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肺癌検診の精度管理の方向性

—大阪府の試み—

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The 24th Lung Cancer Mass Screening Seminar

肺癌検診の精度管理の方向性
—大阪府の試み—

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Promoting Quality Assurance of Lung Cancer Screening in Osaka Prefecture

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ABSTRACT —— ***Objective.*** It is necessary to establish a system to evaluate the quality of lung cancer screening in prefecture, because there is a large variation in quality in each municipalities and facilities. ***Method.*** The Osaka Prefectural Committee for Management of the Lung Cancer Screening System has published the referral rate standings, the detailed consultation rate and the detection rate of lung cancer by municipality and speculating as to why accuracy was low, in the annual reports since 2005. ***Results.*** A chart, compared with a table of conventional analysis, was easier for the prefectural clerical officers to understand the analysis. Osaka Prefecture has posted annual data from each municipality using a chart on its website since 2006. ***Conclusion.*** Displaying quality assurance data on the website was useful for analysis by the prefectural officers, but merely expecting voluntary improvement in the municipalities is insufficient. Based on the present analysis, the prefectural committee must suggest a concrete remedial plan.

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KEY WORDS —— Lung cancer screening, Quality assurance, The Prefectural Committee for Management of the Cancer Screening System

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要旨 —— **目的．** 現状の肺癌検診においては，各市町村および検診機関の間に大きな精度の差があるため，府県において肺癌検診の精度を評価するシステムを確立する必要がある．**方法．** 大阪府生活習慣病検診管理指導協議会肺癌部会では，各市町村別の要精検率・精検受診率・がん発見率をランキングしたグラフを作成し，精度が悪い市町村に対する理由の考察を添えたものを2005年度分の報告書から導入した．**結果．** 従来の集計表のみの報告書に比べてグラフを用いた分析は，府県の事務担当者にも理解しやすく，好評であった．2006年度より各がん検診の精度指標を市町村別にランキングしたグラフを，大阪府のホームページに公開している．**考察．** ホームページへの精度管理指標の公開は，府県の職員にも受け入れられやすい方法であるが，これだけでは各市町村の自発的な自浄能力を期待することになり不十分である．分析結果に基づいて，生活習慣病検診管理指導協議会は各市町村に具体的な改善策を提示することが必要である．

索引用語 —— 肺癌検診，精度管理，生活習慣病検診管理指導協議会

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1. はじめに

がん検診は精度管理が重要であると言われて久しいが，検診に従事するもの以外からみると，「医療の質」に比べて非常にわかりづらいものとなっている．特に肺癌検診については，撮影や読影に関する認定制度が存在せず，誰でも参入できる状況にある．このため撮影や読影の質を外部のものが評価することは困難な状況にあり，そのせいもあってか社会的な信頼も低い．各地域で行われる住民検診については，各府県の生活習慣病検診管理指導協議会（以下協議会）が府県・市町村・検診機関ごとにその精度を評価し，問題があれば指導すると厚生労働省が示した指針には記載されている．[1] しかし撮影や読影の技術評価という手間のかかることは実質上行うことはできず，要精検率や精検受診率，発見率などの指標の解釈がこの協議会の実務となる．これらの数値指標の解釈は難しく，年１回という一般的なスケジュールからいって，機能しているとは言い難い．また府県の協議会は，問題のある市町村および検診機関に指導をするようにと，国の指針には記載されているものの，法的な権限は存在せず強制力はない．筆者は大阪府の協議会に事務局という形で関与し，大阪府健康福祉部(現健康医療部)とともに，がん検診の精度管理について検討してきた．その間に，市町村および検診機関の自浄作用を期待し，積極的な精度管理指標の公開化に取り組んできた．その動きについて概説する．

2. 精度のバラツキについて

大阪府内の 2003～2006 年度の平均がん発見率の各検診機関別の成績を示す（Figure 1）．過去４年間の平均がん発見率については，0～160/10 万人と幅広く分布している．このように，検診機関別にみると，大きな精度のバラツキが存在する．このようなバラツキの大きさは，10 年以上前から協議会の肺がん部会でも問題となっていたが，当時は具体的な行動はできていなかった．

3. 公開化の動き（第一段階）

宮城県での市町村別の精度管理指標の把握状況に関するホームページ(HP)への公開化の動き[2]を参考に，議論が始まった．年一回の協議会においては，話題に上ったものの，各委員の反応は乏しく，公開するか否かの結論は出ず，継続審議となった．大阪府健康福祉部では協議会での結論を待たず，2005 年に同部の HP 上に各市町村の成績を公開した（Figure 2）．しかしこれは単に集計表を PDF 化し，掲載したものであったがために，1）視覚的にみにくいこと，2)専門的な指標値のどこに問題があるのかわかりにくいこと，3)評価を示す文章が加えられていないことなどから，閲覧者も少なく反響は乏しかった．

4. 公開化の動き（第二段階）

2005 年度末の肺がん部会での検討資料として，Figure 3 を作成した．これは過去３年間の平均要精検率・精検

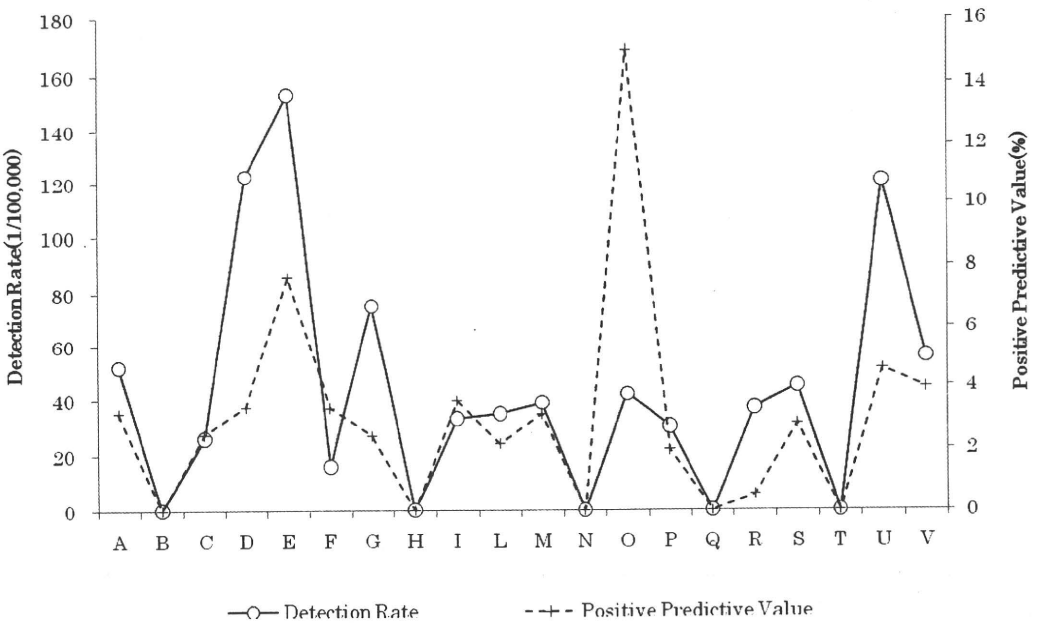

Figure 1. Quality dispersion of lung cancer screening according to facilities in Osaka Prefecture.

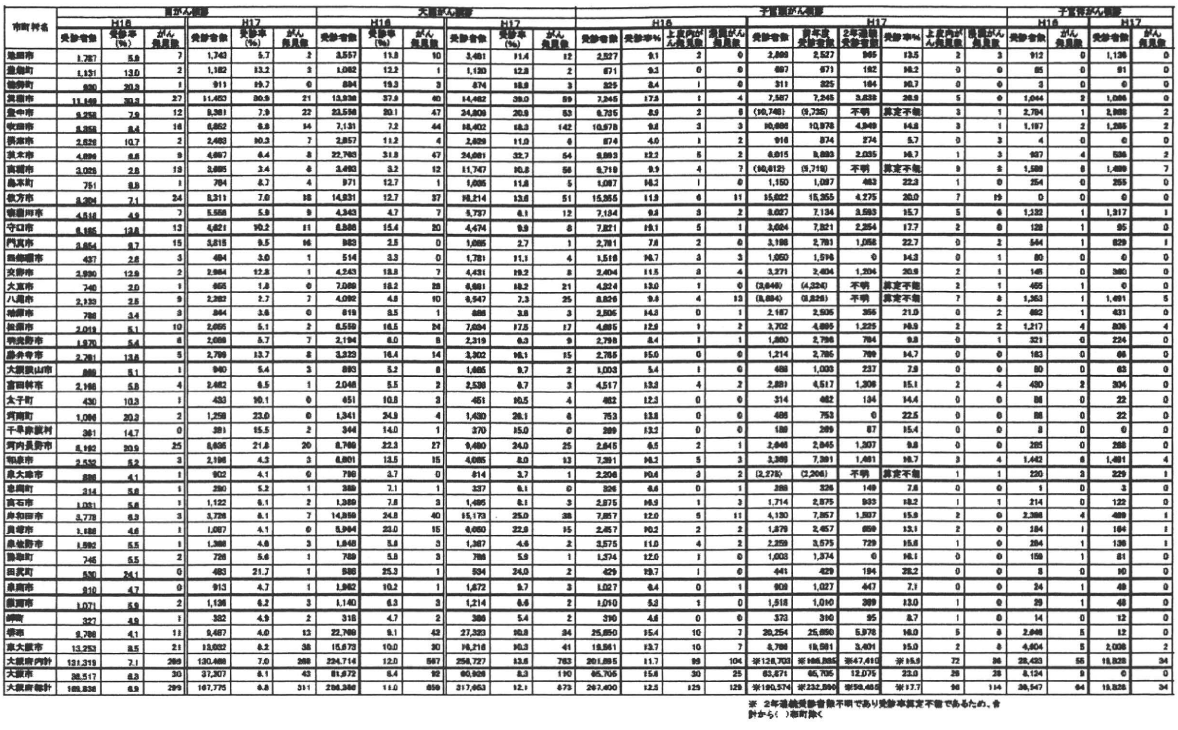

Figure 2. The 1st version of cancer screening results according to municipality shown on the website in Osaka Prefecture in 2005. It was difficult to understand this table because technical results were displayed in a small font, without explanation.

受診率・がん発見率を各市町村別に並べてランキングしたものである．さらに精度管理指標の悪い市町村に対しての理由を考察した文書を添え，健康福祉部の担当者と協議した．精度管理指標が悪い理由については，1997年度の「成人病検診管理指導協議会のあり方に関する調査研究」班の報告書[3]を参考にした．健康福祉部の担当者はこの資料を基に，該当市町村を訪問し，問題点について聞き取り調査を行い，その経過を肺がん部会に報告した．従来の表の形に比べて図を用いた市町村別ランキングは，がん検診に関する専門知識を有さないものにとっても理解しやすいと好評であった．

その頃一部の府議会議員より，がん検診の精度管理についての抜本的な対策を練るべきであるという意見が提言された．このときの提言も，市町村別の検診成績を積極的に公開すべきであるという内容であり，我々の主張と一致した．これを受けて健康福祉部では，2006年より，各市町村の受診率・要精検率・精検受診率・がん発見率の4つの指標について，市町村別にランキングし，市町村名も明記した形で，健康福祉部のHPに公開した．

5. 公開化の動き（第三段階）

2005年度には厚生労働省から「がん検診の事業評価のためのチェックリスト」[1]が公開されていた．これは各種がん検診に関しての精度管理を遵守できているかどうかを自己チェックするツールであり，都道府県版・市町村版・検診機関版がある．これを受けて，大阪府では府内全市町村を対象とした各がん検診に関するチェックリストの調査を行った．この調査内容に解説を加えた報告書を，PDFファイル化して同様にHP上に公開した．チェックリストの解説に関しても，実施率が低い市町村名は実名で本文に記載されている．2008年からは大阪府自身のチェックリストの結果も同様に公開している．今後検診機関のチェックリストの公開が課題である．

6. 考　察

医療機関の質の評価と同様に，がん検診の精度についても，評価は様々な問題を抱えている．1）技術的な問題，2）部外者にとっての理解の困難さ，3）法的面での整備などである．1）の技術的な問題とは，そもそも要精検率・精検受診率・がん発見率・陽性反応的中度といった指標がどの範囲内にあればよいのか？　といった基準が確保されていないことにある．このため各指標をみても市町村あるいは都道府県が，どの検診機関がよいのか悪いのかといったことが判断しづらい状況にあった．しか

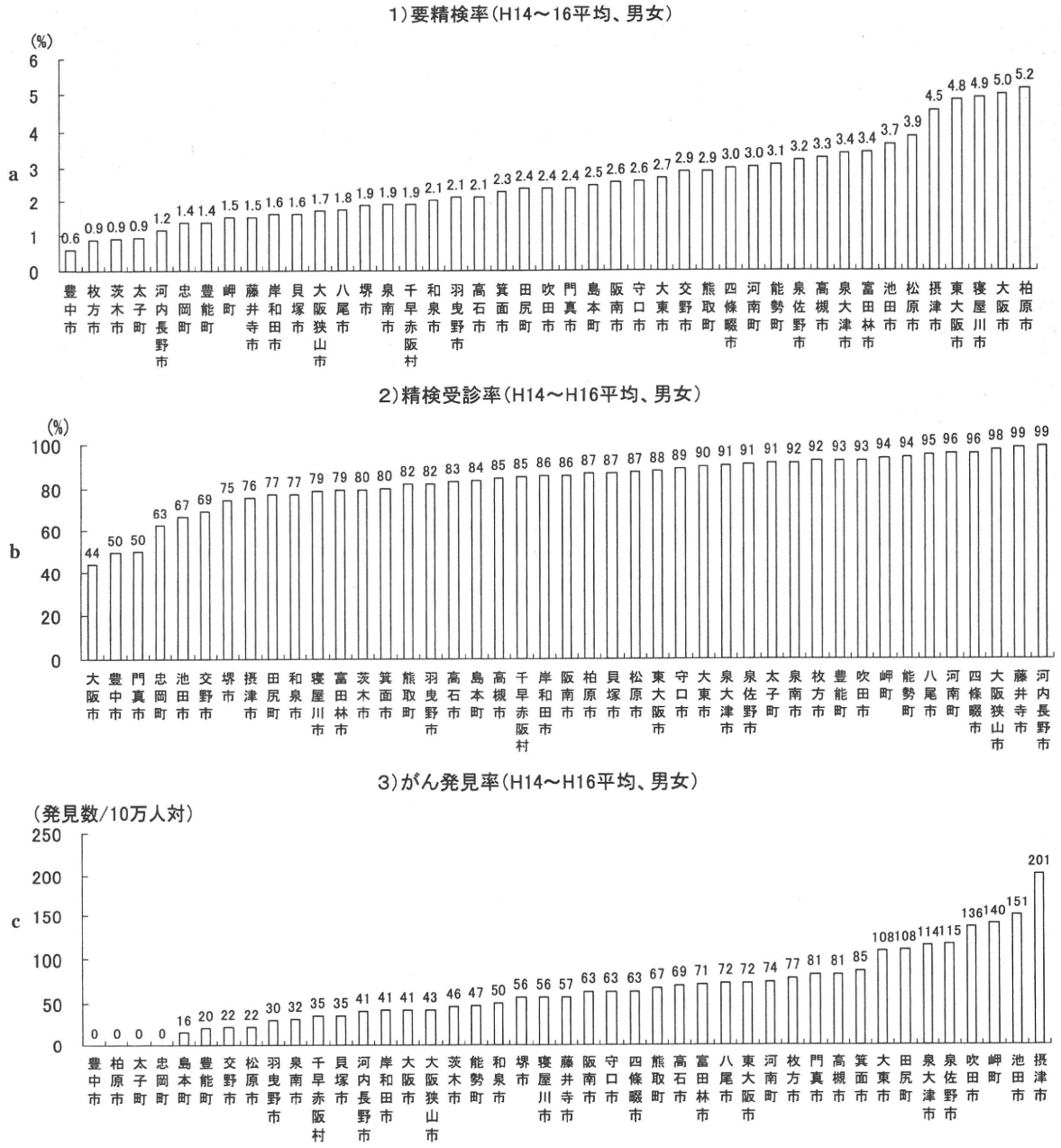

Figure 3. The 2nd version of cancer screening results according to municipality in Osaka Prefecture in 2006. **a)** Average referral rate (%) according to municipality of both men and women from 2002 to 2004. **b)** Average detailed consultation rate (%) according to municipality of both men and women from 2002 to 2004. **c)** Average detection rate of lung cancer (1/100,000) according to municipality in both men and women from 2002 to 2004.

しこの問題に関しては，厚生労働省のがん検診の事業評価に関する検討会報告書[1]において，事業評価に指標値・基準値が定められており，これを用いることで一定の評価が可能となっている．

次に部外者にとっての理解の困難さ，わかりにくさという点である．『精度がよい』『精度が悪い』といった言葉をいくら用いても，集計表のままでは理解が困難である．住民が自分の市町村での検診を受けるべきか，人間ドックを受けるべきか判断しようと思っても，集計表しか入手できない場合，解釈は無理である．グラフ化し，全国や府県の平均との比較により，自市町村の状況が誰にも容易に把握が可能となる．ただしグラフだけでは位置関係がわかるものの，要精検率などの言葉の説明も併せて行う必要がある．大阪府の現状の HP では用語の説明が

なく，課題となっている．

法的面での整備は，検診機関を評価する際に，問題になってくる．医療機関は医療法第25条に基づき保健所の立ち入り検査を受けている．また血液検査や細胞診を行う臨床衛生検査所は，臨床検査技師等に関する法律第20条に基づき，同様の検査を受けている．しかし検診機関については，立ち入り検査を行うことに対する法的根拠はない．肺がん検診については，比較読影・二重読影が必須とされるものの，正しく行われているか否かを知る方法はないのである．大阪府では府・市町村の精度管理指標を公開しているものの，検診機関に関しては，まだ公開をしていない．法的整備がないため，公開にあたっては，検診機関自体の同意が必要であり，まだ実現にいたっていない．

次に，公開にあたっての，技術的な側面と社会的な側面について議論を展開する．

大阪府は肺がん多発地帯として，肺がん対策が長らく課題となっていた．老人保健法開始前から先駆的に一部の市町村では肺がん検診が行われており，1983年からは順次全市町村に行き渡った．当時組織された成人病管理指導協議会の肺がん部会は，日本肺癌学会の重鎮数名をメンバーとし，設立当初から精度管理の重要性について議論してきた．しかし地区医師会との衝突を避けるという当時の府担当者の姿勢から，なかなか実効性のある対策を行うことはできなかった．特に1999年度からのがん検診費用の一般財源化に伴い，国と都道府県からの検診費用の負担もなくなり，市町村にとっては国や都道府県は『金も出さないで文句だけはつける』という立場になってしまい，市町村に対しての指導性を行使しづらい状況になってしまった．年1回の協議会と報告書という閉鎖的なものでは，この状況を打破することはできなかった．宮城県での，精度管理指標の把握率を市町村名を開示して公開する先駆的な取り組み[2]は，予算を要さず，HPという媒体を通じた方法であり，画期的な方法であると考えられた．しかし，それを導入するにしても市町村を『さらしもの』にしてよいのか？　という意見があり，必ずしも容易に話しが進んだ訳ではない．今回大阪府での実施にあたっては，議会の協力があったことが強い後押しになっている．特にロビー活動をした訳ではないが，がん多発地帯という悪名返上という希望に関しては府議会と同じ思いを共有していたのであろう．公開化に伴う市町村からのクレームはなかった．公開化されたことは，新聞の全国紙にも掲載されたが，必ずしも市町村の担当職員がすべてそのことを知っている訳でもなかった．HPへの公開化は，市町村の検診担当者の緊張感を呼び起こすきっかけになるかもしれないが，それに合わせた行動も必要である．現在肺がん部会では，がん発見率が極端に悪い市町村に対しては，府の担当職員による聞き取り調査を行い，改善を図るようにしている．また胃がん部会では精検受診率の低い市町村の首長に対して，部会長名で改善依頼を書面で発行している．HP上への成績の公開は，方法としては容易な方法であるが，それだけで精度管理が向上する訳ではなく，直接意見を言い指導することが欠かせない．ただし府県の担当職員が市町村に意見を言うといっても，どこが問題でどうしたらいいのか？　という技術的な側面については，専門的知識を持たない事務職員にとっては難しい．専門的知識を持っている協議会委員が分析し対策を立て，府県の担当職員がそれに沿って市町村と交渉するという役割分担が必要である．

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THE ANNALS OF THORACIC SURGERY

Sublobar Resection Provides an Equivalent Survival After Lobectomy in Elderly Patients With Early Lung Cancer

Jiro Okami, Yuri Ito, Masahiko Higashiyama, Tomio Nakayama, Toshiteru Tokunaga, Jun Maeda and Ken Kodama

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Sublobar Resection Provides an Equivalent Survival After Lobectomy in Elderly Patients With Early Lung Cancer

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Background. Sublobar resection is indicated for early-stage non-small cell lung cancer in patients with a perioperative risk associated with impaired medical conditions. This study was conducted to investigate the clinical impact of this procedure in the elderly.

Methods. The patients who underwent complete resection for stage IA non-small cell lung cancer from 1990 and 2007 were enrolled (n = 764). Two age groups were defined as elderly (≥75 years) and younger (<75 years) patients. The 5-year survival, recurrence, and postoperative complications after sublobar resection were compared with those after standard lobectomy according to age group.

Results. There were 133 elderly patients (79 standard lobectomies and 54 sublobar resections) and 631 younger patients (539 standard lobectomies and 92 sublobar resections). While the 5-year survival after sublobar resection was significantly inferior to that after standard lobectomy in the younger group (64.0% and 90.9%, respectively, $p < 0.0001$), however, no substantial difference was observed in the elderly (67.6% and 74.3%, $p = 0.92$). Locoregional recurrence rates were higher in patients after sublobar resection than those after standard lobectomy in both the elderly (11.1% vs 1.3%) and the younger (12.0% vs 1.5%) groups. No significant difference in postoperative complications was observed between the types of surgery in the elderly.

Conclusions. Sublobar resection for stage IA is considered to be an appropriate treatment in the elderly patients as this procedure provides an equivalent long-term outcome in comparison with lobectomy. A larger scale study with matching patients is necessary to confirm the noninferiority of sublobar resection in comparison with standard lobectomy in this population.

(Ann Thorac Surg 2010;90:1651–7)

Lung cancer is the leading cause of cancer-related deaths in many countries and patients older than 80 years account for 14% of all lung cancers [1, 2]. The number of elderly lung cancer patients is increasing rapidly worldwide. Comorbid illness and adverse medical conditions due to aging is a significant concern to treat elderly patients with lung cancer [3]. Lobectomy is the current standard treatment for early-stage non-small cell lung cancer (NSCLC) in the general population. Sublobar resection such as wedge resection and segmentectomy could be indicated in patients with stage I NSCLC, who may tolerate operative intervention but not a lobar or greater lung resection because of comorbid disease or decreased cardiopulmonary function [4]. When treating elderly patients, decisions regarding the treatment strategy, lobectomy, or sublobar resection, must therefore carefully balance the risks of postsurgical morbidity and mortality with those affecting cancer recurrence and long-term survival.

This study was conducted to investigate the clinical impact of sublobar resection in the elderly patients in comparison with their younger counterparts. The short-term and long-term outcomes after sublobar resection for stage IA NSCLC were compared with those after standard lobectomy according to the age group.

Patients and Methods

Patients

This study conducted a retrospective review of 984 patients who underwent complete resection for stage IA NSCLC at the Osaka Medical Center for Cancer and Cardiovascular Diseases from January 1991 to December 2007. The ethics committee gave its approval for the publication of this retrospective study with a waiver of informed consent (N0.1003175124) from the individual patients. The institutional prospective database of the general thoracic department included clinicopathologic variables and the postoperative clinical course. The pri-

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mary variables were gender, age, smoking status, preoperative treatment, comorbidity, surgical procedure, curability, diameter of surgical tumor specimen, histology, and pathologic (p) stage. The outcomes included postoperative complications, type of recurrence, and survival time. The type of surgery was categorized into two groups according to the extent of the pulmonary resection; standard surgery including a lobar or greater lung resection and sublobar resection such as segmentectomy and wedge resection. Any patients undergoing sublobar resections with a radical intent for the treatment of small-sized (2 cm or smaller) noninvasive carcinoma (n = 220) were excluded from the study. Definition of radical intent sublobar resection was described in detail in the previous report [5]. Briefly, the indications for radical intent sublobar resection were determined according to the diameter of the nodule and the percentage of ground-glass opacity on high-resolution computed tomographic (CT) scans. Finally, 618 patients who had standard surgery and 146 patients who underwent sublobar resection were enrolled in the study. Two age groups were defined as elderly (≥75 years) and younger (<75 years) patients.

Preoperative and Intraoperative Evaluation and Staging

The preoperative evaluation included a detailed clinical history and physical examination, chest radiography, chest and upper abdominal CT scans, brain magnetic resonance imaging, and bone scintigraphy or fluorodeoxyglucose-positron emission tomography scan for staging and assessment of respectability. All patients were staged intraoperatively and pathologically according to the sixth TNM (tumor-nodes-metastasis) classification at the time of surgery, and the TNM descriptions were converted to the seventh edition which has been recently updated [6]. Hilar and (or) mediastinal lymph nodes were sampled or systematically dissected during lobectomy or segmentectomy to evaluate for the possibility of occult nodal metastases. On the other hand, only swollen nodes were sampled in the patients who underwent wedge resection. A lavage cytologic examination was routinely used to assess the resection margins for tumor presence intraoperatively, as previously reported [7].

Reasons for Selecting Sublobar Resection and Postoperative Complications

Comorbid diseases and postoperative complications were diagnosed by laboratory, radiologic, and physiologic examinations. The reasons for selecting sublobar resection were defined as the following: insufficient pulmonary function or chronic lung diseases (abnormal spirometry test and [or] apparent interstitial shadow or emphysema detected by chest CT); insufficient cardiac function or cardiovascular diseases; previous lung surgery (greater than lobectomy) or active multiple lung cancer; cancer history; and diabetes mellitus. Multiple reasons were allowed. Complications were defined as the following: life-threatening complications which required any kind of emergent interventional treatment, or transfer to an intensive care unit; major complications were those that were potentially life threatening but did not require emergency intervention; and minor complications included those that required therapy and a prolonged hospital stay.

Recurrence of the Disease and Survival

Recurrence was diagnosed by daily clinical practice and defined as locoregional if it occurred within the same lobe, the mediastinal lymph nodes, or the hilum. All other types of recurrence were categorized as distant recurrence. The survival time was measured from the date of surgery to the date of the most recent follow-up examination or the date of death. The patients lost to the follow-up within ten years after surgery were censored at the date of last contact with the institution.

Statistical Analysis

The χ^2 test or Fisher exact test was used to compare the frequencies of categoric measures. Survival was calculated by the Kaplan-Meier method and differences in survival were assessed by a log-rank analysis. To adjust the effect of death due to other causes and to control the difference in the age and gender distribution between the sublobar resection group and the standard surgery, we calculated the relative survival and performed an age stratified analysis. The relative survival was estimated using the maximum-likelihood approach for individual data with the publicly available STATA program *strel* (StataCorp, College Station, TX) [8, 9]. The relative survival was the ratio of the observed survival rate in the patient group and the expected survival rate derived from the population life tables after matching for the age, calendar year, and sex. It can be interpreted as the survival from cancer after adjustment for other causes of deaths. A multivariate analysis for prognostic factors was performed using the Cox proportional hazard regression model. The p values less than 0.05 were considered to be statistically significant.

Results

Patient Characteristics

Table 1 summarizes the patient characteristics from the age groups. The tumor histology was as follows: adenocarcinoma in 637 patients; squamous cell carcinoma in 105; large cell carcinoma in 11; adenosquamous carcinoma in 8; and 3 pleomorphic or sarcomatoid carcinoma. The standard surgery group in the total cohort included 2 pneumonectomies, 12 bilobectomies, and 604 lobectomies, while the sublobar resection group included 90 segmentectomies and 56 wedge resections. There were more males ($p = 0.0189$), more squamous cell carcinomas ($p = 0.001$), and more ex-smokers or current smokers ($p < 0.0001$) in comparison with those in the standard lobectomy group. The histology and smoking status were significantly different between the types of surgery in the elderly patients (≥75 years of age). All of the patients had macroscopically negative surgical margin. Operative mortalities, which included deaths within the first 30

Table 1. Patients' Characteristics From the Overall Cohort and Each Age Group

Characteristic	Younger (<75 Years)			Elderly (≥75 Years)		
	Standard (n = 539)	Sublobar (n = 92)	*p* Value	Standard (n = 79)	Sublobar (n = 54)	*p* Value
Age (years)						
Median (mean)	64	68		77	78	
Range	35–74	38–74	<0.0001	75–87	75–84	0.2080
Gender						
Male	258	72	0.0189	45	39	0.1074
Female	281	20		34	15	
T stage						
T1a (≤20 mm)	198	46	0.1885	25	22	0.4976
T1b (>20 mm)	341	46		54	32	
Histology						
Adenocarcinoma	468	67	0.0010	66	36	0.0400
Squamous cell carcinoma	59	19		10	17	
Others	12	6		3	1	
Surgery						
Pneumonectomy	2	0	NA	0	0	NA
Lobectomy	537	0		82	0	
Segmentectomy	0	57		0	33	
Wedge	0	35		0	21	
Smoking status						
Ex- or current smoker	256	65	<0.0001	44	40	0.0481

NA = not applicable.

days after surgery or during the same hospitalization, were not recorded in this study.

Reasons for Selecting Sublobar Resection

The reasons for selecting sublobar resection are listed in Table 2. Insufficient pulmonary function or chronic lung disease was the most common and insufficient cardiac function or cardiovascular disease was the second. All of the patients with cancer history were examined thoroughly before pulmonary resection to confirm that they had no active recurrence or metastatic lesion other than primary lung cancer.

Survival Analyses

The 5-year survival rates were 84.6% for the overall cohort, 89.3% for the standard surgery, and 65.2% for the sublobar resection. The long-term survival after sublobar resection was significantly inferior to that after the standard surgery ($p = 0.0015$, Fig 1A). A multivariate analysis showed advanced age, sublobar resection, and nonadenocarcinoma to be independent significant unfavorable factors for the overall survival (Table 3). We further calculated the relative survival and performed an age-stratified analysis in each age group between the types of surgery. The 5-year relative survival rates of the younger patients were 90.9% (95% confidence interval [CI], 87.7% to 93.3%) for the standard surgery group and 64.0% (95% CI, 51.9% to 73.8%) for the sublobar resection group (Fig 1B). On the other hand, the difference between the types of surgery disappeared in the elderly patients (Fig 1C). The 5-year relative survival rates of the elderly patients were 74.3% (95% CI, 60.8% to 83.7%) for the standard surgery and 67.6% (95% CI, 51.7% to 79.3%) for the sublobar resection. To examine the survival effect between the types of surgery according to age group, we divided the patients into the following four groups: (I) younger patients who underwent standard lobectomy; (II) younger patients who underwent sublobar resection; (III) elderly patients who underwent lobectomy; and (IV) elderly patients who underwent sublobar resection. Thereafter, we calculated the hazard ratios for death of each patient group based on a multivariate Cox proportional model. Group I was used as a control group. As shown in Figure 2, while the hazard ratio of group II was 2.83 (95% CI, 1.84 to 4.35) as compared with the control group, the hazard ratio of group IV (2.64; 95% CI, 1.61 to 4.31) was similar to that of group III (2.97; 95%CI, 1.79 to 4.95).

Table 2. Reasons for Selecting Sublobar Resections

Reasons	Younger (<75 years) (n = 92) (%)	Elderly (≥75 years) (n = 54) (%)
Insufficient pulmonary function or chronic lung diseases	50 (54.3)	25 (46.3)
Insufficient cardiac function or cardiovascular diseases	22 (23.9)	20 (37.0)
Previous lung surgery or multiple lung cancer	14 (15.2)	7 (13.0)
Cancer history	9 (9.8)	3 (5.5)
Diabetes mellitus	4 (4.3)	6 (11.1)
Other	4 (4.3)	3 (5.5)

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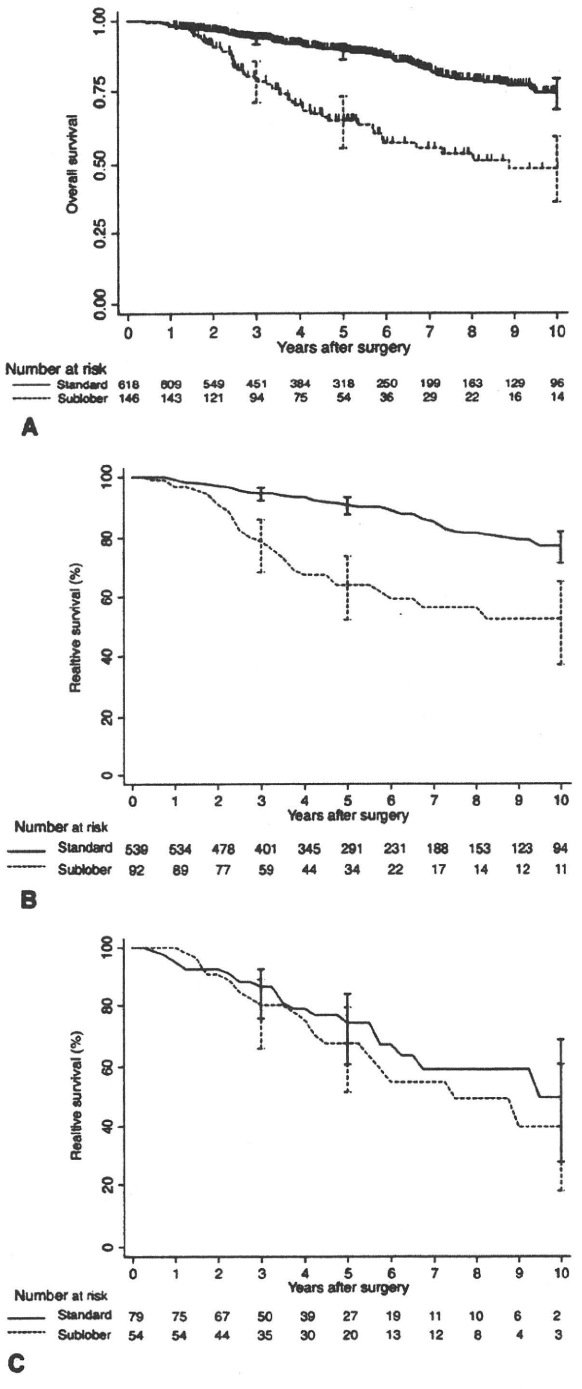

Fig 1. Postoperative survival curves according to the types of surgery (standard surgery or sublobar resection) with 95% confidence intervals at 3, 5, and 10 years after surgery. (A) The overall survival of the overall cohort (all ages); (B) the relative survival of the younger patients (<75 years); and (C) the relative survival of the elderly patients (≥75 years).

Table 3. Multivariate Analysis of Survival: Cox Proportional Hazard Model

Variable	HR	95% CI	*p* Value
Age	1.045	1.023–1.068	<0.0001
Operative procedure			
Standard surgery	ref		
Sublobar resection	1.835	1.261–2.670	0.0015
Histology			
Adenocarcinoma	ref		
Nonadenocarcinoma	1.739	1.160–2.604	0.0074
Gender			
Female	ref		
Male	1.324	0.786–2.231	0.2919
T stage			
T1a	ref		
T1b	1.018	0.716–1.447	0.9196
Smoking status			
Nonsmoker	ref		
Ex- or current smoker	1.178	0.687–2.020	0.8490

CI = confidence interval; HR = hazard ratio.

Postoperative Complications in the Elderly Patients

Thirty-five of the elderly patients (26.3%) experienced postoperative complications (Table 4). Life-threatening complications included two cases of acute myocardial infarction and one drug-induced anaphylactic shock. The occurrence of a life-threatening or a major complication was not associated with the types of surgery ($p = 0.3146$).

Recurrence of the Disease

Any recurrences of the disease during the follow-up period are summarized in Table 5. The percentages of distant metastasis ranged from 11.3% to 13.0% regardless the types of surgery or the patients' age. On the other hand, the local recurrence in the overall cohort apparently occurred more commonly in the patients who had

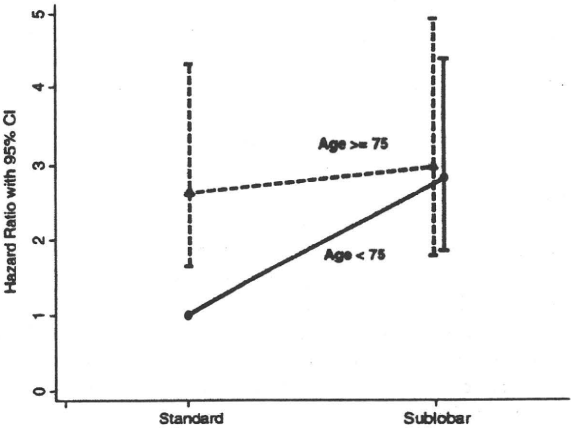

Fig 2. Comparison of the hazard ratio between standard surgery and sublobar resection in younger patients (solid line) and elderly patients (dashed line). (CI = confidence interval.)

Table 4. Postoperative Complications in the Elderly Patients

Complications	Standard (n = 79)	Sublobar (n = 54)
Life threatening (%)	1 (1.3)	2 (3.7)
Major (%)	4 (5.1)	5 (9.3)
Minor (%)	15 (19.0)	8 (14.8)

sublobar resection than in patients who had standard surgery (11.6% and 1.5%, respectively).

Comment

Removing the entire lobe, which contains the primary tumor, provides the highest probability for a complete resection of the disease including tumor cells spreading into adjacent pulmonary parenchyma and occult metastasis in the regional lymph nodes. However, surgeons often hesitate to recommend lobectomy for patients under comorbid conditions or with poor pulmonary function. Instead, sublobar resection such as wedge resection and segmentectomy are often offered to those patients in daily clinical practice to reduce surgical stress and to preserve more pulmonary function. This study revealed that sublobar resection provided an equivalent long-term outcome to that of lobectomy in the elderly patients.

The difference in the survival after lobectomy and sublobar resection has been debated even after one randomized trial demonstrated that sublobar resection for stage IA had a higher local recurrence rate and a shorter survival [10]. Nationwide retrospective studies in Japan and the US identified extent of surgical resection as a significant prognostic factor after curative resection for stage IA [11, 12]. These findings support the fact that lobectomy is the gold standard for stage IA lung cancer. On the other hand, studies focusing on elderly patients with stage IA revealed that anatomic segmentectomy was associated with reduced surgical risks and comparable oncologic efficacy [13]. Furthermore, according to the data from The National Cancer Registry in the United States, the statistical difference between survival curves of lobectomies and limited resections for stage I or II disappeared at 71 years of age [14]. In addition, the Japanese Joint Committee of Lung Cancer Registry also found no significant difference in the survival after lobectomy or sublobar resection for c-stage I of octogenarian patients [15].

Previously, several reports have demonstrated that sublobar resection was not inferior to standard lobectomy regarding the prognosis of patients with small-sized NSCLC [16, 17]. When comparing the outcomes of sublobar resection with that of lobectomy, it is important to mention the peripheral nodules, which are identified as a shadow containing ground-glass opacity by CT scanning. Most of such nodules are histologically diagnosed as early adenocarcinoma or minimally or noninvasive bronchioloalveolar carcinoma. The long-term result of this disease is excellent and the 5-year survival rate reaches to more than 96% even after sublobar resection [18, 19]; in contrast, the 5-year survival of NSCLC at stage IA is reported to be 83.9% [20]. Therefore, in order to elucidate the outcomes after sublobar resection in compromised patients, it is necessary to exclude the patients who underwent wedge resection or segmentectomy for this distinct subset of early-stage lung cancer. Otherwise, the outcome of the sublobar resection group might be spuriously superior to that of patients who underwent the same treatment due to their impaired medical condition. We have established institutional criteria based on the CT findings to indicate a sublobar resection with a radical intent for peripheral noninvasive carcinoma [5]. These criteria defined the patients who underwent sublobar resection due to the patients' medical and (or) physiologic condition. Therefore, the results of sublobar resection shown in this study were solely derived from patients who demonstrated medically impaired conditions.

The long-term results of p-stage IA based on the new staging system in the present study, 89.0% after the standard surgery and 65.3% after sublobar resection without any operative mortality, were satisfactory. As previously reported [12], age proved to be an independent predictor of survival in patients with stage IA. The patients were stratified by age group to eliminate an effect of the different distribution of the patients' age between the standard surgery and the sublobar resection. Furthermore, to consider the effect of background mortality, the relative survival was calculated and the prognosis was compared adequately between the types of surgery. One of the important findings in this study is that sublobar resection was a strong independent predictor for shortened survival in the overall cohort, but the types of surgery, standard or sublobar resection, did not affect the survival in the elderly patients. Multivariate analysis revealed that the unfavorable effect of sublobar resection on survival was apparent in the younger patients whereas the hazard ratio of sublobar resection was similar to that of standard lobectomy among elderly patients.

Following the equivalent survival in the elderly, postoperative complications were also studied. The occurrence of complications after sublobar resection did not increase in comparison with that after standard lobectomy even though the patients in the sublobar group were compromised. The reduced surgical intervention using lesser extent of pulmonary resection may contribute to this favorable result. The types of recurrence were

Table 5. Recurrence of the Disease From the Overall Cohort and Each Age Group

	Younger (<75 years)		Elderly (≤75 years)	
Type of recurrence	Standard (n = 539)	Sublobar (n = 92)	Standard (n = 79)	Sublobar (n = 54)
Locoregional (%)	8 (1.5)	11 (12.0)	1 (1.3)	6 (11.1)
Distant (%)	61 (11.3)	12 (13.0)	10 (12.7)	7 (13.0)

associated with the types of surgery but not with the patients' age group. It should be noted that the rate of locoregional recurrence was much higher in the patients after sublobar resection than in those after standard surgery and that the rate of distant metastasis did not increase in the patients who underwent sublobar resection.

The strengths of this study are that a single institutional study provided complete clinical and pathologic information, homogeneous treatment strategy, and well-controlled surgical quality. There are limitations that need to be acknowledged. The period of patient accrual was relatively long. The patients who underwent surgery from 1991 to 2007 were enrolled into the study, although the treatment strategy for stage IA did not change during this period. In addition, the number of elderly patients was smaller than that of the younger population. Secondly, sublobar resection cannot provide as much information for a final staging as lobectomy. Third, we should recognize that such retrospective analyses were inherently affected by predilections for several patients' factors between the types of surgery and the selection bias associated with surgical procedure chosen by thoracic surgeons in this study. There were more male patients, more nonadenocarcinoma, and more smokers in the sublobar group. These are known to be unfavorable prognostic factors in the patients with stage IA NSCLC. It should be noted that survival after sublobar resection was equivalent to that after lobectomy in the elderly.

In conclusion, sublobar resection in the elderly provides a long-term outcome which is equivalent to that obtained after standard lobectomy. This finding suggests that this procedure is considered to be an appropriate treatment strategy for elderly patients with stage IA NSCLC. A larger scale study with patients matched for the principal factors is necessary, however, to confirm the noninferiority of sublobar resection to standard lobectomy in this population.

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INVITED COMMENTARY

Okami and colleagues [1] have presented a retrospective review on the survival of elderly patients (age > 75) with stage 1A nonsmall cell lung cancer treated with a sublobar resection compared with elderly patients treated with a standard lobectomy between 1999 and 2007. There were 133 elderly patients in the study with 79 patients treated

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Sublobar Resection Provides an Equivalent Survival After Lobectomy in Elderly Patients With Early Lung Cancer

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Review Article

The Japanese Guideline for Cervical Cancer Screening

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Cervical cancer is the 11th leading cause of death from cancer for females in Japan. In 2005, there were 2486 deaths from cervical cancer, accounting for 1.8% of the total number of cancer deaths in Japan. Cervical cancer screening using conventional cytology has been conducted worldwide. The guideline for cervical cancer screening was developed based on the established method. The efficacies of conventional and liquid-based cytology, human papillomavirus testing alone and two combination methods were evaluated. On the basis of the balance of the benefits and harms, recommendations for population-based and opportunistic screening were formulated. Five methods of cervical cancer screening were evaluated. On the basis of the analytic framework involving key questions, 3450 articles published from January 1985 to October 2007 were selected using MEDLINE and other methods. After the systematic literature review, 66 articles were confirmed. The results of 33 studies were consistent, and the evidence was sufficient to evaluate the effect of conventional cytology screening. The accuracy of liquid-based cytology was almost equal to that of conventional cytology. Although human papillomavirus testing and combination methods showed high sensitivity, no study has evaluated the reduction in mortality from cervical cancer. Except for the possibility of overdiagnosis, no serious adverse effects of cervical cancer screening were found. Cervical cancer screening using conventional and liquid-based cytology is recommended for population-based and opportunistic screening due to sufficient evidence. Cervical cancer screening using either human papillomavirus testing alone or two combination methods is not recommended for population-based screening due to insufficient evidence.

Key words: cervical cancer – cancer screening – guideline – recommendation – conventional cytology – liquid-based cytology – HPV testing

INTRODUCTION

Cervical cancer is the 11th leading cause of death from cancer for females in Japan. In 2008, there were 2486 deaths from cervical cancer, accounting for 1.8% of the total number of cancer deaths in Japan (1). The incidence of cervical cancer among all age groups decreased gradually until 1990 and then flattened. For two decades until 2002, although the incidence among women over age 40 years

decreased, the incidence among women in the 20–39 years age group gradually increased. On the other hand, the mortality of the 40–59 years age group increased, with a peak in the 55–59 years age group in 2006.

In 2001, the Research Group for Cancer Screening Guidelines funded by the Ministry of Health and Welfare of Japan recommended the following six cancer screening programs (the Hisamichi reports) (2): gastrofluorography for gastric cancer; fecal occult blood testing for colorectal cancer; a combination of chest radiography and sputum cytology (added for current smokers only) for lung cancer; Pap smear for cervical cancer; a combination of physical examination and mammography for breast cancer and hepatitis virus markers for hepatocellular carcinoma. These guidelines did not recommend cervical cancer screening using human papillomavirus (HPV) testing because of insufficient evidence. However, liquid-based cytology was not included in that evaluation.

Since the publication of the previous guidelines, new studies dealing with HPV testing alone and in combination have been reported worldwide. Meanwhile, a new research group established a standardized method for developing the Japanese Guidelines for Cancer Screening (3). On the basis of this methodology, the effects of conventional, liquid-based cytology and HPV testing for cervical cancer screening were evaluated, and a new guideline was developed.

PATIENTS AND METHODS

The target audiences for the cervical cancer screening guideline include the public health professionals working in cancer screening programs, providers of cancer screening programs and policy makers. The members of the guideline development group for cervical cancer screening (Japanese Research Group for Development of Cervical Cancer Screening Guidelines) were selected from various specialties. The cervical cancer screening guideline was developed using the standardized method (3).

Target Methods

The efficacies of conventional and liquid-based cytology, HPV testing alone and two combination methods were evaluated. Conventional cytology is the traditional method of collecting cells from the surface of the uterine cervix and analyzing the smeared cells directly using a microscope. Liquid-based cytology is a new technique for transferring the cellular material to a microscope slide. The sampling device carrying the material is immersed in a container with a special liquid transport medium. Most clinical investigations of HPV testing have used the Hybrid Capture (HC) system. The HC system is a nucleic acid hybridization assay with signal amplification for the qualitative detection of DNA of high-risk, cancer-associated HPV types in cervical specimens.

Analytic Framework

The target population for cervical cancer screening was defined to be asymptomatic females with an average risk of cervical cancer. To select appropriate evidence, an analytic framework for cervical cancer screening was developed (Fig. 1). For each stage of the analytic framework, key

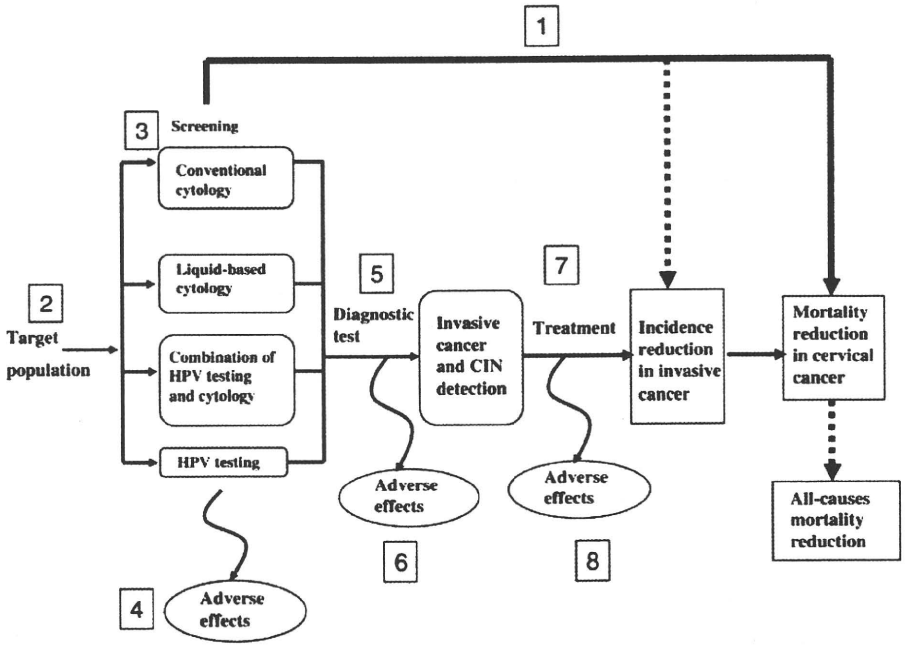

Figure 1. Analytic framework and key questions for cervical cancer screening. The numbers in the analytic framework refer to the key questions, which are listed in Appendix 2.

questions based on the PICO (population, intervention, comparison and outcome) format were prepared. Direct evidence was defined as evidence provided by a study that evaluated the effect of cancer screening for reducing cervical cancer incidence and mortality (Fig. 1, arrow 1). However, to determine the level of evidence appropriately, the primary outcomes of mortality from cervical cancer and incidence of invasive cancer were differentiated. Other studies that provided indirect evidence were selected based on key questions related to other stages of the analytic framework (Fig. 1, arrows 2–8).

Systematic Literature Review

A systematic literature review was conducted by the members of the review committees for cervical cancer screening. A search of the literature published from January 1985 to October 2007 was performed using MEDLINE, EMBASE and the Japanese Medical Research Database (Igaku-chuo-zasshi). Key journals were searched manually, including the Journal of the Japanese Association for Obstetrics and Gynecology and the Journal of the Japanese Association for Clinical Cytology. Further references were obtained through the IARC handbook (International Agency for Research on Cancer) (4), previous guidelines (2) dealing with the evaluation of cervical cancer screening were checked and relevant articles were included. Additional references recommended by the Review Committee were identified and included as needed. If the result from a branch of a large-scale randomized-control trial (RCT) was published during guideline development, the study was included. To select appropriate evidence, a systematic review of the retrieved articles was conducted using the checklist according to the study design (3).

Translation into Recommendations

Considering the balance of the benefits and harms, five grades of recommendations were determined for population-based and opportunistic screening (3). The recommendations were assessed in conjunction with the board members of the Japanese Research Group for Cancer Screening Guidelines. The body of evidence for each screening method was summarized in an evidence table based on the analytic framework's key questions. The benefit of each screening modality was determined based on the level of evidence (3). The evidence was divided into eight levels based on study design, quality and consistency. The harms, including overdiagnosis and LEEP (loop electrosurgical excision procedure) with conization as complications of diagnostic tests and treatment, were assessed.

Since they are supported by sufficient evidence, both Grade A and B recommendations could be conducted as both population-based and opportunistic screening programs. A Grade A recommendation is supported by RCTs, and a Grade B recommendation is supported by observational studies. However, a method with a Grade D recommendation should not be used for either population-based or opportunistic screening programs. A Grade C recommendation implies that the method should not be used for population-based screening. However, a Grade C recommendation implies that the method could be used in clinical settings if both adequate risk management and informed consent with respect to the harms were assured. Screening methods for which there is insufficient evidence are graded as I; they are not recommended for population-based screening or as routine screening methods in clinical settings, although the decision to undergo screening could be made at the individual level based on proper information provided by health professionals in clinical settings.

Formulating the Guideline

A draft guideline was written and released on the Promoting Evidence-based Cancer Screening website (http://canscreen.ncc.go.jp/). To improve and confirm the guideline, two types of consultation were conducted. First, the guideline was reviewed in draft form by nine independent referees from two expert groups: an expert group for cervical cancer and another specialty group. In addition, major issues identified during review of the draft were discussed at the guideline forum that everyone could attend. Taking into account the comments received from external reviewers and the guideline forum, the appropriateness of the recommendation and its language was again discussed, and the guideline was refined. After the consultations were completed, the guideline was published and posted on the Promoting Evidence-based Cancer Screening website.

FINDINGS

Systematic Literature Review

On the basis of the literature search using MEDLINE and other databases, 3450 articles published from January 1985 to October 2007 were identified. The abstracts were reviewed, and 161 articles were selected for the full text review. After the full text review, which included a new paper from a Swedish study that was published after the above literature search, 33 articles were confirmed as providing direct evidence dealing with the reduction in incidence and mortality of cervical cancer by screening, and 33 articles were confirmed as providing indirect evidence (Table 1).

Level of Evidence

Conventional Cytology (Level of Evidence: 2++)

There is no evidence to evaluate the reduction in mortality from cervical cancer based on RCTs. Three cohort studies, 11 case–control studies and 21 ecological studies dealing with conventional cytology were identified. Since the results

Table 1. Evidence for cervical cancer screening

Methods	Level of evidence	Total number of references	Direct evidence (AF1): reduction in mortality from cervical cancer or incidence of invasive cancer (numbers of references)			Indirect evidence			
			Cohort study	Case–control study	Time series and ecological studies	AF3 (test accuracy)	AF4 (overdiagnosis)	AF7 (Survival)	AF7-8 (LEEP)
Conventional cytology	2++	55	3	11	21[a]	8	1	1	10
Liquid-based cytology	2+	5	0	0	0	5[b]	–	–	–
HPV testing (alone)	2–	17	0	0	0	13[c]	4[d]	–	–
(i) Combination of HPV testing and cytology and (ii) HPV testing with cytology triage	2–	8	0	0	0	8[c]	–	–	–

AF, analytic framework (see Fig. 1); HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure.
[a]Reference including duplication of one reference for cohort study and one for case–control study.
[b]Reference including duplication of three references for conventional cytology.
[c]Reference including duplication of two references for conventional cytology.
[d]Reference including duplication of four references for test accuracy studies of HPV testing alone.
[e]Reference including duplication of eight references for HPV testing alone.

of these studies were consistent, the evidence was sufficient to evaluate the effect of conventional cytology screening.

Cohort Studies. The outcome of the Danish and Japanese studies was mortality from cervical cancer and that of the Italian study was incidence of invasive cancer of the cervix (Table 2) (5–7). In the Japanese study, the cohort from 45 local municipalities, involving a total of 53 003 subjects, was followed from 1988 to 2003 (6). On the basis of the screening history within the previous year of the questionnaire survey at the time of enrollment, the subjects were divided into screened and unscreened groups. However, during the follow-up periods, participation in screening was unclear in both groups. Mortality from cervical cancer in the screened group was reduced 70% compared with that in the unscreened group (hazard ratio 0.30, 95% CI: 0.12–0.74). The rate of reduction was greater for cervical cancer mortality than for deaths other than cervical cancer deaths (hazard ratio 0.73, 95% CI: 0.68–0.78).

Case–control Studies. The outcome of the Scottish and Japanese studies was mortality from cervical cancer, whereas that of other studies was incidence of invasive cancer (8–18). The details of the studies are shown in Table 3. In the Japanese study, which had a small sample size, a 78% reduction in mortality from cervical cancer was shown, but this was not significant (odds ratio = 0.22, 95% CI: 0.33–1.95) (9). Although the outcome was different, the incidence of invasive cancer was reduced by 84% in other Japanese studies (odds ratio = 0.16, 95% CI: 0.090–0.278) (13). In a recent report from Australia, 96% of invasive cancer could be prevented in women with a regular screening history compared with women without a screening history (RR = 0.043, 95% CI: 0.033–0.057) (11).

Ecological Study. All studies reported reduced cervical cancer mortality by screening (5,8,19–37). The impact of the reduction was greater in the countries that conducted organized screening than in countries that did not. Although the target age group and screening interval differ among these countries, the incidence of invasive cancer was reduced by at least 80% (4). In the Japanese study, mortality from cervical cancer decreased by 63.5% in high-participation areas compared with a 33.3% reduction in low-participation areas (29).

The incidence of invasive cancer decreased with an accompanying mortality reduction in all studies. Although the incidence of cervical cancer has decreased in the 30 years and over age group, which is the target for the screening program in Miyagi Prefecture, that of the 20–29 years age group has gradually increased (31). Similar trends could be observed in several developed countries that conducted population-based screening.

Test Accuracy

Test accuracy studies for conventional cytology were conducted using diagnostic testing with colposcopy as the reference (Table 4) (38–41). In a Japanese study using low-grade

Table 2. Cohort studies for cervical cancer screening using conventional cytology

Authors	Research area	Reported year	Target age (years)	Control group	Numbers in target population		Follow-up	Outcome	
					Intervention group	Control group		Endpoint: mortality of invasive cancer	Endpoint: incidence of invasive cancer
Berget (5)	Denmark	1979	≥20	No participation	13 148	2109	1976–1975	Participation 3.8 (4 of 13 148); no participation 47.4 (8 of 2109)	Participation 425.9 (56 of 13 148); no participation 1232.8 (26 of 2109)
Aklimunnessa et al. (6)	Japan	2006	30–79	No participation	24 417	28 586	1988–2003	Hazard ratio 0.30, 95% CI: 0.12–0.74	–
Ronco et al. (7)	Italy	2005	25–64	No invitation; no participation	9972	9973	1992–1998	–	Invitation/no invitation RR 0.8 (95%CI: 0.59–1.09); participation/no participation RR 0.25 (95% CI: 0.13–0.50)

RR, relative risk; CI, confidence interval.

squamous intraepithelial lesion as the cut-off point, the sensitivity to detect cervical cancer was 94.7% (38). The result of the Italian study was similar results for 1-year follow-up based on the regional cancer registry. Although the finding of atypical squamous cells of undetermined significance was mostly used as a cut-off point, the target disease differed among studies. In a Canadian study, the sensitivity of conventional cytology was around 50% when CIN2 (cervical intraepithelial neoplasia) or worse was targeted (42). On the other hand, in a Swedish study, the sensitivity was maintained when either CIN2 or CIN3 was used for the threshold (43). The accuracy of conventional cytology differed among the studies because of different reference tests and different target groups (44,45). However, the sensitivity ranged from 50% to 80%, and the specificity ranged from 70% to 90%.

Survival Analysis

In the report from the Osaka cancer registry, the relative survival of patients with screening-detected cancer (30–54 years, 84.3%; and 55–64 years, 75.4%) was higher than that of symptomatic patents (30–54 years, 77.6%; and 55–64 years, 67.1%) (46).

Liquid-based Cytology (Level of Evidence: 2+)

No study using liquid-based cytology has evaluated the reduction in mortality from cervical cancer. Although there is no RCT evaluating conventional cytology, mortality reduction from cervical cancer has been evaluated by many observational studies conducted worldwide. Except for the method used to prepare the sample, liquid-based cytology is almost the same as conventional cytology. Thus, evidence for conventional cytology could be used for evaluation of liquid-based cytology. Since the sensitivity and specificity of liquid-based cytology are similar to those of conventional cytology, we concluded that the evidence for conventional cytology could be employed. Therefore, the evidence was sufficient to evaluate the effect of liquid-based cytology. However, since no study has compared the sensitivity and specificity of both methods in Japan, an evaluation study, including investigation of unsatisfactory samples of conventional cytology, is needed before introduction of population-based screening.

Test Accuracy

Five studies to investigate the accuracy of liquid-based cytology were selected (Table 4) (39,40,44,47,48). In an RCT compared with conventional cytology, the sensitivity to detect CIN2 or worse was 69.1% (95% CI: 55.2–80.9) for conventional cytology and 60.3% (95% CI: 47.4–71.9) for liquid-based cytology (39). On the other hand, the specificity was 94.5% (95% CI: 93.5–95.4) for conventional cytology and 94.1% (95% CI: 93.2–94.9) for liquid-based cytology. Neither the sensitivity nor the specificity was statistically different. In another RCT, the ratio of the detection rate for liquid-based cytology compared with that of conventional