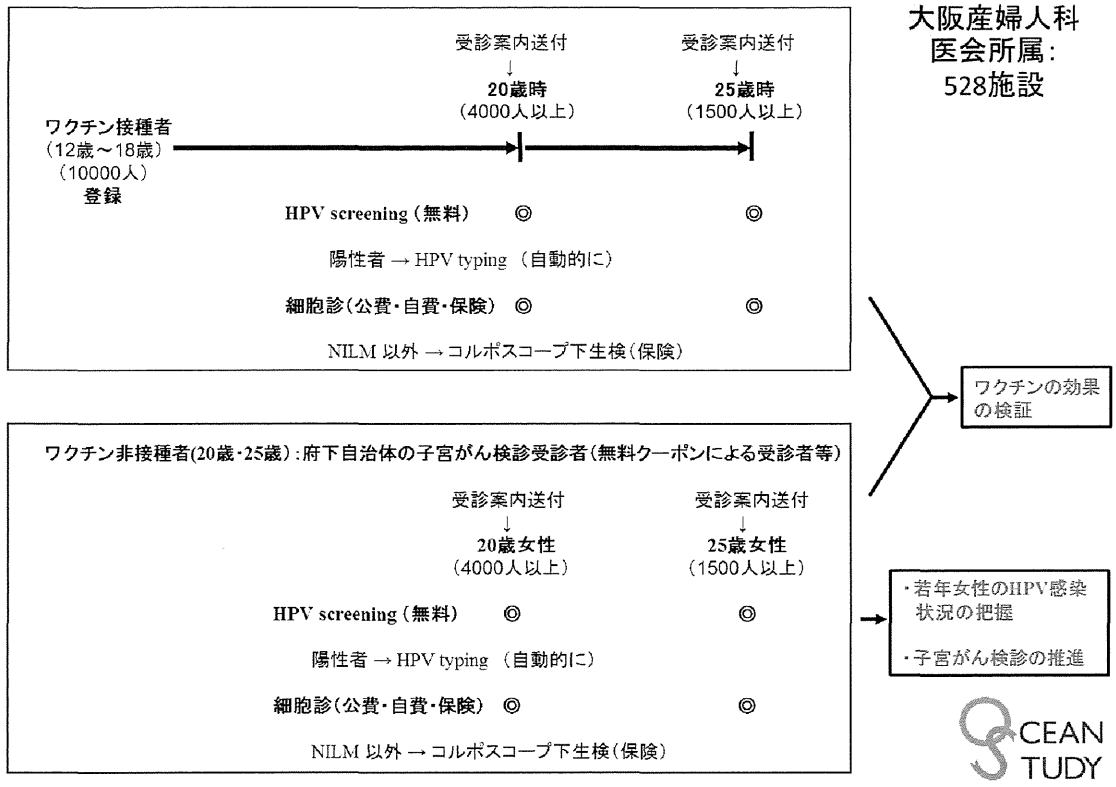
A．研究目的

若年健常女性におけるHPVの感染状況（HPV-16型・18型の割合）を大規模に解析すること、および学童期女子に対するHPVワクチンの中・長期予防効果を明らかにすることを検証することを目的とする。また、20歳・25歳のコントロール群の被験者を募るに際し、自治体の子宮がん検診の無料クーポン送付時に研究案内を同封し、細胞診に合わせてHPV検査（無料）の受診を促進することで、若年者の子宮がん検診受診率向上も図れるものと考える。

B．研究方法

大阪産婦人科医会に所属する施設において12-18歳でHPVワクチン接種を行った者を登録、20歳および25歳になった時点での子宮頸部細胞診異常の発現頻度とHPV感染を解析し、20歳および25歳の非接種者で子宮頸部細胞診の検診を受けた群と比較する。子宮頸部細胞診が異常であった場合はコルポスコープ下の生検等の精査を行う。登録は3年を予定。目標症正常例数は、推定されるHPV感染率・細胞診異常の割合を元に、ワクチンの効果の有意な統計学的解析が可能と考えられる症例数、すなわち20歳および25歳時でそれぞれ少なくとも4000人程度・1500人程度とし、これを目標にワクチン接種者の登録は10000人を目安とした。

＜研究概要＞



(倫理面への配慮)

当研究推進にあたり、疫学研究に関する倫理指針に基づき、順守すべき事項を研究実施医師に周知するため、これまでに 6 回の倫理講習会を開催した (平成 24 年度 : 4 回、平成 25 年度 : 2 回)。また、個人情報が各施設からデータセンターに出ることに関しても説明の上、同意を得ている。

C. 研究結果

12 歳から 18 歳までの HPV ワクチン接種症例の登録は平成 23 年 4 月から開始したが、開始後まもなくの HPV ワクチン(サーバリックス)の供給が停止したため、当初は接種者の登録が進まなかった。しかし、供給が安定した夏以降は順調に登録が進み、本年 3 月末までに 2561 症例の登録を得た。 これは HPV ワクチンの中・長期的効果について検討している他の先行研究の 5-6 倍の人数で、予定追跡期間も最長 13 年と際立って長いのが特徴である。

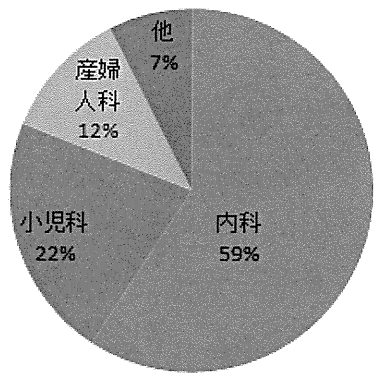
HPV ワクチンの中・長期的効果の検証
先行研究との比較

	ワクチンの種類	追跡期間	対象者数
Roteli-Martins et al.	サーバリックス	最長 8.4 年	436 人
Villa et al.	ガーダシル	平均 5.0 年	552 人
Konno et al.	サーバリックス	4 年	406 人
本研究	サーバリックス ガーダシル	最長13年 （予定）	2561 人 （登録数）

（平成25年3月31日現在）

しかし、現在までの登録は 3 年間で 10000 症例登録という当初の目標数を下回るペースであった。新潟県では HPV ワクチン接種は 59%が内科で行われ、産婦人科では 12%しか摂取されていない。これは大阪府下でも同様と考えられる。

新潟県におけるHPVワクチン接種機関



そこで大阪府内科医会に協力を依頼し、平成24年3月からは内科機関等からの登録も可能とした。今後、内科からの登録も含め、十分な登録が得られるものと期待するところである。

平成25年度からは、登録者およびコントロール群の検診（子宮頸部細胞診・HPV検査）が始まる。特にコントロール群については、大阪府下の各自治体が、がん検診の無料クーポンを20歳・25歳の市民に送付する際に、当研究への参加を依頼する案内書を同封して被験者を確保することを予定しており、今年度は箕面市で案内書の同封を試験的に実施した。また、検診も箕面市の全施設および他地域の一部施設で試験的に実施、平成25年3月31日までに24施設から317症例のデータが集積された。まだ予備的なデータではあるが、202症例中、ハイリスク型HPV感染を認めた症例は54症例（17%）あり、特にHPV-16型・18型の感染は14症例（4%）（重複感染の2症例を含む）に認めた。

研究のスムースな推進を図るため、在阪5大学（大阪大学・大阪医科大学・大阪市立大学・関西医科大学・近畿大学）から推薦されたコアメンバーの会議も2回開催した。

D．考察

現在は解析対象の症例を登録している段階であり、結果は明らかになっていないが、倫理面への配慮を含め、研究体制は整ってきている。登録数の伸び悩みについては、大阪府内科医会の協力を得て、内科施設からの登録も可能とした。これによって、登録も進むものと考える。

また、来年度からの検診に備え、一部地域・一部施設で試験的に検診を開始した。さらに、府下の自治体の6割から協力を得ることができ、コントロール群の被験者の確保も実現可能なものとなった。

E．結論

現在、12-18歳のHPVワクチン接種者の登録が進んでいる。また、来年度以降に本格的に始まる検診の準備も順調に進んでいる。来年度以降も府下自治体の協力を得ながら、研究を推進していく予定である。子宮頸癌予防HPVワクチンの日本における中・長期的効果について検証しようとする研究はこれが唯一の研究で、有益な結果が得られるものと期待される。特に、HPVワクチンが定期接種化されることもあり、当研究の重要性はさらに高まっていると考えられる。

F．健康危険情報

これまでに被験者に危険が及んだ事例はない。

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2. 学会発表

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大阪産婦人科医会 OCEAN STUDY 第 7 回説明会・第 5 回倫理講習会・臨床セミナー・第 6 回実務者会議（平成 24 年 10 月 20 日、大阪）

＜合同事務局会議＞

第 1 回合同事務局会議（平成 24 年 6 月 5 日、大阪）
第 2 回合同事務局会議（平成 24 年 12 月 21 日、大阪）
第 3 回合同事務局会議（平成 25 年 2 月 2 日、新潟）
第 4 回合同事務局会議（平成 25 年 3 月 23 日、大阪）

H. 知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3.その他

なし

雑誌

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GYNECOLOGIC ONCOLOGY

Investigating the relative efficacies of combination chemotherapy of paclitaxel/carboplatin, with or without anthracycline, for endometrial carcinoma

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Received: 20 April 2011 / Accepted: 8 July 2011 / Published online: 30 November 2011

Abstract
Purpose Recently a combination of paclitaxel and carboplatin (TC) (without an anthracycline) has begun to be used as an adjuvant or remission induction therapy, without any critical supportive evidence of its efficacy relative to a combination chemotherapy of taxane, platinum and anthracycline such as TEC (paclitaxel, epirubicin and carboplatin). The aim of our present study was to conduct the required clinical evaluations of the relative effectiveness of TC compared to TEC.
Methods A retrospective comparison between the efficacy of TEC and TC regimens used for endometrial carcinoma at the Osaka University Hospital and the Osaka Medical Center for Cancer and Cardiovascular Diseases in Osaka, Japan, respectively, from 1999 to 2009 was performed. The clinical characteristics of the patients who received either TEC or TC were not significantly different, and TEC and TC therapies were initiated based on similar indications for chemotherapy. TEC regimen was paclitaxel (150 mg/m^2), epirubicin (50 mg/m^2) and carboplatin (AUC 4). TC regimen consisted of paclitaxel (175 mg/m^2) and carboplatin (AUC 5).
Results TEC was demonstrated to provide significantly better survival than TC as an adjuvant therapy for resected Stage III/IV diseases ($p = 0.017$ for progression-free survival and $p = 0.014$ for overall survival, by the log-rank test). However, in recurrent or more advanced cases, TC and TEC demonstrated similar effects on survival ($p = 0.55$ for progression-free survival and $p = 0.63$ for overall survival).
Conclusions TEC should be offered as an adjuvant therapy to Stage III/IV patients. TC may be considered for recurrent or unresectable cases as a remission induction therapy.

Keywords Endometrial carcinoma · Platinum · Taxane · Anthracycline · Survival

Abbreviations

TAP or AP	Doxorubicin and cisplatin (with or without paclitaxel)
TC or TEC	Paclitaxel and carboplatin (without or with epirubicin)
TEP	Paclitaxel, epirubicin and cisplatin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration versus time curve
CR	Complete response
G-CSF	Granulocyte-colony stimulating factor
GOG	Gynecologic Oncology Group
5-HT$_3$	5-Hydroxytriptamine-3
JGOG	Japanese Gynecologic Oncology Group
OS	Overall survival

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PD Progressive disease
PFS Progression-free survival
PR Partial response
SD Stable disease

Introduction

Endometrial cancer is the most common gynecological cancer in the United States, and its incidence has increased significantly during the last three decades. Current surgical endometrial cancer therapy consists of a hysterectomy, bilateral salpingo-oophorectomy and retroperitoneal lymph node dissection [1, 2]. A randomized study by the Gynecologic Oncology Group (GOG) revealed that a combination chemotherapy of AP (doxorubicin and cisplatin) was superior to the traditional whole abdominal irradiation as an adjuvant therapy (GOG #122). Unfortunately, significant hematological and cardiac toxicity and treatment-related death was soon associated with AP treatments [3].

Platinum and anthracycline have long been used as the gold standard drugs for advanced or recurrent endometrial carcinomas [4, 5]. Recently, taxane has been added to this group [6, 7]. A recent study showed better survival following a TAP therapy (paclitaxel, doxorubicin and cisplatin) than for AP (GOG #177) [8]; however, neurological toxicity was even greater for patients receiving TAP, with 39% of the patients suffering Grade 2–3 peripheral neuropathy.

Lissoni et al. [9] reported that TEP (paclitaxel, epirubicin and cisplatin) exhibited superior anti-tumor activity against advanced endometrial carcinoma. Recently, TEC (paclitaxel, epirubicin and carboplatin) was shown to have improved activity against metastatic and recurrent endometrial carcinomas, and was found to be relatively tolerable when given with G-CSF support [10]. In our own recent phase I/II prospective studies of TEC, we analyzed the optimal dose for TEC therapy of our Japanese population, which we subsequently determined to be 150 mg/m^2 paclitaxel, 50 mg/m^2 epirubicin, and AUC 4 carboplatin Takata et al. [18]. Based on these findings, TEC has become our new standard for endometrial carcinoma treatment. Recently, however, TC (paclitaxel and carboplatin) has been begun to be widely applied for treatment of endometrial carcinoma, based on its initial reported effectiveness and high tolerability [11–13]. However, its equivalency or superiority to TEC has never been rigorously demonstrated, thus TC therapy is not currently an established regimen for endometrial carcinoma.

Gynecologic Oncology Group (GOG) has an ongoing study (#209) to compare TC with TAP, and the Japanese Gynecologic Oncology Group (JGOG) is performing a similar prospective study (JGOG #2043) to compare three combination chemotherapies: TC, DP (docetaxel and cisplatin) and AP. It has been of great interest to gynecologists whether TC alone is a sufficient chemotherapy for endometrial carcinoma or whether anthracycline is additionally required.

In our present study, we performed a retrospective comparison of TEC versus TC against endometrial carcinoma. We compared the patients' data for TEC therapy, which was exclusively performed at the Osaka University Hospital as part of our phase II study of TEC therapy (submitted), with those of TC, which was administered at our sister Osaka Medical Center for Cancer and Cardiovascular Diseases.

Materials and methods

A retrospective comparison was conducted between the relative efficacies of the TEC and TC regimens, which were performed for endometrial carcinoma cases at the Osaka University Hospital and the Osaka Medical Center from 1999 to 2009. During this period, TEC therapy was exclusively used at the Osaka University Hospital for all its endometrial carcinoma cases with indications for chemotherapy. A TEC dosage of 150 mg/m^2 for paclitaxel, 50 mg/m^2 for epirubicin and AUC 4 for carboplatin was used, based on our phase I results with a Japanese population (submitted). On the other hand, at the Osaka Medical Center, a TC regimen of paclitaxel 175 mg/m^2 and carboplatin AUC 5 (based on the results of our phase I study for ovarian carcinoma in a Japanese population, preliminarily reported by Ueno et al. [14]) was used instead of TEC for all their endometrial carcinoma cases with indications for chemotherapy. The gynecologic surgeons who performed the surgical treatments were all trained at the Osaka University Hospital, and the surgical procedures, and the indications for pelvic and para-aortic lymph node dissection, were identical in the two hospitals. Moreover, adjuvant chemotherapy was performed using the similar indicators.

Eligibility for TEC and TC chemotherapies required that the patient have adequate findings in the following: hematology (WBC $\geq$3,000/μl, platelets $\geq$100,000/μl, granulocytes $\geq$1,500/μl and hemoglobin $\geq$10 g/dl), renal (creatinine $\geq$2 mg/dl) and hepatic [bilirubin $\geq$3 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\geq$2 times the international normal value]. A relative performance status of 0–2 was needed. The tumors needed to be histopathologically diagnosed as being either a primary or recurrent endometrial carcinoma. In the current study, the clinicopathological features of the cases in which TEC or TC chemotherapy were performed, including the age of the patient, the histology and the stage of the disease, and the adverse effects of each chemotherapy regimen were retrospectively reviewed utilizing their clinical records,

including physical examination notes, radiological reports, operative records, and histopathology reports. The histological diagnoses were made by authorized pathologists from the Departments of Pathology of the Osaka University and the Osaka Medical Center, who were all trained at the Osaka University Hospital.

In order to evaluate the efficacy of TEC and TC chemotherapies against endometrial carcinoma, progression-free survival (PFS) and overall survival (OS) were calculated. PFS was measured from the administration of chemotherapy to the date of the radiologic or pathologic diagnosis of relapse, or to the date of the last follow-up. OS was defined as the period from the start of chemotherapy to the patient's disease-specific death or to the date of the last follow-up. In order to evaluate the anti-tumor effect of TEC and TC chemotherapies against the advanced diseases which were unresectable by surgery and the recurrent diseases, previously described standard criteria from the World Health Organization [15] and Pectasides et al. [16] were used. The tumors were assessed by CT scan and/or MRI at baseline and every three treatment courses thereafter. A complete response (CR) was defined as the disappearance of all known disease, determined by two observations not less than 4 weeks apart. We used RECIST (Response Evaluation Criteria in Solid Tumors, version 1.0) for evaluating the therapy response. A CR required regression of all tumors. A partial response (PR) required >30% reduction in the largest diameter of the largest lesion. A progressive disease (PD) was defined as one in which new lesions appeared, or the largest diameter of the largest lesion enlarged more than 20%. All others were considered to be stable disease (SD).

Adverse treatment effects were also analyzed. They were graded based on the National Cancer Institute's Common Toxicity Criteria (version 2.0). Granulocyte-colony stimulating factor (G-CSF) was administered to improve immune function whenever the total WBC/neutrophil count decreased to under 1,000/500 per μl, or when febrile neutropenia was observed. A histamine H1 5-HT_3 antagonist was administrated orally before the paclitaxel to prevent both emesis and an allergic reaction. Other antiemetic drugs were administered as needed.

A regimen of either TEC or TC was administered every 3–4 weeks for 3 weeks against resected Stage I/II diseases with risk factors, which included a myometrium invasion depth of >1/2 and or an atypical histology (such as endometrioid adenocarcinoma Grade 3, clear cell carcinoma or serous papillary carcinoma). TEC or TC was given as an adjuvant therapy for 6 weeks against resected Stage III/IV diseases and unresectable or recurrent diseases. The cases which were classified as Stage IIIa due to positive peritoneal cytology alone, without any other risk factors, were excluded from as having an indication for adjuvant chemotherapy. In order to compare the efficacy of TEC and TC regimes accurately, all the cases in which these chemotherapies were attempted were included in this analysis, including the cases in which these chemotherapies were canceled underway due to severe toxicities or to the patient's intermittent desire to stop chemotherapy.

The Osaka University Hospital protocol for TEC administration was to be given to only patients who were 70 years of age or less; the Osaka Medical Center protocol for TC allowed few patients who were over 70 years of age. The present comparative analysis was conducted only for those patients who were 70 years of age or less. In all cases, chemotherapy was performed only in those patients who were expected to have an estimated remaining survival of greater than 3 months.

Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for the statistical analyses. The distribution of patients' age, tumor histology and stage were analyzed by the Mann–Whitney *U*-test, the Chi-square test, or Fisher's exact test. PFS and OS curves were constructed using the Kaplan–Meier method and were evaluated for statistical significance by the log-rank test. The frequency of adverse effects in the two groups and the response of each chemotherapy were compared by Fisher's exact test. Results were considered to be significant when the p value was less than 0.05.

Results

Clinical characteristics of the patients with unresectable or recurrent disease who received TEC or TC chemotherapy as a remission induction therapy

TEC therapy was intended for 28 patients with unresectable or recurrent disease at the Osaka University Hospital, and TC therapy was attempted in 23 patients with similar diseases at the Osaka Medical Center. Distributions of age, histology and disease status did not exhibit any significant differences between the TEC and the TC groups (Table 1).

In the recurrent cases, all the patients underwent surgical treatment as a first treatment. The initial tumor stage in the TEC group was Stage I in three cases, II in one case and III in six cases; in the TC group it was I in five cases, II in two cases, III in three cases and IV in one ($p = 0.42$ by the Chi-square test). Adjuvant chemotherapy or radiation had been performed postoperatively in 8 (80%) of 10 cases in TEC group and 8 (73%) of 11 cases in TC group. TEC or TC was administered as the first treatment in all the recurrent disease cases. In advanced cases with unresectable disease, 7 cases were at Stage III and 11 cases were in Stage IV in

Table 1 Clinical characteristics of the advanced and recurrent cases in which TEC or TC chemotherapy was performed as a remission induction therapy

Characteristic	TEC ($n = 28$)	TC ($n = 23$)	p value
Age	57 (34–69)	56 (32–70)	0.95
Histology			0.54
Endometrioid	10 (36%)	7 (30%)	
Non-endometrioid	18 (64%)	16 (70%)	
Disease status			0.41
Advanced	18 (64%)	12 (52%)	
Recurrent	10 (36%)	11 (48%)	

Clinical characteristics of the primary endometrial carcinoma cases with unresectable diseases and the recurrent cases are shown. Distributions of age, histology and disease status did not exhibit any significant differences between the TEC and TC groups

the TEC group, and 5 cases were in Stage III and 7 cases were in Stage IV in the TC group, demonstrating no significant difference ($p = 0.88$ by Fisher's exact test).

Anti-tumor effect of TEC and TC therapies in the patients with unresectable or recurrent disease

Complete response (CR) or PR was achieved in 14 of 18 (78%) and 6 of 12 (50%) advanced cases by TEC and TC, respectively ($p = 0.11$ by Fisher's exact test), and 5 of 10 (50%) and 6 of 11 (55%) recurrent cases by TEC and TC, respectively ($p = 0.83$ by Fisher's exact test) (Table 2). In total, the response rate of TEC therapy against recurrent or advanced diseases was 68% (19 of 28 cases), and that of TC was 52% (12 of 23 cases). This 16% better difference in response rates between TEC and TC therapies was not statistically significant ($p = 0.25$ by Fisher's exact test).

Survival effect of TEC and TC therapies in the patients with unresectable or recurrent disease

Both OS and PFS did not demonstrate any significant difference between the TEC and TC groups ($p = 0.63$ for OS and $p = 0.55$ for PFS, by the log-rank test) (Fig. 1). By analyzing the effect of TEC and TC on survival in subgroups of recurrent cases and advanced (unresectable) cases, TEC therapy was demonstrated to be relatively more effective than TC in unresectable cases ($p = 0.17$ and $p = 0.75$ for PFS and OS, respectively). TC therapy, on the other hand, provided a better survival effect than TEC in recurrent cases ($p = 0.32$ and $p = 0.22$ for PFS and OS, respectively), however these differences were not statistically significant.

Table 2 Anti-tumor effect (response rate) of TEC and TC chemotherapies

Response to chemotherapy	TEC ($n = 28$)	TC ($n = 23$)
CR/PR	19 (68%)	12 (52%)
SD/PD	9 (32%)	11 (48%)

The anti-tumor effect of TEC and TC was evaluated in advanced or recurrent cases. Response rates were 68% in the TEC group and 52% in the TC group. This difference was not statistically significant

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

$p = 0.25$ (Fisher's exact test)

Clinical characteristics of the completely resected patients in Stage III/IV who received TEC or TC chemotherapy as an adjuvant therapy

Because in our previous study (submitted for publication), we could not demonstrate a significant survival improvement in Stage I/II cases using TEC compared to radiation as the adjuvant therapy, and because the effects of TEC and TC therapy on survival were not different significantly in our present study, a comparison analysis of the survival effects of TEC and TC was focused completely on resected Stage III and IV cases.

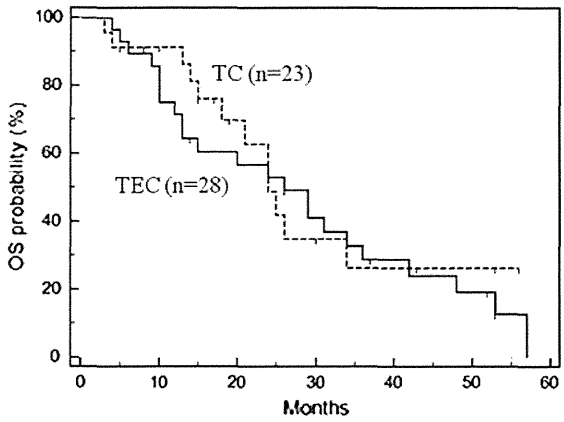
TEC was administered to 47 patients at the Osaka University Hospital, and TC to 30 patients at the Osaka Medical Center. Their clinical features are shown in Table 3. Distributions of age, histology and stage did not exhibit any significant difference between the TEC and the TC groups. The cases which were classified as being in Stage IIIa due to positive peritoneal cytology alone (without any other risk factors) were excluded from adjuvant chemotherapy, and thus this study.

Survival effect of adjuvant TEC and TC therapies in the completely resected patients in Stage III/IV

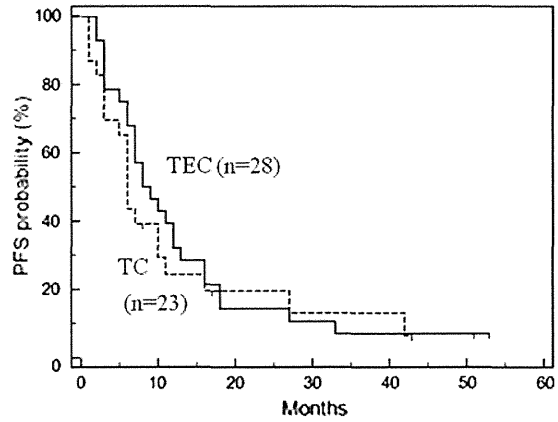
The OS and PFS curves of the TEC and TC groups were shown in Fig. 2. The median follow-up period was 38 months (2–105 months). PFS exhibited a statistically significant difference between the TEC and TC groups ($p = 0.017$ by the log-rank test, Hazard Ratio: 0.3838; 95% CI: 0.1709–0.8623). Moreover, OS also exhibited a statistically significant difference between TEC and TC groups ($p = 0.014$ by the log-rank test, Hazard Ratio: 0.3108; 95% CI: 0.1048–0.9214). Thus, TEC therapy was demonstrated to provide a significant improvement of survival as an adjuvant therapy for resected Stage III/IV diseases.

Adverse effects of TEC and TC therapies

Adverse effects of the TEC and TC chemotherapies were evaluated in 187 patients whose accurate data were available (Table 4).Hematological toxicity tended to be more



(p=0.63 by log-rank test)



(p=0.55 by log-rank test)

Fig. 1 PFS and OS of TEC and TC groups for unresectable or recurrent diseases. Both PFS and OS were not demonstrated to be significantly different between the TEC and TC groups ($p = 0.63$ and $p = 0.55$ by log-rank test, respectively). *Solid line* TEC group. *Broken line* TC group

Table 3 Clinical characteristics of the completely resected Stages III and IV patients to whom TEC or TC chemotherapy was performed as an adjuvant therapy

Characteristic	TEC ($n = 47$)	TC ($n = 30$)	p value
Age	56 (3–69)	59 (34–70)	0.23
Histology			0.54
Endometrioid	33 (70%)	23 (77%)	
Non-endometrioid	14 (30%)	7 (23%)	
Stage			0.83
IIIa	14 (30%)	8 (27%)	
IIIb	1 (2%)	1 (3%)	
IIIc	26 (55%)	15 (50%)	
IVb	6 (13%)	6 (20%)	

The endometrial carcinomas, confined to the uterus, which were classified in Stage IIIa based on only positive peritoneal cytology, were excluded. Distributions of age, histology and stage did not exhibit any significant differences between the TEC and TC groups

frequently observed in the TEC group than in the TC group ($p = 0.065$); however, a statistical significance was not detected. Non-hematological toxicity was observed to be similar in the TEC and TC groups ($p = 0.49$). The non-accomplishment rates of the scheduled TEC and TC therapies (due to severe toxicities) were not different between the two regimens ($p = 0.81$). Those due to the patients' intermittent desire to stop chemotherapy were also not statistically different between the two regimens ($p = 0.37$).

Conclusions

Adjuvant chemotherapy for endometrial carcinoma is one of the hottest topics in gynecologic oncology. Platinum, anthracycline and taxane derivatives are regarded as critical drugs for treatment of advanced or recurrent endometrial carcinomas [4, 6, 7]. Although combination chemotherapies using these drugs, such as TAP, TEP and TEC, are effective, moderate-to-severe side effects are sometimes observed by Fleming et al. [8], Lissoni et al. [9], Papadimitriou et al. [10] and our previous study (Takata et al. [18]).

TC, which uses only paclitaxel and carboplatin, is the current gold standard therapy for ovarian carcinoma due to its high effectiveness coupled with its high tolerability [17]. TC chemotherapy was somewhat effective for endometrial carcinoma [11–13]. It is, therefore, easy to understand why TC, although not yet an established standard therapy, has been frequently applied worldwide for the treatment of endometrial carcinoma cases. However, until this current work, a comparison of the usefulness of TC to other combination chemotherapies using these three key drugs, such as TAP, TEP and TEC, has not been reported.

A GOG study to compare the combination of TC with TAP (GOG #209) has finished recruitment of the patients; however, analysis of the survival effects of the two regimens may require a few years; a similar JGOG study to compare the combination chemotherapies TC, DP and AP (JGOG #2043) is even less far along; it is still under registration of patients. Thus, our present study to address whether anthracycline is still required in addition to TC chemotherapy for successful treatment of Stage III/IV endometrial carcinoma is quite important.

There are minor drawbacks to our study; it was a retrospective analysis of TC and TEC and thus was not the ideal, which is a prospective randomized study. In addition, the treatment data were from two center hospitals for gynecologic malignancies; the Osaka University Hospital, in which TEC regimen was conducted, and the Osaka Medical Center for Cancer and Cardiovascular Diseases, in which TC was used. Both hospitals shared common practices for

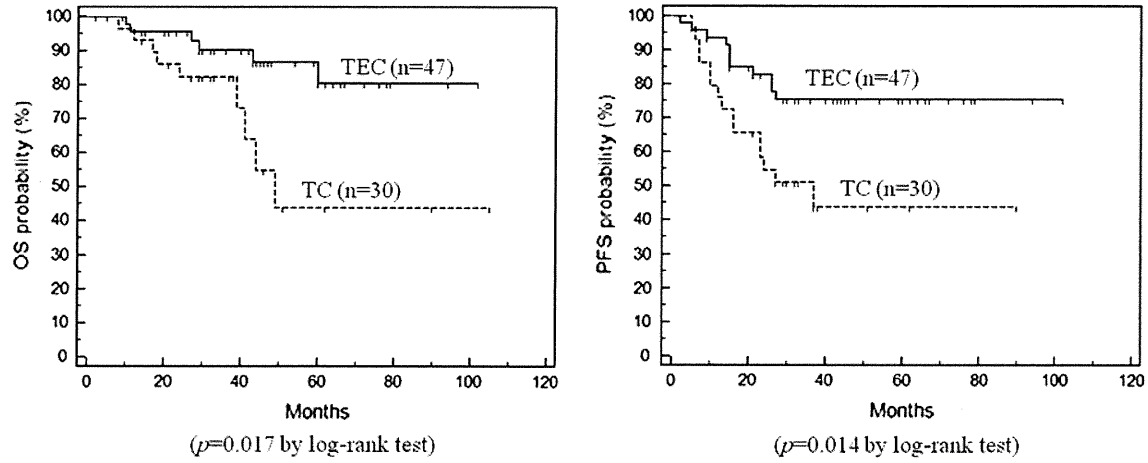


Fig. 2 PFS and OS of TEC and TC groups for adjuvant therapy (Stage III/IV). Both PFS and OS were significantly better in the TEC group than the TC group ($p = 0.017$ and $p = 0.014$ by the log-rank test, respectively). *Solid line* TEC group. *Broken line* TC group

Table 4 Adverse effects of TEC and TC therapies

Toxicities	TEC	TC	*p* value
Hematological (Grade 4)	67/115 (57%)	32/72 (44%)	0.065
Non-hematological (Grades 3, 4)	4/115 (3%)	4/72 (6%)	0.49

Grade of adverse effects was based on the National Cancer Institute's Common Toxicity Criteria (version 2.0)

surgery, chemotherapy indications and treatment procedures. We believe that typical types of bias derived from a retrospective study were minimized as much as possible. The background features of the patients compared in the current study were not significantly different between the TC and TEC groups.

Comparison of the adverse effects of the TEC and TC chemotherapies showed that hematological toxicity, especially neutropenia, tended to be more frequently observed in the TEC group than in the TC group ($p = 0.065$), however the neutropenia was tolerable when given G-CSF support. Non-hematological toxicity was observed similarly in the TEC and TC groups ($p = 0.49$). These toxicities should always be taken into consideration as part of the effectiveness of any chemotherapy.

Our previous study showed that significant survival improvement was not demonstrated using TEC compared to radiation as an adjuvant therapy in Stage I/II cases (submitted), and the positive effects of TEC and TC therapy on survival were not significantly different in the present study, indicating that TC therapy may take the place of an adjuvant therapy for Stage I/II endometrial carcinoma.

Finding similar survival effects for TC and TEC in the most advanced and intractable unresectable cases and recurrent cases ($p = 0.63$ for OS and $p = 0.55$ for PFS, by the log-rank test) implied that TC may be used as a remission induction chemotherapy due to the abjectly poor prognosis of those cases and the lower rate of severe side effects for TC therapy than for TEC. The tendency for improved survival in recurrent cases following TC therapy ($p = 0.32$ and $p = 0.22$ for PFS and OS, respectively) compared to TEC especially suggested that TC may be appropriate for recurrent cases, too. On the other hand, in advanced unresectable cases, TEC therapy tended to be more effective than TC ($p = 0.17$ for PFS). For these cases, although the TEC may improve PFS, it will require G-CSF administration for its associated severe neutropenia. Alternatively, TC may be proposed because, even though it is marginally less effective than TEC, it is more tolerable.

In the completely resected Stage III/IV cases, TEC therapy was demonstrated to provide significantly better PFS than TC ($p = 0.017$ by the log-rank test, Hazard Ratio: 0.3838; 95% CI: 0.1709–0.8623) and OS ($p = 0.014$ by the log-rank test, Hazard Ratio: 0.3108; 95% CI: 0.1048–0.9214) with a median follow-up period of 38 months (2–105 months). The reasons for these epic results are uncertain as yet, although the synergistic or additive effect of a third drug mechanism is anticipated to be the cause. The fact that TEC was much more effective, especially for the completely resected cases in Stage III/IV which were at high risk of recurrence, may imply that the TEC regimen might play a role in not only attacking the carcinoma cells forming the tumor mass but also in killing remaining carcinoma stem cells and metastases elsewhere, such as in the bone marrow, after the complete resection of the tumor mass.

In this study, we proposed to question the apparent increasing application of TC regimen to all forms of endometrial carcinoma with an indication for chemotherapy. Based on our results, TEC should be offered as the preferred adjuvant therapy to Stage III/IV patients, after complete surgical resection of their tumors. TEC may also be effective as a remission induction therapy for patients in