厚生労働科学研究委託費（革新的がん医療実用化研究事業）
委託業務成果報告 （業務項目）

妊孕性温存を希望する子宮頸癌患者に対する腹式子宮頸部摘出術の外科的有用性の検討

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研究要旨

若年の子宮頸癌患者が増加しており、新規妊孕性温存手術である子宮頸部摘出術野の必要性が増している。2005 年より我々は浸潤子宮頸癌症例に対して、病巣を含んだ子宮頸部に周囲靭帯と腟壁をつけて摘出後に、子宮と腟を再吻合する腹式広汎子宮頸部摘出術および準広汎・単純子宮頸部摘出術の臨床試験を行ってきた。今回、surgical outcome（術式の安全性と治療効果）に関して解析することとした。

病巣サイズに関する適格基準に“横径と奥行き”という 2 方向の概念を初めて導入することにより適応拡大を試みた。そのための安全性強化の目的で、術中にセンチネルリンパ節に転移が無いことと、切断頸部に 5mm 以上のマージン(非癌部のりしろ)が確保できることを確認した。2014 年 10 月までに術前適格条件を満たした 152 例に試み、術中検査を経て 137 例に頸部摘出術を完遂できた。約 1 割の再発ハイリスク症例には全身化学療法を主とする術後追加治療を行った。10 月までの観察期間は 2-114 ヶ月（中央値 41 ヶ月）であるが全例再発なく経過している。頸部摘出術に特異的な術後合併症として、子宮断端部(neocervix)感染、頸管狭窄、子宮性無月経、不妊症などがあったが、下肢リンパ浮腫や骨盤リンパ嚢胞に関しては、センチネルノード・ナビゲーションサージャリーが行われたため、頻度は激減した。現在まで、国内外と比較しても良好な surgical outcome が得られているが、適応拡大が安全に行えた理由として、1) 病巣の横径よりリスクが高いと思われる奥行きに関して、別個に新たな適格基準を設けたことと、2) センチネルノード・ナビゲーションサージャリー臨床試験を併用したことが挙げられる。

頸がんの若年化と共に今後ますます必要性が増していくと思われる本術式を普及させるためには、良好な surgical outcome と obstetrical outcome を確立することが必須である。次年度は obstetrical outcome の解析を行い、本法のさらなる改善（特に妊娠率向上と安全な分娩への工夫）に取り組みたい。

A. 研究目的

年々、未婚あるいは未産婦の子宮頸癌患者が増加してきており、妊孕性温存手術の確立が必要となってきている。2005年より我々は、標準治療では子宮摘出を要する浸潤子宮頸癌症例で将来の挙児を強く希望する患者に対して、病巣を含んだ子宮頸管に周囲靭帯と腟壁をつけて摘出後に子宮と腟を再吻合する腹式（準）広汎子宮頸部摘出術（abdominal semi-radical or radical trachelectomy: semiART or ART）と、子宮頸部のみを摘出後に子宮を再建する腹式単純子宮頸部摘出術（abdominal simple trachelectomy: AST）を行い、妊孕性の温存を試みる臨床試験を行ってきた。術式の安全性と治療効果（surgical outcome）および妊娠して生児を得るにいたる頻度および妊娠・分娩時合併症等（obstetrical outcome）関して検討することとしたが、今回はsurgical outcomeに関して解析することとした。

B. 研究方法

以下の術前適格基準を全て満たす患者を本試験に登録した。

1．扁平上皮癌に関してはⅠB1期までの症例（わずかな腟浸潤の初期ⅡA1期も含む）。腺癌（腺扁平上皮癌を含む）に関しては横径3cmまでのⅠB1期の症例
2．画像診断にて内子宮口から癌病巣の辺縁まで1cm以上の余裕を持って病巣が含まれる症例（腺癌の場合は少なくとも2cmが必要とする）
3．画像診断等にてリンパ節を含む転移病巣や子宮外浸潤が疑われないこと
4．予後不良の特殊な組織型でないこと
5・活動性重複癌や重篤な合併症や重度の精神障害を有さないこと
6．患者あるいはパートナーに非常に治療困難な不妊因子がないこと
7．原則として16歳以上45歳以下で強い挙児希望のある症例
8．本治療のリスクと術後検診の必要性に関して充分理解できていること
9．患者本人から文書による同意が得られていること

希望する患者に対しては、カンファレンス等で十分な適格性の評価を行った後、適格症例にのみ担当医師から詳細な説明を行い、自由意志による同意を文書で得た。加えて、以下の術中適格基準を満たさない場合、本術式から子宮全摘出を含む標準術式へ変更することにも同意を得た。

1．開腹後の所見で子宮外への転移が判明した場合
2．センチネルリンパ節の術中病理診断で転移を認めた場合
3．摘出頸部切断後の術中病理診断で病巣側に5mm以上のマージン（非癌部のりしろ）が確保できないと

判明した場合

妊孕性温存を希望しない場合の標準術式が単純子宮全摘出術である症例にはASTを、準広汎子宮全摘出術である症例にはsemiARTを、広汎子宮全摘出術である諸例にはARTを施行した。

（倫理面への配慮）

対象患者の選定、説明と同意については2005年からの症例は九州大学病院、2013年からの症例は鹿児島大学病院の施設内倫理委員会（IRB）の承認を受けた臨床試験計画書に基づき行った。個人情報の取扱い及び管理に関しては、連結可能匿名化で取り扱った。本試験は妊孕性温存手術の有用性と安全性を検討する探索型試験であるため、登録期間内で集積可能な症例数を設定した。

C. 研究結果

2014年10月までに術前の適格条件を満たした152例に本術式を試みたが、術中にセンチネルリンパ節に転移有りと判明した11例と頸部断端に5mmのマージンを確保できなかった4例の計15例で妊孕性温存を断念して子宮を摘出した。残る137例のうち、摘出標本の病理組織検査で頸部間質浸潤が2/3を超え、かつ脈管侵襲を有する症例は再発のハイリスクとして術後追加治療を行った。約1割の症例に追加治療が行われた。化学療法を追加治療とする場合には、全身化学療法（TC療法）を施行したが、妊孕性温存の観点からGnRHアゴニストによる卵巣保護下に行うことを推奨した。

腹式子宮頸部摘出術を完遂できた137例のうち、123例にsemiARTあるいはARTが行われ、14例にASTが行われたが、2-114ヶ月（中央値41ヶ月）の観察期間で再発症例はなく経過している。

頸部摘出術に特異的な術後合併症として、子宮断端部(neocervix)感染、頸管狭窄、子宮性無月経、不妊症などがあったが、腸閉塞や臓器損傷などの一般的術後合併症は、それぞれに対応する子宮全摘出術式と同等であった。下肢リンパ浮腫や骨盤リンパ嚢胞に関しては、センチネルリンパ節が転移陰性と術中に確認できた症例には骨盤リンパ節郭清を省略（センチネルノード・ナビゲーションサージャリー）して子宮頸部摘出術を完成させるので、通常の標準術式より頻度は激減した。

D. 考察

これまでの子宮頸部摘出術の再発率、死亡率およびリスク因子などに関する報告は、主に長径2cm以下の腫瘍を対象とする腟式子宮頸部摘出術（vaginal radical trachelectomy: VRT）のデータを中心になされており、再発率が上昇しない径2cmまでを適格基準とすべき、との論調が目立つ。ARTが術式の主流である本邦でも実際にはRTを施行している施設の88%が径2cm以下のものを対象としている。しかし子宮周囲靭帯を十分骨盤側(Piver typeⅢ)で切断する本邦の広汎子宮全摘出術に準じるARTはVRTよりも更に大きな病巣を対象にできると考え、扁

平上皮癌は横径 3cm まで、腺癌は横径 2cm 以下なら可能とした。ただし、頸管を少なくとも 5mm は残したい本術式にあって、病巣の頸管に沿った奥行きの危険性は子宮腟部表面の横方向への拡がりと同一には論じられないと考え、術前 MR による評価で「扁平上皮癌病巣の奥行きは内子宮口まで少なくとも 1cm 以上の cancer-free space を有すること」とし、「腺癌（腺扁平上皮癌含む）の場合は 2cm 以上の cancer-free space を必要とし、浸潤の浅い表在型か外向発育型が望ましい」とした。すなわち、病巣サイズに関する適格基準に“横径と奥行き”という 2 方向の概念を初めて導入することにより適応拡大を試みた。また、適応拡大に対して安全性を強化する目的で、術中に、1) 生検したセンチネルリンパ節に転移がないこと、2) 切除頸部断端とそれより 5mm の断面に病変がないことを確認した。2 ヶ所の断面を術中に評価したのは特に skip lesion がありうる腺癌に対して安全性を高めるためである。

100 例を超えて再発なく経過している施設は国内外でも珍しく、良好な surgical outcome が得られている。腫瘍長径の適格基準における適応拡大が安全に行えた最大の理由は、1) 子宮を温存する場合、病巣の横径よりリスクが高いと思われる奥行きに関して、別個に新たな適格基準を設けたことと、2) センチネルノード・ナビゲーションサージャリー臨床試験の併用にあると考えている。

E. 結論

浸潤子宮頸癌に対して、広汎子宮頸部摘出術しか将来の妊娠を可能とする治療法が無い本邦の現状では、頸がんの若年化と相まって今後ますます本術式の必要性が増していくと思われる。根治的術式でありながら妊孕性も温存できるこの子宮頸部摘出術を普及させるためには、良好な surgical outcome と obstetrical outcome を確立することが必須と考える。次年度は obstetrical outcome の解析を行い、本法のさらなる改善（特に妊娠率向上と安全な分娩への工夫）に取り組み、その成果を報告したい。

G. 研究発表

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H. 知的財産権の出願・登録状況（予定含）

１．特許取得
　　なし
２．実用新案登録
　　なし
３．その他
　　なし

学 会 等 発 表 実 績

委託業務題目「 早期子宮頸がんに対する機能温存低侵襲手術の確立に関する研究 」

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２．学会誌・雑誌等における論文掲載

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Clinical Trial Note

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Clinical Trial Note

Non-randomized confirmatory trial of modified radical hysterectomy for patients with tumor diameter 2 cm or less FIGO Stage IB1 uterine cervical cancer: Japan Clinical Oncology Group Study (JCOG1101)

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Abstract

A non-randomized confirmatory trial was started in Japan to evaluate the efficacy of modified radical hysterectomy in patients with tumor diameter 2 cm or less FIGO Stage IB1 uterine cervical cancer, for which the current standard is radical hysterectomy. This study began in January 2013 and a total of 240 patients will be accrued from 37 institutions within 3 years. The primary endpoint is 5-year survival. The secondary endpoints are overall survival, relapse-free survival, local relapse-free survival, percent completion of modified radical hysterectomy, percent local relapse, percent pathological parametrial involvement, days until self-urination and residual urine disappearance, blood loss, operation time, percent post-operative radiation therapy, adverse events and severe adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009726 (http://www.umin.ac.jp/ctr/).

Key words: FIGO stage IB1 (≤2 cm) uterine cervical cancer, modified radical hysterectomy, clinical trials, Phase III

Introduction

Uterine cervical cancer (UCC) is the fifth most common disease for women in Japan after breast cancer, colon cancer, gastric cancer and lung cancer. Both the prevalence and the mortality of UCC are currently increasing in women in their 20 and 30 s. Stage IB1 comprises 36% of cases of invasive cancer (Stages IB–IV) in Japan (1).

The standard surgery for Stage IB1 UCC is radical hysterectomy (RHx). The frequency of pathological parametrial invasion and

lymph node (LN) metastasis is reportedly very low and relapse-free survival is good enough, especially when the tumor diameter is 2 cm or less (TD ≤ 2 cm) (2–4). However, RHx causes loss of desire to void because of damage to the pelvic splanchnic nerve due to surgery (5). Self-catheterization is required in some patients for the rest of their life, which often impairs quality of life, especially for young women. Persistent urination disorder can secondarily cause chronic urinary tract infection and renal failure. Because of such disadvantages for patients, a less invasive surgery that does not impair the prognosis should be pursued.

Modified radical hysterectomy (MRHx) has been a standard treatment for minimally invasive cancer of the uterine cervix. Compared with RHx, pelvic splanchnic nerves can be preserved in MRHx and it can prevent urination disorder. It has been reported that MRHx could reduce the number of days until self-urination from catheter removal and the number of days until residual urine disappearance compared with RHx (6,7). Yang et al. reported that MRHx shortened mean time to voiding and reduced post-operative voiding difficulty (8). However, the prognosis of Stage IB1 UCC treated with MRHx has yet to be well examined.

From 2008 to 2009, the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) performed an observational study (JCOG0806-A) of surgical procedures and pathological findings for Stage IB1 UCC (Tomoyasu Kato, unpublished data). Five-year overall survival (OS) was 95.8% and the proportion of pathological parametrial involvement was 1.9% in patients with TD ≤ 2 cm Stage IB1 UCC treated by RHx. Five-year OS was 97.0% in patients with TD ≤ 2 cm Stage IB1 UCC treated by MRHx. From the results of this study, MRHx is considered to be a promising treatment, even in terms of the efficacy, but this should be confirmed in a prospective study.

A randomized controlled trial (RCT) is the gold standard to establish a new standard treatment. However, the five-year OS of RHx is known to be as high as 95% and this high proportion would not differ even if we conduct a RCT. On the other hand, if the 5-year OS of MRHx is proven to be similarly high, it can be accepted as the new standard because the complications of MRHx are definitely less than those of RHx. Therefore, we set this trial as a non-randomized confirmatory trial to evaluate the efficacy of MRHx in patients with TD ≤ 2 cm Stage IB1 UCC (Fig. 1).

The Protocol Review Committee of JCOG approved the protocol in November 2012 and the study was activated in January 2013. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009726 (http://www.umin.ac.jp/ctr/index.htm].

Protocol digest of JCOG 1101

Purpose

The aim of this study is to evaluate the efficacy of MRHx compared with RHx in patients with TD ≤ 2 cm FIGO Stage IB1 UCC.

Study setting

A multi-institutional non-randomized Phase III study.

Endpoints

The primary endpoint is 5-year OS, which is defined as days from enrollment to death from any cause and censored at the latest day without events. The secondary endpoints are OS, relapse-free survival, local relapse-free survival, percent completion of modified radical hysterectomy, percent local relapse, percent pathological parametrial involvement, days until self-urination and residual urine disappearance, blood loss, operation time, percent post-operative radiation therapy, adverse events and severe adverse events. Relapse-free survival is defined as days from enrollment to any disease relapse or death from any cause and censored at the latest date when the patient is alive. Local relapse-free survival is defined as days from enrollment to local disease relapse or death from any cause and censored at the latest date when the patient is alive. Days until self-urination and residual urine disappearance are defined as days from post-operative urethral catheter removal to self-urination and residual urine disappearance (residual urine 50 cc or less and self-urination volume more than residual urine).

Eligibility criteria

Inclusion criteria

For inclusion in the study, the patient must fulfill all of the following criteria:

(i) Any one of the following histologies in the primary lesion located at the uterine cervix.
   1. Squamous cell carcinoma (keratinizing or non-keratinizing type)
   2. Adenosquamous carcinoma (except for glassy cell carcinoma)
   3. Adenocarcinoma (endocervical-type mucinous adenocarcinoma, intestinal-type mucinous adenocarcinoma or endometrioid adenocarcinoma)

(ii) Clinical Stage IB1 fulfilling (1 or 2) (The General Rules for Clinical and Pathological Management of Uterine Cervical Cancer in Japan, 3rd edition, 2012)
   1. To fulfill (a or b), in the case that a tumor with maximum diameter (MD) of 2 cm or less is confirmed in a pelvic magnetic resonance image (MRI) within 56 days before registration
      (a) When diagnostic conization of the cervix is performed within 28 days before registration after MRI, MD is confirmed as 2 cm or less (a colposcopy is not essential)
      (b) When diagnostic conization of the cervix is not performed, an invasive cancer is not detected or the length

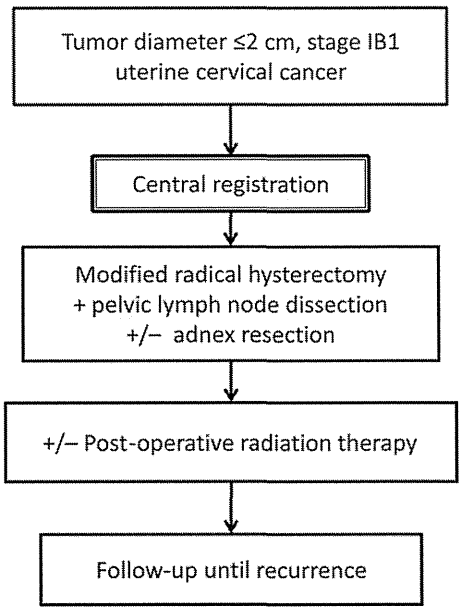

Figure 1. Schema of the study.

of invasion is confirmed as 2 cm or less in a colposcopy within 28 days before registration

2. To fulfill (a or b), in the case that a tumor is not detected in a pelvic MRI within 56 days before registration
   (a) When an invasive tumor is not confirmed in a colposcopy within 28 days before registration, the length of invasion is confirmed as 2 cm or less by diagnostic conization of the cervix within 28 days before registration
   (b) When an invasive tumor is confirmed in a colposcopy within 28 days before registration, the length of invasion is confirmed as 2 cm or less in the colposcopy

(iii) Neither distant LN metastasis nor distant metastasis in abdominal and pelvic computed tomography (CT) within 28 days before registration
(iv) Aged 20–70 years old
(v) ECOG performance status (PS) of 0 or 1
(vi) No following prior treatment
   1. Surgery except for cervical conization for UCC
   2. Surgery for lower abdominal or pelvic malignancy
   3. Radiation therapy or chemotherapy for other malignancies
(vii) Adequate organ functions
(viii) Written informed consent

Exclusion criteria

Patients are excluded if they meet any of the following criteria:

(i) Simultaneous or metachronous (within 5 years) double cancers except carcinoma *in situ* or intramucosal tumor
(ii) Active infectious disease to be treated
(iii) Body temperature of 38°C or more
(iv) Women during pregnancy or breastfeeding
(v) Psychiatric disease
(vi) Systemic and continuous steroid medication
(vii) Uncontrolled diabetes mellitus
(viii) Uncontrolled hypertension

Treatment methods

The protocol treatment consists of MRHx and post-operative radiation therapy.

Modified radical hysterectomy

RHx is a method of hysterectomy defined as being intermediate between simple hysterectomy and radical hysterectomy. The surgical procedure must be compliant with the following (The General Rules for Clinical and Pathological Management of Uterine Cervical Cancer, 3rd edition): the protocol surgery is to cut the anterior layer of the vesicouterine ligament of the uterus, mobilize the ureter laterally, and remove the part of the parametrial tissue and vaginal wall away from the uterine cervix. The posterior layer of the vesicouterine ligament must not be resected. It is recommended that bilateral adnexa be resected, but they can be preserved if the following criteria are met: (i) premenopausal patients who wish for their ovaries to be preserved, (ii) pre-operative histological diagnosis is squamous cell carcinoma and (iii) no macroscopic metastasis.

Dissection of regional LNs (common iliac LNs, external iliac LNs, internal iliac LNs, obturator LNs, sacral LNs and cardinal ligament LNs) must be carried out. Para-aortic LN biopsy must be performed when macroscopic metastasis is suspected.

Laparoscopic and robotic surgeries are not allowed.

Radiation therapy

Whole-pelvic irradiation is administered when pelvic LNs are positive, parametric invasion is positive, or depth in the cervical wall is 2/3 or more in the post-operative pathological diagnosis. Irradiation of the para-aortic LN region is added when the para-aortic LN is positive in the post-operative pathological diagnosis. Intracavitary brachytherapy for the vaginal cuff is administered when cancer is positive within 1 cm of the vaginal end. Radiation therapy is administered from Day 21–42 after surgery.

Whole-pelvic irradiation comprises a total dose of 50.4 Gy in a fraction of 1.8 Gy five times a week. In case irradiation for para-aortic LNs is added to that for the whole-pelvic region, irradiation comprises a total dose of 45 Gy in a fraction of 1.8 Gy five times a week. Intracavitary brachytherapy for the vaginal cuff comprises a total dose of 30 Gy in a fraction of 6 Gy once a week by itself, a total dose of 8 Gy in a fraction of 4 Gy once or twice a week when combined with whole-pelvic irradiation, and a total dose of 12 Gy in a fraction of 4 Gy once or twice a week when combined with irradiation for the whole-pelvic and para-aortic LN region. The dose of intracavitary brachytherapy is prescribed at a depth of 0.5 mm from the vaginal surface.

For external beam irradiation, CT simulation is mandatory. The gross tumor volume is not defined in this trial because the macroscopic site of disease is resected before irradiation. The clinical target volume (CTV) includes CTV vaginal cuff, CTV paracolpium and CTV LN subclinical. The planning target volume (PTV) includes PTV vaginal cuff, PTV paracolpium and PTV LN subclinical. PTV vaginal cuff and PTV paracolpium are defined as 1–1.5 cm margins for anterior and posterior directions and 0.5–1 cm margins for the lateral direction around the CTV vaginal cuff and paracolpium, respectively, to compensate for setup variations and internal organ motion. PTV LN subclinical is defined as 0.5–1 cm margins for all directions around CTV LN subclinical to compensate for setup variations and internal organ motion.

Follow-up

All enrolled patients are followed up for at least 5 years. Tumor marker, vaginal stump cytology, physical examination and safety are to be evaluated at least every 3 months for the first 3 years and every 6 months in the fourth and fifth years. Chest X-ray and abdominal and pelvic CT are to be evaluated at least every 6 months for the first 3 years and every 12 months in the fourth and fifth years.

Study design and statistical analysis

This trial is a non-randomized confirmatory trial designed to evaluate the efficacy of RHx in patients with tumor diameter 2 cm or less FIGO stage IB1 UCC.

In our previous observational study (JCOG0806-A), the 5-year survival of the current standard procedure, radical hysterectomy, was 95.8%. Thus, we anticipate in this study that the expected 5-year survival of RHx is also 95.8%. RHx is a less toxic procedure in terms of urination disorder than radical hysterectomy, and it would be a non-inferiority trial if we conducted a RCT to compare both procedures. Considering the difference of toxicity, we would set the non-inferiority margin as 5%. Thus, we set the threshold 5-year survival of this study as 90.8%.The planned accrual period is 3 years, and the follow-up period is 5 years after completion of accrual. In this trial, the planned sample size is 240 patients, which was calculated based on an expected 5-year survival of 95.8% and a threshold of 90.8%, with a one-sided alpha error of 0.05 and a beta error of 0.1.

Interim analysis and monitoring

In this trial, an interim analysis is not planned because this is a single-arm trial and it is not appropriate to judge that the primary endpoint is met or not based on preliminary data. However, when the efficacy is unexpectedly low, patient accrual should be stopped and the result should be published early. Therefore, the Data and Safety Monitoring Committee will check monitoring reports issued twice a year and discuss early termination when tumor recurrence is observed in >24 patients, 10% of the total of 240 registered patients.

Central monitoring will be performed every 6 months by the JCOG Data Center to evaluate study progress and improve study quality.

Participating institutions (from North to South)

Hokkaido University Hospital, Sapporo Medical University Hospital, Iwate Medical University Hospital, Tohoku University Hospital, Tsukuba University Hospital, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, Saitama Medical University, Jikei Kashiwa Hospital, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Keio University Hospital, Jikei University Hospital, Cancer Institute Hospital, The University of Tokyo Hospital, Juntendo University Hospital, NTT Medical Center Tokyo, Kitasato University School of Medicine, Niigata Cancer Center Hospital, Shinshu University, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, Kyoto University Hospital, Osaka City University Hospital, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Hyogo Cancer Center, Tottori University, Shikoku Cancer Center, Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Saga University, Kumamoto University Medical School and Kagoshima City Hospital.

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Conflict of interest statement

None declared.

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Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A)

Tomoyasu Kato [a,*], Atsuo Takashima [b], Takahiro Kasamatsu [a], Kenichi Nakamura [b], Junki Mizusawa [b], Toru Nakanishi [c], Nobuhiro Takeshima [d], Shoji Kamiura [e], Takashi Onda [f], Toshiyuki Sumi [g], Masashi Takano [h], Hidekatsu Nakai [i], Toshiaki Saito [j], Kiyoshi Fujiwara [k], Masatoshi Yokoyama [l], Hiroaki Itamochi [m], Kazuhiro Takehara [n], Harushige Yokota [o], Tomoya Mizunoe [p], Satoru Takeda [q], Kenzo Sonoda [r], Tanri Shiozawa [s], Takayo Kawabata [t], Shigeru Honma [u], Haruhiko Fukuda [b], Nobuo Yaegashi [v], Hiroyuki Yoshikawa [w], Ikuo Konishi [x], Toshiharu Kamura [y],
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HIGHLIGHTS

- Stage IB1 cervical cancer patients with <2-3% parametrial involvement and ≥ 95% 5-year OS would be candidates for less invasive surgery.
- The primary target population was patients with tumor diameter ≤ 2 cm as preoperatively assessed by MR imaging and/or cone biopsy.
- They had lower risk of parametrial involvement (1.9%) and more favorable 5-year OS (95.8%), and could therefore be good candidates.

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ABSTRACT

Objective. In order to determine indications for less radical surgery such as modified radical hysterectomy, the risk of pathological parametrial involvement and prognosis of FIGO stage IB1 cervical cancer patients undergoing standard radical hysterectomy with pre-operatively assessed tumor diameter ≤2 cm were investigated.

Methods. We conducted a retrospective multi-institutional chart review of patients with FIGO stage IB1 cervical cancer who underwent primary surgical treatment between 1998 and 2002. The eligibility criteria for the analyses were (i) histologically-proven squamous cell carcinoma, adenocarcinoma or, adenosquamous cell carcinoma, (ii) radical hysterectomy performed, (iii) clinical tumor diameter data available by MR imaging or specimens by cone biopsy, and (iv) age between 20 and 70. Based on the clinical tumor diameter, patients were stratified into those with the following tumors: i) 2 cm or less (cT ≤ 2 cm) and ii) greater than 2 cm (cT > 2 cm). We expected 5-year OS of ≥95% and parametrial involvement <2–3% for patients with cT ≤ 2 cm who underwent radical hysterectomy.

Results. Of the 1269 patients enrolled, 604 were eligible for the planned analyses. Among these, 571 underwent radical hysterectomy (323 with cT ≤ 2 cm and 248 with cT > 2 cm). Parametrial involvement was present in 1.9% (6/323) with cT ≤ 2 cm and 12.9% (32/248) with cT > 2 cm. Five-year overall survivals were 95.8% (95% CI 92.9–97.6%) in cT ≤ 2 cm and 91.9% (95% CI 87.6–94.8%) in cT > 2 cm patients.

Conclusion. Patients with cT ≤ 2 cm had lower risk of parametrial involvement and more favorable 5-year overall survival. They could therefore be good candidates for receiving less radical surgery.

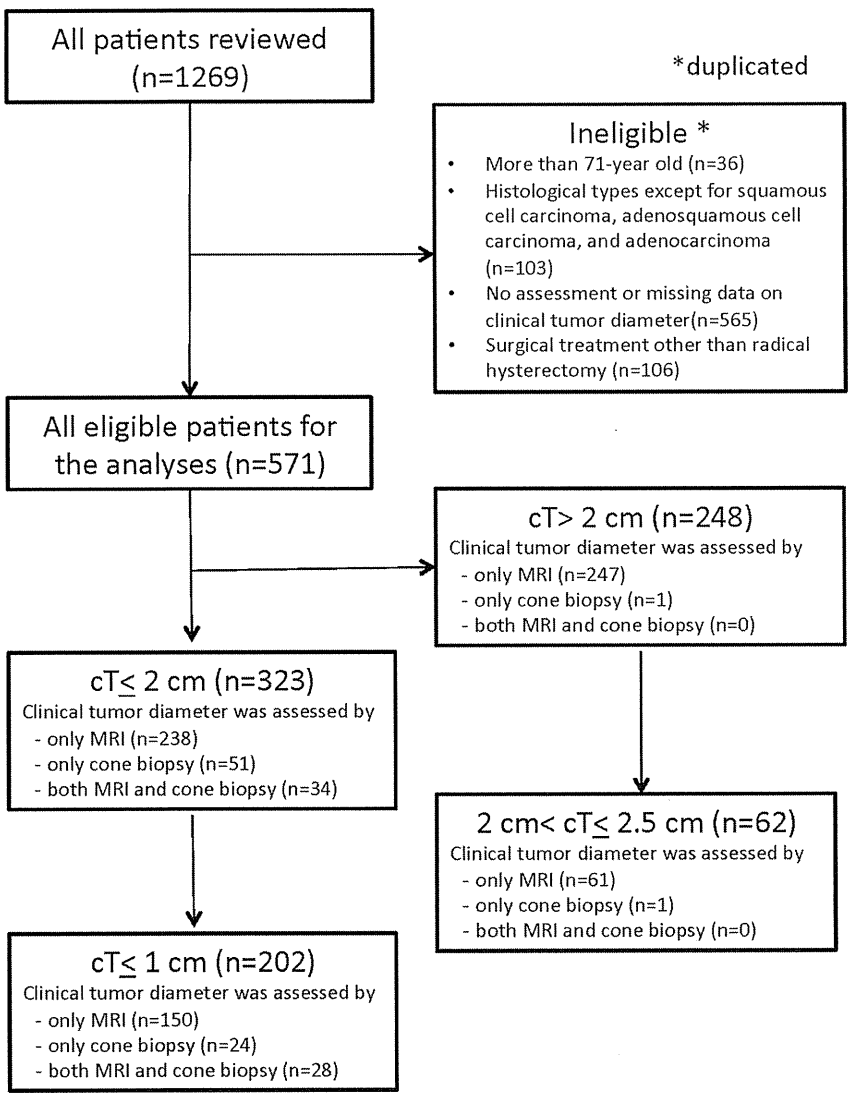

Fig. 1. Flow diagram.

Introduction

The worldwide standard surgical treatment for patients with the International Federation of Gynecology and Obstetrics (FIGO) stage IB1 cervical cancer is radical hysterectomy with pelvic lymphadenectomy [1–3]. The report from FIGO showed that 5-year overall survival (OS) of FIGO stage IB1 was 89.1% [2]. Although the prognosis of patients who underwent radical hysterectomy was favorable, early and late morbidity such as problematic urinary voiding and stress incontinence occur frequently [4–10]. These complications depended on the extent of necessary resection of the parametrium or paracolpium [8].

As compared with radical hysterectomy, modified radical hysterectomy had a lower incidence and severity of morbidity [11–13]. Modified radical hysterectomy is a method of hysterectomy defined as lying between simple hysterectomy and radical hysterectomy. This surgery cuts the anterior layer of vesicouterine ligament of the uterus, mobilizes the ureter laterally, and removes part of the parametrial tissue and vaginal wall away from uterine cervix. This less radical resection of the parametrium contributed to decreased damage to autonomic nerves, although the efficacy could theoretically be compromised.

In order to apply the less radical surgery, a patient population with good prognosis and less risk of pathological parametrial involvement needs to be identified. Tumor diameter as well as lymph node metastasis, histological type, and lymph-vascular space invasion (LVSI) are proposed prognostic factors in cervical cancer [14–17]. Thus, tumor size ≤2 cm, histological subtype limited to squamous cell carcinoma [13], no LVSI [18,19], and stromal invasion ≤10 mm [20] indicate lower risk of parametrial disease. Kinney et al. reported that patients with stage IB squamous cell carcinoma of the cervix with pathological tumor diameter ≤2 cm had no parametrial involvement and had a 5-year disease-free survival of 97.6% [21]. A review of less radical or no radical surgery for early cervical cancer showed that in patients with favorable prognostic factors, such as tumor size <2 cm, limited depth of invasion, absence of LVSI and negative lymph nodes on frozen section, the risk of parametrial involvement is approximately 1% or less [22,23]. Three large prospective trials of non-radical surgery are ongoing worldwide [24–26].

However, these risk factors can be assessed only after excision, whereas identification of patients appropriate for less radical surgery must be determined preoperatively. MR imaging is currently the standard modality for assessing tumor size of invasive cervical cancer [27–29]. Two reports showed that no pathological parametrial involvement was found in patients with the tumor diameter less than 2 cm measured by MR imaging [30,31].

We focused on the tumor size preoperatively assessed to select the population of good candidate for less radical surgery. We expected that patients with <2–3% parametrial involvement and ≥95% 5-year OS would be good candidates for less invasive surgery. The primary target population was patients with tumor diameter ≤2 cm as preoperatively assessed by MR imaging and/or cone biopsy. To this end, we conducted a retrospective multi-institutional chart review in order to investigate prognosis and risk of pathological parametrial involvement for patients with cervical cancer stage IB1 who underwent radical hysterectomy.

Materials and methods

Study design

This study was a multi-institutional retrospective chart review design.

Patients

Patients with FIGO stage IB1 cervical cancer who underwent primary surgical treatment between 1998 and 2002 in 24 institutions belonging to the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) were enrolled. The eligibility criteria for the analyses were the following: (i) histologically proven squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma, (ii) radical hysterectomy, (iii) clinical tumor diameter data available, as measured by MR imaging or specimens by cone biopsy, and (iv) age between 20 and 70.

Eligible patients who had had radical hysterectomy were stratified into 2 groups according to the clinical tumor diameter, one with 2 cm or less (cT ≤ 2 cm) and the other with tumors larger than 2 cm (cT > 2 cm). The primary target population was the former group, which we expected would show <2–3% parametrial involvement and ≥95% 5-year OS.

Endpoint of this study

The primary endpoint was 5-year OS. A key secondary endpoint was the incidence of pathological parametrial involvement. Other secondary endpoints were 5-year recurrence-free survival (RFS), the incidence of pelvic node metastases, the incidence and site of recurrence, and the degree of discrepancy between clinical diagnosis and pathological diagnosis of tumor diameter.

Definition of clinical tumor diameter

Clinical tumor diameter was defined as the greatest tumor diameter measured on T2-weighted or contrast-enhanced T1-weighted images in any transverse, coronal, or craniocaudal direction by MR imaging. If the tumor was not visible on MR imaging, its maximum diameter was coded as ≤2 cm. If the tumor was not evaluated by MR imaging, the length of invasion was registered as tumor diameter using cone biopsy specimens. When subsequent MR imaging revealed residual disease after cone biopsy, the clinical tumor diameter was determined in a comprehensive evaluation.

For an intensive analysis, patients with cT ≤ 2 cm were stratified into those with cT ≤ 1 cm (or invisible on MR imaging), and 1 cm < cT ≤ 2 cm. Among the cT > 2 cm group, patients with clinical tumor diameter >2 cm and ≤2.5 cm (2 cm < cT ≤ 2.5 cm) were selected.

Histology

Preoperative histopathological type was defined as the dominant pathological finding in specimens obtained by punch or cone biopsy.

Table 1
Characteristics of the patients who underwent radical hysterectomy by clinical tumor diameter.

	cT ≤ 2 cm	cT > 2 cm
Number of cases	323	248
Median age (range)	44 (19–70)	47.5 (26–70)
Histology, n (%)		
Squamous cell carcinoma	212 (65.6)	170 (68.6)
Adenocarcinoma	100 (31.0)	73 (29.4)
Adenosquamous carcinoma	11 (3.4)	5 (2.0)
MRI, n (%)		
Not carried out	49 (15.2)	0 (0.0)
Carried out	274 (84.8)	248 (99.3)
Detection of tumor		
Yes	114 (58.4)	247 (99.6)
No	160 (41.6)	1 (0.4)
Conization, n (%)		
Carried out	104 (32.2)	7 (2.8)
Not carried out	219 (67.8)	241 (97.2)
Postoperative therapy, n (%)		
Not carried out	246 (76.2)	132 (53.2)
Carried out	77 (23.8)	116 (46.8)
Kind of therapy*		
Radiotherapy	38	72
Chemotherapy	31	31
Chemoradiotherapy	9	16

* Duplicated.

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Table 2
Pathological findings of the patients who underwent radical hysterectomy.

	cT ≤ 2 cm (n = 323)	cT > 2 cm (n = 248)
Pathological diameter, n (%)		
2 cm or less	196 (60.7)	44 (17.7)
Greater than 2 cm to 4 cm	49 (15.2)	136 (54.8)
Greater than 4 cm	1 (0.3)	29 (11.7)
Missing	77 (23.8)	39 (15.7)
Pathological parametrial involvement, n (%)		
Negative	310 (96.0)	215 (86.7)
Positive	6 (1.9)	32 (12.9)
Missing	7 (2.2)	1 (0.4)
Cervical stromal invasion, n (%)		
Inner 1/3	160 (49.5)	35 (14.1)
Middle 1/3	51 (15.8)	50 (20.2)
Outer 1/3	36 (11.1)	105 (42.3)
Missing	76 (23.5)	58 (23.4)
Regional lymph node metastases, n (%)		
Negative	299 (92.6)	193 (77.8)
Positive	24 (7.4)	55 (22.2)
Histology, n (%)		
Squamous cell carcinoma	194 (60.1)	156 (62.9)
Adenocarcinoma	92 (28.5)	66 (26.6)
Microinvasive squamous cell carcinoma	10 (3.1)	1 (0.4)
Adenosquamous carcinoma	22 (6.8)	20 (8.1)
Others*	5 (1.5)	5 (2.0)

* Glassy cell carcinoma, adenoid basal cell carcinoma, undifferentiated carcinoma, and others.

Histopathologic types were categorized according to the WHO classification [32].

Recurrence assessment

Sites of recurrence were classified into local and distant. Local recurrence included central (i.e. around the vaginal stump or paracolpium) or pelvic sidewall. Para-aortic lymph node or other distant node metastases were defined as distant metastases. Recurrences were diagnosed during regular follow-up visits and/or confirmed by CT and/or MR imaging. Whenever possible, histological or cytological confirmation was obtained.

Statistical methods

OS was calculated from the date of surgery to the date of death from any cause, or the last contact. RFS was defined as the time from the date of surgery to that of death from any cause, last follow-up or recurrence, whichever was earlier. The RFS and OS curves were estimated by the Kaplan–Meier method. All statistical analyses were carried out at JCOG Data Center with SAS release 9.1 or 9.2 (SAS Institute, Cary, NC).

IRB

The study protocol was approved by the Protocol Review Committee of the JCOG as well as the Institutional Review Board of each participating institution.

Results

Patient characteristics

A total of 1269 patients with FIGO stage IB1 cervical cancer were enrolled in this study (Fig. 1). Of 1269 patients, 665 patients were ineligible for the analyses because of the following: 1) they were more than 71-years old (n = 36); 2) they did not have histologically proven squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma (n = 103); 3) no assessment or missing data on clinical tumor diameter (n = 565); or 4) surgical treatment other than radical hysterectomy (n = 106). Some patients were ineligible for more than one reason. There were 571 patients finally eligible for the analyses.

Table 1 summarizes the characteristics of those who underwent radical hysterectomy (n = 571) of whom 323 had cT ≤ 2 cm. The distribution of preoperative histological types was similar between the two groups. In patients with cT ≤ 2 cm, 104 (32.2%) underwent cone biopsy, but only 7 (2.8%) did so in the cT > 2 cm group, almost all of whom were assessed by MR imaging alone. None had positive parametrial findings on MR imaging in the two groups.

Pathological findings

The discrepancy between clinical diagnosis and pathological diagnosis of tumor diameter is shown in Table 2. The clinical tumor diameter was determined by MR imaging or specimens by cone biopsy, as is previously described in the Materials and methods section. Of 246 patients with available data in the cT ≤ 2 cm group, pathologically-estimated tumor size of ≤2 cm was confirmed in 79.7% (196/246), whereas 19.9% (49/246) had tumors 2–4 cm in diameter and just one patient >4 cm (0.4%, 1/246).

Pathological parametrial disease was observed in 1.9% (6/323) and 12.9% (32/248) of patients with cT ≤ 2 cm and cT > 2 cm, respectively. Among the cT ≤ 2 cm group, parametrial involvement was present in

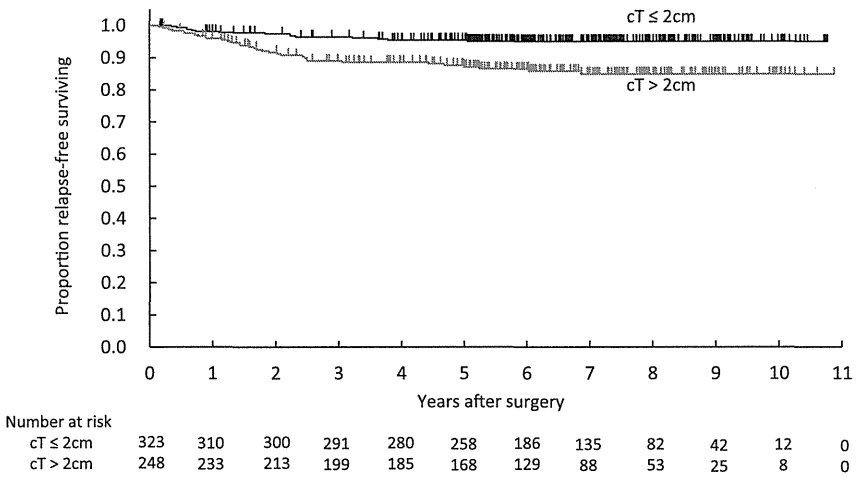

Fig. 2. Recurrence-free survival.

Table 3
Recurrence by clinical tumor diameter.

Recurrence, n (%)	cT ≤ 2 cm (n = 323)	cT > 2 cm (n = 248)
None	309 (95.7)	217 (87.5)
Yes	14 (4.3)	31 (12.5)
Site of first recurrence*	**(n = 14)**	**(n = 31)**
Local	7	20
Central of pelvis	2	12
Pelvic side-wall	5	10
Distant	8	14
Para-aortic LNs	3	3
Others	5	13
(Both of local and distant sites)	(1)	(3)

* Total number of patients with multiple sites of recurrence.

0% (0/202) with cT ≤ 1 cm and 5.0% (6/121) with 1 cm < cT ≤ 2 cm. The contents of parametrial disease of 6 patients with 1 cm < cT < 2 cm were direct invasion from stromal of the cervix in 3, lymph node metastasis in 3, and LVSI in 1 patient. Parametrial involvement was noted to be as high as 11.3% (7/62) in the 2 cm < cT ≤ 2.5 cm group.

Moreover, regional lymph node metastasis was found in 7.4% (24/323) of patients with cT ≤ 2 cm but in 22.2% (55/248) of cT > 2 cm (Table 2). Positive nodes were observed in 5.9% (12/202), 9.9% (12/121) and 27.4% (17/62) with cT ≤ 1 cm, 1 cm < cT ≤ 2 cm and 2 cm < cT ≤ 2.5 cm, respectively.

Recurrence

The 5-year RFS was 95.5% (95% CI, 92.5 to 97.3%) for cT ≤ 2 cm and 87.1% (95% CI, 82.1% to 90.8%) for cT > 2 cm, as shown in Fig. 2. During the follow-up period, 45 patients recurred: 14 in the cT ≤ 2 cm group and 31 in the cT > 2 cm group. Distribution of initial recurrence site in the two groups is shown in Table 3. Central recurrence was observed in 0.6% (2/323) of patients with cT ≤ 2 cm and 4.8% (12/248) with cT > 2 cm.

Survival

The 5-year OS was 95.8% (95% CI, 92.9 to 97.6%) in the cT ≤ 2 cm group and 91.9% (95% CI, 87.6% to 94.8%) in the cT > 2 cm group, as shown in Fig. 3.

For reference, the 5-year OS and RFS in the entire cohort of 1269 stage IB1 cervical cancer patients was 93.3% (95% CI, 91.7% to 94.6%) and 89.5% (95% CI, 87.6 to 91.1%), respectively.

Discussion

The purpose of this analysis was to establish indications for less radical surgery. Because this needs to be determined before surgery, we set the primary target population of this study as patients with cT ≤ 2 cm who had received radical hysterectomy. The 5-year OS for this population was 95.8%, which was better than our predefined expected value. In addition, parametrial involvement was observed in only 1.9% of this population, which was also lower than expected. The contents of parametrial disease of 6 patients with cT ≤ 2 cm were direct invasion from stromal of the cervix in 3, lymph node metastasis in 3, and LVSI in 1 patient. These findings suggest that such patients would be good candidates for less invasive surgery such as modified radical hysterectomy.

In contrast, the 5-year OS of patients with cT > 2 cm was 91.9% and parametrial involvement was found in 12.9%, which was worse than our predefined value for less invasive surgery. Central recurrence was also noted to be as high as 4.8% in this group. The relatively low survival may be attributed to the presence of lymph node metastasis [19]. Indeed, regional lymph node metastases were found in 22.2% of patients with cT > 2 cm. Considering these unfavorable data, we propose that patients with cT > 2 cm would not be candidates for less invasive surgery. Parametrial involvement was noted to be as high as 11.3% of patients with 2 cm < cT < 2.5 cm. The validity that set a boundary as clinical tumor diameter 2 cm was indicated.

MR imaging is currently the standard modality for assessing tumor size of invasive cervical cancer [27–29]. For gross tumors > 1 cm, MRI estimates tumor size with an accuracy of 85.3% to 93% [33,34]. Our study showed that among cT ≤ 2 cm patients, agreement between clinical and pathological tumor diameter estimates was about 80%. In other words, 20% of tumor ≤2 cm in clinical diameter actually had a pathological tumor diameter >2 cm. This underestimation of tumor diameter would be critical for selecting candidates for less radical surgery. MR imaging can detect lesions with superficial stromal invasion only with difficulty. Thus, cone biopsy or colposcopy is a prerequisite together with MR imaging to exclude patients with pathological tumor diameters >2 cm. Despite concerns regarding underestimation, our study showed that the 5-year OS of patients with cT ≤ 2 cm was as high as 95.8%. This suggests that underestimation did not exert a negative influence on OS in this population. Further technical progress or innovation in MR to obtain better high-resolution images would allow us to detect small-sized

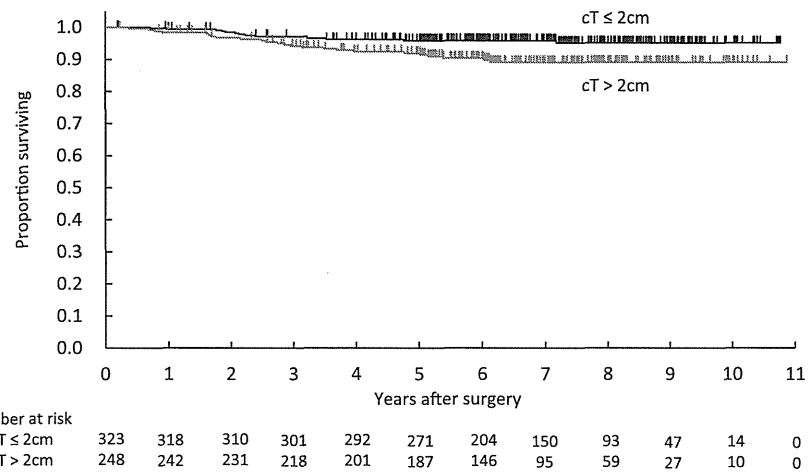

Fig. 3. Overall survival.

cervical cancer tumors and provide more accurate preoperative assessment of tumor diameter and extent.

A confirmatory trial comparing standard radical hysterectomy versus modified radical hysterectomy in patients with cT ≤ 2 cm is now required. A 5-year OS as high as 95.8% in our study means that events rarely occur in this population, so a randomized trial would require an extremely large sample size. In addition, this high OS would not decrease even if we prospectively enrolled patients using more robust eligibility criteria. Therefore, we consider that there is no need to directly compare these two procedures in a randomized controlled trial. Based on the results of this study, we have started a non-randomized confirmatory trial to apply modified radical hysterectomy plus pelvic lymph node dissection for cervical cancer with cT ≤ 2 cm in 2013 (JCOG1101, CC-MoRH, JPRN-UMIN000009726) [35]. This prospective study is expected to provide strong evidence for determining appropriate indications for modified radical hysterectomy for small cervical tumors.

One limitation of our study is its chart review design. Our data were was based on chart reviews from between 1998 and 2002 in 24 institutions belonging to the Gynecologic Cancer Study Group of JCOG. MR imaging techniques and/or supportive care have likely developed further since 2002. Another limitation is that we did not conduct a central review of histopathology of surgically resected specimens, nor preoperative MR imaging for tumor size. We consider the results reflect the level of clinical performance of diagnosis and treatment at that time.

In conclusion, patients with clinical tumor diameters of ≤2 cm had a low risk of pathological parametrial disease and a favorable 5-year OS. This population is considered a good candidate for less invasive surgery such as modified radical hysterectomy. The results of the non-randomized confirmatory trial (JCOG1101) are awaited with the aim of establishing less invasive approaches as standard surgical procedures.

Conflict of interest statement

The author did not report any potential conflicts of interest.

Acknowledgments

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A Dosimetric Analysis of Intensity Modulated Radiation Therapy with Bone Marrow Sparing for Cervical Cancer

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Abstract. *Background/Aim: The purpose of this study was to compare intensity-modulated radiation therapy (IMRT) plan with (Bone Marrow Sparing (BMS) – IMRT) or without (normal-IMRT) an intention of avoiding bone marrow in order to minimize treatment related toxicity. Materials and Methods: Computed tomography (CT) images of 10 consecutive postoperative cervical cancer patients were used. All patients were already treated by normal-IMRT. BMS-IMRTs were created for this study and dose volume histogram parameters were compared. Results: Both planning target volume (PTV) D95% and D97% were statistically lower in BMS-IMRT than normal-IMRT, however, the difference was lower than 3%. There were statistically no difference between BMS-IMRT and normal-IMRT in the mean value of rectum V_{30Gy}, V_{50Gy}; bladder V_{45Gy}, V_{50Gy}; Bowel V_{35Gy}, and V_{50Gy}. Both in whole pelvic bone (WPB) and inner cavity of pelvic bone (ICPB), the mean value of V_{10Gy}, V_{30Gy}, and V_{40Gy} of BMS-IMRT were statistically lower than that of normal-IMRT. Conclusion: Both lower and higher dose for WPB as well as ICPB were effectively lowered by BMS-IMRT.*

Postoperative radiation therapy is an established treatment for intermediate-risk and high-risk cervical patients (1, 2) as well as endometrial cancer patients (3, 4). Conventional radiation techniques for whole-pelvic radiation therapy (WPRT) involve 4 static photon fields. These techniques expose most of the contents of the true pelvis including small bowel equal to the prescribed dose as target volume. The highly conformal technique of intensity-modulated radiation therapy (IMRT) has a potential of delivering radiation dose while avoiding surrounding normal tissues and its advantage has been proven in several anatomical sites such as head and neck cancer (5, 6) or prostate cancer (7, 8). However the profit of using IMRT in the field of gynecological cancer is controversial (9-11). The Radiation Therapy Oncology Group (RTOG) conducted a multi-institutional prospective phase II trial (RTOG 0418) using IMRT for postoperative endometrial and cervical patients in order to determine if IMRT can be performed in multi-institution settings and to test the hypothesis that IMRT can reduce short-term bowel injury and recently positive preliminary results were presented (12, 13). Although in the RTOG 0418 bone marrow sparing was not included in its protocol, weekly cisplatin was administered successfully concurrent with radiation therapy. As much as 83% of patients received 5 or more cycles of weekly cisplatin and 90% at least 4 cycles (13). Compared to results from other series with conventional technique radiation therapy which also used concurrent cisplatin, this result was favorable, although it is difficult to make any direct comparisons (2, 14). Therefore it is supposed that if bone marrow sparing was intended from the beginning, bone marrow protection would lead to better results. The aim of this study is to investigate the difference of dose volume histogram (DVH) parameters between IMRT plan with or without bone marrow sparing intention using computed tomography (CT) images of posthysterectomy cervical cancer patients.

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Key Words: Cervical cancer, radical hysterectomy, postoperative radiation therapy, IMRT, bone marrow sparing.

Materials and Methods

Patients. Ten consecutive patients constitute this retrospective planning study. These subjects underwent radical hysterectomy and

pelvic lymphadenectomy and postoperative radiation therapy for early-stage high-risk cervical carcinoma between May 2012 and June 2013. Eligibility criteria for postoperative adjuvant radiation therapy were: (i) pelvic lymph node metastasis, (ii) parametrial invasion, and (iii) a positive surgical margin.

Radiation therapy. Before simulation CT was taken, a customized immobilization device was fabricated to minimize variability in the daily setup error. Fiducial markers were inserted into the vaginal cuff to visualize it on CT images. CT scans under full and empty bladder were taken in order to account for the motion of vagina influenced by the content of bladder. CT scans of 2 mm slice thickness were taken by Aquilion LB CT scanner (TOSHIBA Medical Systems, Tochigi, Japan). The clinical target volume (CTV) was contoured on the individual axial CT slices of each patient. The overall CTV includes both the vaginal cuff/paracolpium CTV and the nodal CTV. The vaginal cuff/paracolpium CTV was contoured in a manner similar to the Radiation Therapy Oncology Group (RTOG) (15); Cranial margin: 0.5 cm cranial from the upper part of vaginal cuff metallic marker. Anterior margin: posterior border of bladder or retropubic fat pad. Posterior margin: Anterior part of mesorectal fascia or anterior wall of rectum. Lateral margin: medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ishial ramus. Caudal margin: 3 cm below from the upper part of vaginal cuff metallic marker. The nodal CTV included lymph nodes that drain the involved site and adjacent perinodal soft tissue. This included the internal (obturator and hypogastric), external, and common iliac lymph nodes; presacral lymph nodes and soft tissues also included down to the level of S3. The upper limit of the nodal CTV was L4/5 interspace. If a common iliac lymph node metastasis was found pathologically, the nodal CTV was extended at the level of L2/3 interspace. The nodal CTV was based on the Japan Clinical Oncology Group Gynecologic Cancer Study Group (JCOG-GCSG) consensus guidelines for the delineation of CTV for pelvic lymph nodes (16). We used the JCOG-GCSG guideline for reference aiding nodal CTV because it included adipose connective tissue between the iliopsoas muscles and the lateral surface of the vertebral body which was not included in RTOG guideline. This area was also included in an atlas of Taylor *et al.* (17, 18). The CTV was expanded by 7 mm to create the planning target volume (PTV). For normal structures, the small bowel (contoured as a peritoneal space), rectum and bladder (both contoured as a whole organ) and femoral head were routinely contoured according to RTOG normal tissue contouring guideline (19). For the purpose of this study, both pelvic bone and pelvic bone marrow were also contoured. Mahantshetty *et al.* demonstrated that inner cavity of pelvic bone (ICPB) was a better surrogate of active bone marrow than whole pelvic bone (WPB) (20); therefore, both WPB and ICPB were prepared in this study. In order to extract WPB from CT images, bone auto-contouring was performed by including tissue with density of higher than 100 on each slice with 'fill' function activated. Before extracting ICPB, a tentative structure was created using auto-contouring function which includes tissue with density between -100 to 200. This structure includes ICPB as well as extra-bone soft tissue. Therefore, the overlap volume of WPB and the tentative structure was created and this structure became the ICPB. Figure 1 shows representative axial figure of the contour for ICPB and WPB. In this figure, WPB was contoured in pink line while ICPB in green.

Prescription dose was 50 Gy in 25 fractions. The planned goals were to provide a homogenous PTV dose while minimizing the dose delivered to the small bowel, bladder and rectum. Typical input parameters for normal-IMRT plans were as follows: PTV mean dose ranges from 100 to 105% while no more than 2% of the volume of PTV to receive a dose that is 60 Gy or greater; no more than 40% of the volume of the small bowel to receive a dose that is greater than 40 Gy and no more volume of small bowel greater than 1 cc to receive more than 55 Gy; no more than 40% of the volume of the rectum to receive more than 50 Gy and no volume within the rectum receives dose that is 55 Gy or greater; no more than 50% of the volume of the bladder to receive more than 45 Gy and no volume within the bladder receives dose that is 55 Gy or greater; and no more than 20% of the volume of the femoral head to receive more than 30 Gy. Dose constraints of BMS-IMRT planning were as follows: the same dose constraints for PTV and organ at risk (OAR) were used. For the use of DVH-based optimization, virtual structures were created; WPB-PTV and ICPB-PTV which were overlap structure of WPB and PTV, and ICPB and PTV, respectively. The general priority for each structure was presented as below: 70, 90, 65, 50, 65, and 65 for PTV, small bowel, rectum, bladder, WPB-PTV, and ICPB-PTV, respectively.

The way of delivering IMRT was by Volumetric Modulated Arc Therapy (VMAT) using 2 arcs via a computer-controlled auto sequence multileaf collimator on a linear accelerator (Clinac iX, Varian Medical System, Palo Alto, CA, USA) using a 15 MV photon beam. Dose calculation with a calculation grid of 1.0 mm was done and the calculation algorism was Acuros (Link or supplier). The radiotherapy was planned using the Eclipse Planning System (version 10.0, Varian Medical System, Palo Alto, CA, USA).

No chemotherapy was used concurrently with radiation therapy in our institution for early stage high-risk post-hysterectomy cervical cancer patients. DVH parameters between normal-IMRT and BMS-IMRT were compared in this study. The difference of the mean value of each parameter was analyzed by paired *t*-test and *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS™ version 18.0 (SAS Institute, Tokyo, Japan). This retrospective study was approved by the local Institutional Review Board.

Results

Since it was not long before IMRT was introduced in the treatment for postoperative cervical cancer patients in our institution, only 10 patients were included in the current study. Table I shows the patients' characteristics. Median age was 39 (range 25-66) years. Sixty percent of patients were staged as IB1 and there was no IIA patient. Half of the patients had squamous cell carcinoma. Seventy and ninety percent of patients had parametrium invasion and pelvic lymph node metastasis, respectively. All the patients were diagnosed as surgical margin negative.

Figure 2a and Table II shows boxplots and actual numbers of DVH parameters for PTV. Although in PTV $D_{95\%}$ and $D_{97\%}$ the mean value of BMS-IMRT were statistically lower than that of normal-IMRT, the differences were smaller than 3% and the influence of this very minute difference on clinical result is unknown. On the other hand, the mean value of PTV median in BSM-IMRT was statistically higher than that of normal-IMRT. There was no statistical difference in PTV D_{max}