{1,3,1×3}, {2,3,2×3}, {1,2,3}, {1,2,3,1×2,1×3,2×3} and {1,2,3,1×2,1×3,2×3,1×2×3}. For the conventional method, we employed only the overall F-test for the full model, {1,2,3,1×2,1×3,2×3,1×2×3}, for gene selection. For each procedure, we control the FWER. A null distribution of the maximum of statistic (the maximum R^2_{DA} for the proposed method and the F-statistic for the conventional method) was obtained from 500 permutations, which was referred to the observed value of statistic to obtain an adjusted P-value. For each of a selected set of regression coefficients, Table 1 summarizes empirical power for the informative gene obtained from 500 simulations at the significance level of 10% for the adjusted P-value. We first confirmed that the empirical FWER was almost equal to the nominal level (data not shown). The empirical power of the proposed method can be substantially greater than that of the conventional method when models other than the full model are correct for the informative gene. The conventional method outperformed the proposed method when the full model is correct for the informative gene. Although this could be explained by error in model selection, the power loss was relatively small in our simulation setting.

3.2 The bladder cancer example

Tumour-biopsy tissues were collected at diagnosis from 48 patients with bladder transitional cell carcinomas at the Department of Urology, Kyoto University Graduate School of Medicine between 1990 and 2003. Patients were selected on the basis of availability of tumour-biopsy samples, without regard to clinical information. Microarray experiments were performed for frozen tissues using a cDNA array that contains printings of approximately 30 000 oligonucleotides fabricated by Pacific Edge Biotechnology Limited in New Zealand. In each hybridization, fluorescent cDNA targets were prepared from a tumour mRNA sample and a reference mRNA sample contracted from a pool of cell lines of different cancers. Two replicated arrays made from the same sample of RNA (technical replicates) without reverse labelling or dye swap were averaged to improve precision of the estimate of the expression profile for a given RNA sample. After image analysis and spot filtering, the data were normalized by a locally weighted linear regression method. We excluded genes that had low variance of log ratio expressions across samples, because the observed variability for genes with low variance is more likely to be due to measurement noise than actual biological variability (e.g. Simon *et al.*, 2004). We selected six thousands genes with variance in the top 20th percentile.

As clinical phenotypes, cancer stage and grade from pathological reports were confirmed by a pathologist. We classified stage into two categories with distinct treatment modalities, superficial (≦pT1) and invasive tumours (>pT1), to understand the underlying biological difference related to therapeutics. Generally, superficial tumours are treated with transurethral surgery or intravesical instillation therapy, while invasive tumours are treated with radical cystectomy or systemic chemotherapy. Of 48 patients, we had 31 superficial and 17 invasive patients. We also classified grade into two categories, low grade (grade 1 or 2) and more malignant, high grade (grade 3). Of the 31 superficial tumours, 25 and 6 were low and high grade, respectively. Of the 17 invasive tumours, 5 and 12 were low and high grade, respectively.

Although several authors have been interested in genes differentially expressed between stage classes (e.g. Sanchez-Carbayo *et al.*, 2003; Modlich *et al.*, 2004), it would seem more likely that multiple factors are related to gene expression simultaneously. We assumed a multivariate linear regression model for each gene. For a single gene, let Y_i be the log-ratio of gene expression measurement for patient i ($i=1,\ldots,48$). Let stage_i be a binary variable that takes 1 if the stage of patient i is invasive and zero otherwise. Let grade_i be a binary variable that takes 1 if the grade of patient i is high and zero otherwise. We also consider an interaction term of stage and grade, $\text{stage}_i \times \text{grade}_i$. For log-transformed intensity ratios, we assume the following four candidate linear models for differential expression,

$$\text{M1: } \mu_i = \beta_0 + \beta_1(\text{stage}_i)$$
$$\text{M2: } \mu_i = \beta_0 + \beta_1(\text{grade}_i)$$
$$\text{M3: } \mu_i = \beta_0 + \beta_1(\text{stage}_i) + \beta_2(\text{grade}_i)$$
$$\text{M4: } \mu_i = \beta_0 + \beta_1(\text{stage}_i) + \beta_2(\text{grade}_i) + \beta_3(\text{stage}_i \times \text{grade}_i)$$

where $\mu_i = \mathrm{E}(Y_i)$ is the expected value or the mean value of the log-ratio for patient i and β_0, β_1, β_2 and β_3 are regression coefficients. The model M1 was to detect genes just related to stage like in previous studies. For simultaneous relation with stage and grade, M3 and M4 were assumed. Note that M4 is a

Table 1. Empirical power (%) and its standard error in parenthesis of the proposed method and the conventional method for each of a selected set of regression coefficients in differential model

Model for informative gene	Regression coefficients (β_1, β_2, β_3, β_{12}, β_{13}, β_{23}, β_{123})	Proposed method	Conventional method
{1}	(2, 0, 0, 0, 0, 0, 0)	95 (1.0)	83 (1.7)
{1, 2}	(1, 1, 0, 0, 0, 0, 0)	35 (2.1)	20 (1.8)
{1, 2, 1×2}	(−2, −2, 0, 2, 0, 0, 0)	79 (1.8)	61 (2.2)
{1, 2, 3}	(1, 1, 1, 0, 0, 0, 0)	69 (2.1)	56 (2.2)
{1, 2, 3, 1×2, 1×3, 2×3, 1×2×3}	(−2, −2, −2, 2, 2, 2, −2)	22 (1.9)	25 (1.9)

The proportion of correct model selection using the criterion based on R^2_{DA} in the proposed method ranged from 60% to 80% for the first four configurations and 46% for the fifth configuration for model {1, 2, 3, 1×2, 1×3, 2×3, 1×2×3}.

saturated model (four regression parameters for four combinations of binary classes, stage and grade). It covers any differential patterns other than additive effects of stage and grade. They include differential expressions between two classes based on the combination of stage and grade. For example, a differential expression between superficial cancer with low grade (the best type of cancer) and the others is obtained by introducing the constraint $\beta_1 = \beta_2 = -\beta_3$ ($\neq 0$) in M4, which may yield a linear model with a single interaction effect and no main effects. These differential patterns could be identified based on the estimates of parameter coefficients for genes for which M4 is selected as illustrated below.

Table 2 shows an estimate of FDR for each of several cut-off points for the maximum R^2_{DA} obtained by the multivariate permutation procedure with 2000 permutations. We selected the top 100 genes, so that the FDR was around 15%. Table 3 shows classification of 100 selected genes based on selected models and the sign of estimated regression coefficients in selected model. Note that, out of the top 100 genes, the same model was selected for 98 genes based on AIC, as expected by the equality of the criterion on R^2_{DA} with that on AIC as noted in Section 2. Seventeen genes were related to only stage via the model M1; 9 (8) had negative (positive) estimates of the regression coefficient β_1 for stage in M1. In other words, the 9 (8) genes were under-(over-) expressed for invasive cancer. Thirteen genes were related to only grade via the model M2; 10 (3) were under-(over-) expressed for high grade cancer. Interestingly, the rest 70 genes were related to both stage and grade; 39 genes via the model M3 without the interaction term of stage and grade and 31 genes via the model M4 with the interaction term. Of the 39 genes for which the model M3 was selected, negative values for both β_1 and β_2 (under-expression for invasive or high grade cancer) were suggested for 37 genes, while positive values for both β_1 and β_2 (over-expression for invasive or high grade tumours) for two genes. Of the 31 genes for which the model M4 was selected, 15 (16) genes had negative (positive) estimates for β_3, i.e. the interaction of stage and grade.

Figure 1 shows typical mean expression profiles for the selected genes with negative (Fig. 1A and 1C) or positive interaction (Fig. 1B and 1D). Figures 1A and 1B indicate differential expression between invasive cancer with high grade (the worst type) and the others, while Figures 1C and D indicate differential expression between superficial cancer with low grade (the best type) and the others. In general, selected genes for which under-expression was linked to more progressed cancer, i.e. invasive and/or high grade, involved putative tumour suppressor genes. A gene related to tumour protein *p53*, which is a well-known tumour suppressor, was related to grade via the model M2 and the estimate for β_1 (the regression coefficient for grade) was negative. *Glutathione peroxidase (GPX) 2*, which is a member of oxidoreductase and the destruction of it increased the genesis of bacteria-induced intestinal cancer (Chu *et al.*, 2004), was related to both stage and grade via the model M3 and the estimates for β_1 and β_2 (the regression coefficient for stage and grade, respectively) were negative. With respect to genes for which the model M4 was selected, putative tumour suppressor genes, *RNA binding motif protein 3 (RBM3)* (Sutherland *et al.*, 2005) in Figure 1A and *CD-81* (Koenig-Hoffmann *et al.*, 2005) in Figure 1D were under-expressed for the worst type of cancer (invasive and high grade) and for cancers other than the best type (superficial and low grade), respectively.

On the other hand, selected genes for which over-expression was linked to more progressed cancer are suggested to act like as oncogenes. *Amphiregulin* in Figure 1B acts as a protease of the extracellular matrix (ECM) with induction of extracellular matrix metalloproteinase (MMP) –2 and –9, and the expression level was associated with survival of bladder cancer patients (Menashi *et al.*, 2003; Thogersen *et al.*, 2001). Highly aggressive invasive cancers are characterized by their activity of inducing break down of cell– cell or cell– matrix adhesion, modulation of ECM proteolysis and induction of angiogenesis. A family of human endogenous retroviruses (HERVs), *HERV-H*, in Figure 1C was highly expressed in bladder cancer (Stauffer *et al.*, 2004). *Amphiregulin* in Figure 1B and *HERV-H* in Figure 1C were over-expressed for the worst type of cancer (invasive and high grade) and for cancers other than the best type (superficial and low grade), respectively.

Table 2. Estimates of FDR for various cut-offs for the maximum R^2_{DA}

Cut-off	Number of significant genes	Estimate of expected number of false positives	Estimate of FDR (%)
0.10	1351	470.8	34.8
0.20	288	47.3	16.4
0.25	99	14.7	14.8
0.30	37	4.5	12.2

Table 3. Sign of estimated regression coefficients in the selected models for the 100 significant genes

Model	Stage	Grade	Interaction	Number of genes	Total
M1	Negative	–	–	9	17
	Positive	–	–	8	
M2	–	Negative	–	10	13
	–	Positive	–	3	
M3	Negative	Negative	–	37	39
		Positive	–	0	
	Positive	Negative	–	0	
		Positive	–	2	
M4	Negative	Negative	Negative	1	31
			Positive	10	
		Positive	Negative	0	
			Positive	2	
	Positive	Negative	Negative	7	
			Positive	3	
		Positive	Negative	7	
			Positive	1	
Total					100

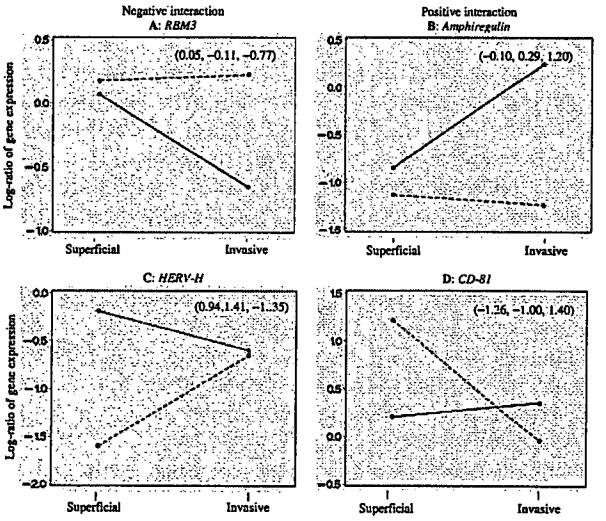

Fig. 1. Typical expression profiles for genes with negative or positive interaction. Each of four plots A–D shows the mean expressions of a gene of the 100 significant genes for the four types of cancer combined by stage, superficial and invasive, and grade, low (dashed line) and high (solid line). The estimates of parameters (β_1, β_2, β_3) for the model M4 are also given.

DISCUSSION

We have developed a method to select genes related to multiple clinical phenotypes via model selection based on a set of multivariate linear regression models. As indicated by the simulation study, our methods with model selection based on the doubly-adjusted R-square, R^2_{DA}, can substantially improve the power for various differential models for multiple phenotypes, compared with the conventional method that uses only a single model for gene selection. Also, the model selection indicates appropriate model for each selected gene, which may be helpful to gain insights on the relationship between gene expression and multiple phenotypes. Hence, our methods would be a useful tool for screening for selecting genes with various differential models for multiple phenotypes. In linear regression models, various types of phenotypic variables including nominal, ordinal and continuous variables with three or more levels can be accommodated. The R^2_{DA} can be generally adopted for both nested and non-nested models. Our methods are hence applicable to a wide variety of correlative analyses of global gene expression profiles from microarrays with multiple phenotypes. Although we have focused on gene selection, the model building process for prediction, e.g. for diagnostic prediction, preferably by generating hybrid models consisting of different kind of models based on a set of genes, is interesting and thus subject to future research.

Because of the large number of genes in microarray experiments, there will always be some genes with a very small sum of squares across samples, so that the value of an overall test statistic will be very large whether or not their averages are large. Tusher *et al.* (2001) have proposed a regularization that avoids this difficulty. For the overall F-test in (4), this regularization may be expressed as

$$F(\phi) = \frac{(TSS - RSS)/k}{RSS/(n-k-1) + \phi}$$

where ϕ is a fudge factor whose value is determined to reduce the dependence of $F(\phi)$ versus ϕ (Tusher *et al.*, 2001). As a simple modification of our methods, we obtain a regularized version of the doubly-adjusted R-square by replacing the usual F-statistic with this regularized F-statistic in (2), (3) and (5). This regularized statistic would be reasonable for gene selection because of its one-to-one correspondence with $F(\phi)$. However, for model selection, one may prefer the criterion of maximizing the original doubly-adjusted R-square to that of maximizing the regularized one because of the equality with popular criteria based on Cp or AIC. Hence, we first select the model for which the original doubly-adjusted R-square is maximized for each gene, followed by gene selection based on the regularized doubly-adjusted R-square for the selected model. We derived this regularization in a heuristic way and its theoretical justification is subject to future research. The approaches to borrow strength across genes via hierarchical modelling (e.g. Baldi and Long, 2001; Efron *et al.*, 2001; Wright and Simon, 2003) may provide a framework for this.

If clinical variables are highly correlated in a set of samples, then the models chosen for individual genes are likely to be highly unstable because of lack of power to discriminate between the different effects. One should select a set of samples to be well balanced especially when specimen banks from large cohort studies or clinical trials are available.

Determination of the set of candidate models is an important issue. One can assume, in principle, many candidate models, for example, by using different categorizing or higher order effects for phenotypic variables or by imposing constraints for regression coefficients to reflect a particular differential pattern such as the constraint in the model M4 described in the bladder cancer example (see Section 3.2). However, a large set of candidate models may suffer from error in model selection seriously. A good strategy would be to prepare a small number of plausible models with biologically different interpretations and one very flexible model to capture other differential patterns (such as the model M4 in the bladder cancer example).

We illustrated the methods using the bladder cancer data. We selected 100 genes with various patterns of differential expression for stage and/or grade (Table 3). Different models or differential expression patterns suggested from Table 3 have the potential to reflect different biologic aspects in stage and grade progressions of bladder cancer. Although some selected genes in our analyses have already been identified and studied for bladder cancer and other cancer, many genes were newly identified by our analyses. These genes have the potential to provide new insights on molecular alternation related to disease biology and progressiveness in bladder cancer. A fraction of these genes are now under investigation. As an initial step, we confirmed reproducibility of differential expression for six selected genes which were related to RNA processing and/or

translation (1, 3 and 2 genes for which the model M1, M3 and M4 was selected, respectively), but have not been studied for bladder cancer, for additional 74 samples by quantitative real time PCR assays (M. Ito, unpublished data).

Our methods could also indicate candidate molecular markers for more accurate classification of cancer. For example, genes for which the linear model, M1 or M2, were selected could supplement traditional pathological assays in determining stage or grade. Besides, our methods could help in developing new approaches to cancer diagnosis incorporating multiple diagnostic factors. For example, genes for which the model M4 with the interaction effects of stage and grade was selected (e.g. the four genes in Fig. 1) could be candidate genes useful for identifying the best (superficial and low grade) or the worst (invasive and high grade) type of bladder cancer. In such attempts, link with outcome or prognosis information should also be investigated.

Conflict of Interest: none declared.

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②Intensive insulin therapy
3. Intensive insulin therapyの実際

Key words：食道癌、術後管理、強化インスリン療法

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一般外科では術後一過性にみられる高血糖は外科的糖尿病として認識されているが、積極的な血糖管理は実施されてこなかった。2001年、Van den Bergheらは心臓手術患者にインスリンを投与して積極的に血糖管理を行うことで、術後合併症及び死亡率が減少したと報告した。われわれは2002年1月から強化インスリン療法（intensive insulin therapy；以下、IITと略）を導入して食道癌術後に積極的な血糖管理を行ってきた。当院における食道癌術後管理として行っているIITの実際と最近の連続43名の血糖管理状況を報告する。血糖値の平均値の推移は、術当日126 mg/dL、第1病日128 mg/dL、第2病日129 mg/dL、第3病日は118 mg/dL、第4病日は127 mg/dL、第5病日は130 mg/dL、第6病日は129 mg/dLで、血糖値は100～150 mg/dLの範囲でコントロールされていた。インスリン投与量は漸増し、第4病日で平均38 IUと最大になっていた。IITによる50 mg/dL以下の低血糖は1名に1回認められたのみであった。食道癌術後患者で血糖値を150 mg/dL以下（現在は130 mg/dL以下）に管理するIITは安全に実施可能である。

1. はじめに

Van den Bergheらは2001年11月8日号の*New England Journal of Medicine*において強化インスリン療法（intensive insulin therapy；以下、IITと略）の術後管理における有用性について報告した[1]。彼らは、心臓手術後の患者を対象に前向きの無作為化比較試験を行い、糖尿病の有無に関わらず血糖値を80～110 mg/dLの範囲に厳しく管理することにより、術後の合併症及び死亡率が有意に減少したと述べている[1]。一般外科では術後一過性にみられる高血糖は外科的糖尿病として認識されているが、糖尿病でない患者にも積極的にインスリンを投与し、血糖を徹底して管理するという内容はきわめて新鮮であった。論文中の血糖管理の詳細が不明であったため、Van den Berghe先生に直接mailを送った。そして、Leuven大学の集中治療室（intensive care unit；以下、ICUと略）で実施している血糖管理のプロトコールを受け取り、同時にその使用と公表の

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許可も得た。われわれはプロトコールを自分たちの実情にあったものに改変し、2002年1月から食道癌術後管理にIITを導入した。本稿ではIITの現状と過去5年間行ってきた実際について述べる。

2. IITの導入

IITが食道癌術後に実施可能か、またIITは術後合併症の頻度を減少させうるのかを評価するために2002年1月からパイロット的に検討を開始した[2]。IITの実施可能性を調べるにあたり、安全面を担保するために入手したプロトコールを改変した。IITの食道癌術後管理への導入はICUの看護師にとって通常看護業務の増加につながるため、現場の実情に即した単純で分かりやすい血糖管理指示プロトコールになるように配慮した。また、IITの導入にあたり糖尿病のない患者にインスリンを投与するため、低血糖発作を起こさないことを第1条件とした。すなわち、Van den Berghらの基準、①血糖測定は4時間毎、②インスリン投与開始の血糖値を110 mg/dL以上、③目標血糖値は80～110 mg/dLに対し、われわれは①血糖測定は3時間毎、③インスリン投与開始の血糖値は150 mg/dL以上、③目標血糖値は90～150 mg/dLとした。さらにインスリン投与量変更後1時間で血糖値を再度測定した。

当初の17名の検討では、低血糖は1名もみられず、術後平均血糖値は128～148 mg/dLで管理が可能であった[2]。インスリン投与量を変更後1時間での血糖値の再測定でもインスリン投与量の変更は1度も必要としなかった。また、血糖測定の間隔も原法と同じ4時間毎でも十分であると思われた。その結果、目標血糖値の設定は徐々に低下し、現在では80～130 mg/dLで管理を行っている。

3. IITの実際

当院におけるIITの指示スケールを示す（表1）。ICU入室後午後6時から血糖測定を開始し、4時間毎にチェックする。血糖値が131 mg/dL以上の時点でインスリン投与を開始する。インスリンは1 IU=1 mLに調整したものを0.5 mL/hrの速度から微量注入ポンプで注入する。血糖値が80～130 mg/dLの範囲になるようにスケールを用いて管理する。血糖値が50 mg/dL以下となった場合はインスリンを中止し、20%ブドウ糖を20 mL静注する。51～79 mg/dLでは投与速度を1 mL/hr下げる。80～130 mg/dLではインスリンの投与量はそのまま維持する。131～300 mg/dLでは投与速度を0.5 mL/hrずつ上げる。301 mg/dL以上では投与速度を1 mL/hrずつ上げる。血糖値が急激に低下した場合には（前回測定値から50%以上）、インスリンを中止するとともに頻回に血糖をチェックする。血糖測定のための採血は第3病日までは動脈ラインから、動脈ライン抜去後にはピンレッターにより指尖または耳朶から行っている。原則としてIITは術当日ICU入室直後から開始し、一般病棟に戻る第6病日の朝まで行っている。術後合併症も糖尿病もない患者ではその後の血糖測定及びインスリン投与は中止とする。肺炎など感染性の術後合併症を併発している場合には、引き続きIITを継続する。糖尿病患者ではIIT後はインスリンスケールによる皮下注に血糖管理を切り替え、200 mg/dL以下を目標血糖値としてコントロールする。低血糖を避けるためにIITは一般病棟では行っていない。

術後血糖値に大きな影響を与えるものは糖質などの投与量である。以前は、中心静脈栄養と経腸栄養を併用していた[3]。そのため投与カロリー量が

表1　術後インスリン投与スケール

目標値：80～130mg/dL

血糖チェック：4時間毎（6時、10時、14時、18時、22時、2時）

ノボリンR®100 50 単位
生食　　50mL

インスリン開始基準 血糖値131mg/dL 以上 ならば0.5mL/hr で開始

血糖値（mg/dL）	
～ 50	投与中インスリン中止 20% 糖 液20mL 静注
51～ 79	1mL/hr 投与速度を下げる
80～130	投与速度維持
131～300	0.5mL/hr 投与速度を上げる
301～	1mL/hr 投与速度を上げる

表2　輸液・経腸栄養の処方例 (50 kg成人の場合)

	末梢(持続薬ルート)			末梢(負荷ルート)			空腸瘻	
麻酔開始前	本体	ソルラクト[3]	500ml ×1					
	三方	ソル・メドロール125mg[3]	2v					
		生食	50ml ×1					
		手術開始1.5時間前						
	三方	セファメジンα[3]	1v					
		生食	100ml ×1					
		手術開始1.5時間前						
	三方	ザンタック(50)[3]	1A					
		生食	50ml					
		手術開始1時間前						
手術後	本体	ソルラクト[3]	500ml ×3	本体	ロック		インパクト[3]	1パック
				三方	セファメジンα[3]	1.0g		21時から翌朝まで
	三方	プレドパ[3]	ml/hr	(8hr毎)	生食	50ml		
	三方	ディプリバン[3]	mg/kg/hr	三方	ザンタック(50)[3]	2A		
		→抜管後	終了	(朝・夕)	生食	50ml		
	三方	フェンタネスト[3]	ml/hr	三方	(ソルラクト[3])	負荷用		
		→6:00	終了					
第1病日	本体	ソルデム3A[3]	500ml ×4	本体	ロック		インパクト[3]	2パック
	三方	プレドパ[3]	ml/hr	三方	セファメジンα[3]	1.0g		
				(8hr毎)	生食	50ml		
		ノボリン[3]	ml/hr	三方	ザンタック(50)[3]	2A		
				(朝・夕)	生食	50ml		
第2病日	本体	ソルデム3A[3]	500ml ×2	本体	ロック		インパクト[3]	4パック
	三方	プレドパ[3]	ml/hr	三方	セファメジンα[3]	1.0g		
				(朝・夕)	生食	50ml		
	三方	ノボリン[3]	ml/hr	三方	ザンタック(50)[3]	2A		
				(朝・夕)	生食	50ml		
第3病日	本体	ソルデム3A[3]	500ml ×2	本体	ロック		インパクト[3]	4パック
	三方	ノボリン[3]	ml/hr	三方	ザンタック(50)[3]	2A		
				(朝・夕)	生食	50ml		
					終了後抜針			
第4病日	本体	ソルデム3A[3]	500ml ×1	本体			インパクト[3]	6パック
	三方	ノボリン[3]	ml/hr					
第5病日	本体	ソルデム3A[3]	500ml ×1	本体			インパクト[3]	6パック
	三方	ノボリン[3]	ml/hr					
第6病日以降	本体	ソルデム3A[3]	500ml ×1	本体			ハーモニックM[3]に変更	

:スケールで調整する

多くなり、血糖コントロールのためのインスリン量も必然的に多くなっていた。鎖骨下静脈穿刺は気胸、血胸など種々の合併症を引き起こし、またカテーテルに起因した感染症は術後経過に悪影響を及ぼす可能性があるので、現在は末梢静脈経路のみで術後輸液管理を行っている。現在の輸液、経腸栄養の実際の処方例を示す（表2)。

術後輸液：末梢輸液本体は細胞外液または3号維持液で行う。IIT中は輸液ポンプで投与速度を一定に保ち、血糖値の急激な変動を防ぐようにしている。インスリンの投与ルートはIIT以外の目的では用いない。術当日は60 mL/kg/dayの速度で細胞外液を投与する。第1病日は50 mL/kg/day、第2～3病日は30～40 mL/kg/day、第4病日以降

は40 mL/kg/dayの輸液を投与する。アルブミン製剤は循環動態が安定し、低アルブミン血症に伴う症状が出現しなければ使用しない。輸血もヘモグロビン値が7 g/dL以上あれば行わない。

栄養管理：栄養管理は術前から開始する。手術5日前からインパクト®を3パック（750 mL）/日を摂取する。手術時に9 Frのジェジュノストミイカテーテル®で空腸瘻を造設する。経腸栄養を手術終了3時間後から1 kcal/mLの濃度で30 mL/hrの速度で開始する。体重50 kgの成人では第1病日に500 mL/日、第2～3病日に1,000 mL/日、第4～5病日には1,500 mL/日に増量する。第6病日以降は同量をハーモニックM®に変更する。第8病日に術後透視を行い、問題がなければ7分粥の6回食で経口摂取を開始する。食事摂取の状況がよければ経腸栄養剤の量を漸減する。

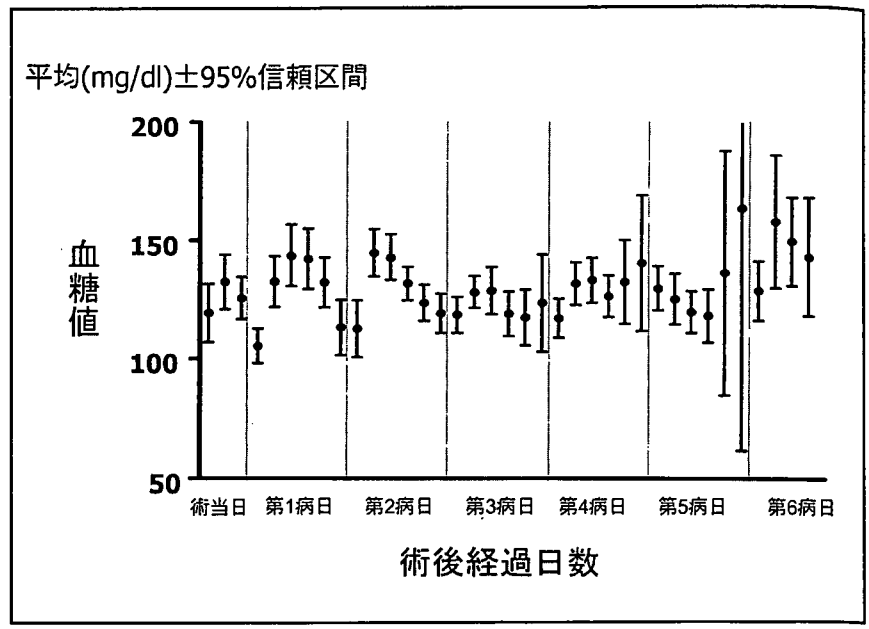

図1　術後血糖値の経時的変化

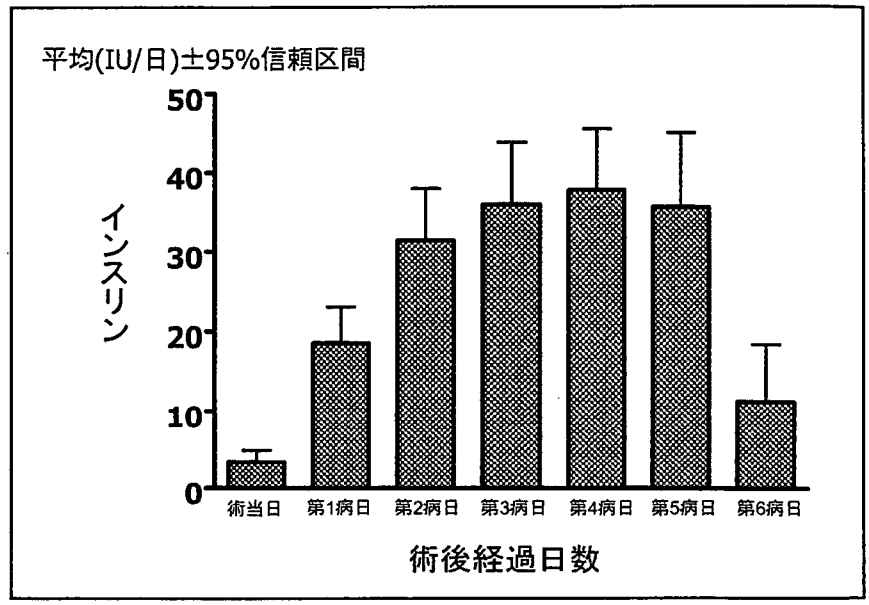

図2　術後インスリン投与量の推移

IITを施行した最近の連続43名の術後血糖値の経時的変化とインスリン投与量を示す（図1、2）。43名のうち糖尿病患者は2名であった。1名のみ乳糜胸のため完全静脈栄養を行った。当初の17名以後は目標血糖値を90～140 mg/dLで管理し、最近では80～130 mg/dLで管理している。血糖値の平均値の推移は、術当日126 mg/dL、第1病日128 mg/dL、第2病日129 mg/dL、第3病日は118 mg/dL、第4病日は127 mg/dL、第5病日は130 mg/dL、第6病日は129 mg/dLであった。図1の中で第4、5病日の5、6回目の血糖値の95%信頼区間が大きくなっている。これは血糖値が安定している場合、血糖チェックの回数を6回/日から4回/日に減らし5、6回目の測定値が欠損しているためである。この時期、血糖値が安定している場合には血糖測定で夜中に患者を起こさないため、現実的な対応として測定回数を減らすようにしている。血糖値が50 mg/dL以下となる低血糖は2名にみられた。1名は糖尿病患者で術当日にインスリンを使用していない状態で35 mg/dLであった。もう1名はインスリン投与中第3病日に41 mg/dLとなった。いずれも低血糖による症状はみられなかった。インスリンの平均投与量は術当日3 IU、第1病日19 IU、第2病日31 IU、第3病日は36 IU、第4病日は38 IU、第5病日は36 IU、第6病日は11 IUであった（図2）。経腸栄養量が維持量となる第4病日で、インスリン投与量も最大となっていた。インスリン投与が不要であったものは1名であっ

た。術後合併症は感染を伴うものは43名のうち7名（16%）で、肺炎2名、縫合不全2名、膿胸1名、創感染2名であった。

4. 考察

われわれは食道癌の術後管理の一貫として2002年1月からIITによる血糖管理を取り入れてきた。周術期管理としては術前栄養（インパクト750 mL×5日間）、術直前ステロイド投与、術直後高濃度酸素による創感染予防、術後早期からの経腸栄養、IITを行っている。これらの管理により、以前と比べて術後管理が格段に平易になっている印象を持っている。

IITは食道癌術後患者に非常に適している。心臓病患者は術後早期から食事摂取を開始するので、血糖値が摂取栄養量に左右されIITによる血糖管理が行いにくい。一方、食道癌患者では通常第7病日まで禁食である。その間、経静脈または経腸から一定の速度で栄養輸液管理が行われるため、血糖値が急激な変動をきたすことは少ないからである。

Finneyらは、IITによる術後管理において手術死亡率に影響を与える因子としてインスリンの投与量と血糖コントロールを比較した場合、血糖コントロールがより重要であるとし、145 mg/dL以下に血糖を維持することが手術死亡率の低下につながったと述べている[4]。また、Van den Berghe らは2つの臨床試験の解析を行い、手術死亡率は血糖値が110～150 mg/dLの患者群に較べて、150 mg/dL以上で高く、110 mg/dL以下で低いとしている[5]。このように血糖値は低いほうがよいとされているが、どこまで下げるべきか現時点では分っていない。

糖尿病の有無に関係なく血糖値を80～130 mg/dLに維持するわれわれの方法は食道癌の術後患者に安全に実施可能であった。縫合不全があるため感染性合併症はなかなかゼロにはならないが、今後目標血糖値を80～110 mg/dLにした、より厳しい血糖管理を実施してみたいと考えている。

5. まとめ

われわれが2002年から現在までに行ってきたIITの実際について述べた。IITによる血糖管理にはICUの看護スタッフの協力が不可欠である。IITに関する基本を押さえておけば、IITの導入はさほど困難ではない。不安があれば、緩めの基準で開始すればよい。今後の術後血糖管理の参考にしていただければ幸いである。

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Endoscopic submucosal dissection of recurrent or residual superficial esophageal cancer after chemoradiotherapy

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Background: Treatment of local recurrent or residual superficial esophageal squamous-cell carcinoma (SCC) with conventional EMR often results in a piecemeal resection that requires further intervention.

Objective: The aim of this study was to evaluate the efficacy of endoscopic submucosal dissection (ESD).

Design: A case series.

Patients: Between January 2006 and September 2006, 4 local recurrent or residual superficial esophageal SCCs were treated by ESD.

Interventions: ESD procedures were performed by using a bipolar needle knife and an insulation-tipped knife. After injection of glycerol into the submucosal (sm) layer, a circumferential incision was made, and an sm dissection was performed. All lesions were determined to be intramucosal or sm superficial, without lymph-node metastasis by EUS before treatment.

Main Outcome Measurements: Tumor size, en bloc resection rate, tumor-free lateral margin rates, and complications were recorded.

Results: All 4 ESD cases were successfully resected en bloc, and the tumor-free lateral margin rate was 75% (3/4) by histopathology examination. The mean tumor size of the resected specimens was 35 mm (range, 15-50 mm). There were no complications.

Limitations: The number of ESDs in our series was limited, and there are no long-term follow-up data.

Conclusions: ESD for recurrent or residual superficial esophageal tumors after chemoradiotherapy achieves the goal of an en bloc resection, with a low rate of incomplete treatment without any greater risk than the EMR technique.

Esophageal cancer is one of the most difficult GI cancers to detect at an early stage, even by endoscopy. Recently, a narrow-band imaging endoscope was developed and was shown to be advantageous for the early detection of squamous-cell carcinoma (SCC) in the esophagus and the pharynx, although it still is not widely in use.[1,2]

Some esophageal cancers have been detected as invasive tumors, and surgery has been the standard treatment for such lesions. However, higher mortality rate because of surgery has been reported (range 2.1% to 13.7%), as has poor patient quality-of-life after surgery.[3,4]

There is a current preference to treat esophageal SCC by primary chemoradiotherapy (CRT),[5,6] but 13% of patients treated for esophageal SCC with CRT have a recurrence or a residual tumor. Surgery after CRT is unsatisfactory,[7,8] and endoscopic treatment can be proposed when the tumor is superficial,[9-13] but a strip biopsy is difficult, because fibrosis and piecemeal resection frequently occur even for small lesions. A search of the literature confirmed that en bloc resection by endoscopic submucosal dissection (ESD) provides better results in the stomach.[14-17] ESD was recently reported to be useful in the treatment of superficial esophageal SCC[18-20]; however, the feasibility and safety of ESD for local recurrent or residual tumors is unclear. Previously, we reported on

Abbreviations: B-knife, bipolar needle-knife; CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; IT-knife, insulation-tipped-knife; NCCH, National Cancer Center Hospital; SCC, squamous-cell carcinoma; sm, submucosal.

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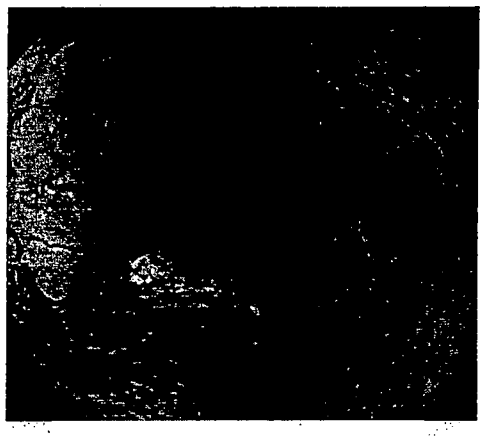

Figure 1. The primary tumor before CRT was diagnosed as a type 1 SCC, with a circumferential intraepithelial lesion, which had been located in the mid esophagus at a previous hospital.

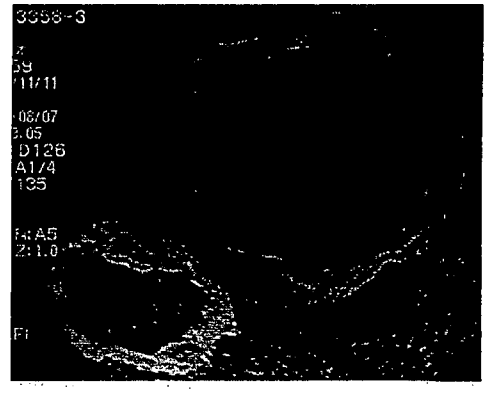

Figure 2. An endoscopy revealed a 0-IIC superficial residual lesion, 40 mm in diameter, located in the mid esophagus. After iodine staining, the lesion became more apparent and was larger than 50% in circumference.

the effectiveness and safety of ESD for colorectal tumors by using a bipolar needle-knife (B-knife) and an insulation-tipped knife (IT-knife), neither of which has any coagulation effect at the needle tip.[21-24] The aim of our study was to evaluate the efficacy and safety of ESD for local recurrent or residual esophageal tumors by using a B-knife and an IT-knife.

PATIENTS AND METHODS

Four patients with esophageal SCC, each of whom had developed a local recurrent or residual tumor (2 recurrent tumors and 2 residual tumors) after CRT, were included in this study, which was conducted between January 2006 and September 2006 at the National Cancer Center Hospital (NCCH) in Tokyo. Three of the ESD cases involved stage I lesions treated by CRT, and the other case was of a stage II lesion. The 4 ESDs were performed from 217 days to 1377 days after the initial CRT.

ESDs by using a B-knife and an IT-knife were performed on all 4 patients, with Glyceol (Chugai, Tokyo, Japan)[25] used in each case as the submucosal (sm) injection solution to maintain proper sm elevation. All of the local recurrent or residual tumors were confirmed as intramucosal or sm superficial, without lymph-node metastasis, by EUS and a CT before treatment.

Endoscopic operating system

ESD procedures were performed by using video endoscopes (GIF-Q240 or GIF-Q260; Olympus Optical Co, Ltd, Tokyo, Japan).

ESD procedure

A transparent disposable attachment (D-201-1074; Olympus) was fitted onto the tip of the endoscope to retract the sm layer and to facilitate dissection. Lesion margins were delineated before ESD by using 1.5% iodine staining (Figs. 1 and 2). After sm injection of Glyceol, a circumferential incision in the mucosa was made by using a B-knife and an IT-knife.[21-24] Additional Glyceol was then injected into the sm layer to lift the lesion, and the thickened sm layer was dissected by using an IT-knife (Figs. 3 and 4). The B-knife was mainly used for the dissection of fibrosis caused by CRT.[21-24] The operation time was recorded for all patients.

Sedation

Midazolam (3-5 mg intravenously) was administered in all cases. An additional 2 mg was given as necessary, whenever indicated, based on the individual endoscopist's judgment.

Histologic assessment

All specimens were evaluated after being cut into 2-mm slices; they were examined microscopically for histologic type, depth of invasion, lateral resection margin, and vertical resection margin.

Follow-up care

All patients who had an ESD at the NCCH were regularly observed, with annual endoscopic and EUS examinations and CTs. Complete follow-up care was available for all 4 patients in the ESD group.

Statistical analysis

All variables in this study were described as mean (SD). All statistical analyses were performed by using SAS version 8.0 (SAS Institute Inc, Cary, NC). The P value was 2 sided, and $P < .05$ was used to determine statistical significance.

Ethics

The ethics committee at the NCCH approved the study protocol, and written informed consent was obtained from all 4 patients in the ESD group before entering the study.

Figure 3. An en bloc resection was achieved without complication in 100 minutes.

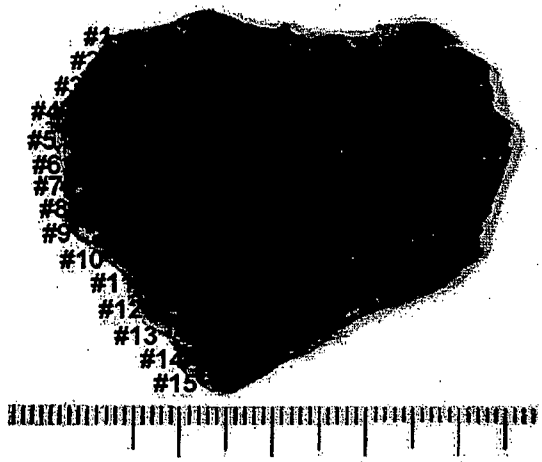

Figure 4. The resected specimen was 50 mm in diameter, with both the lateral and vertical margins negative by endoscopy. Both the lateral and vertical margins were negative on histopathologic examination, and the depth of invasion was m2. A curative local resection was achieved in this case.

RESULTS

During the study period, 4 patients were treated with ESD. All 4 lesions were eligible for outcome analysis. Clinical characteristics of the patients are presented in Table 1. Each of the 4 ESD cases was successfully resected en bloc, with no complications. The mean (SD) ESD time was 58 ± 42 minutes (range 15-100 minutes), and the mean (SD) size of the resected specimens was 35 ± 15 mm (range 15-50 mm). On histopathologic examination, the lateral and vertical margins were negative in 3 of 4 ESD cases, but the depth of invasion was sm1 in 2 of those cases, so additional CRT was performed on those patients. A curative local resection was achieved in the other case. None of the patients developed local recurrence or distant metastasis in the follow-up period. There were no immediate or late complications related to ESD procedures reported. The median (SD) follow-up time was 3 ± 2 months (range 0-6 months) for the ESD group.

TABLE 1. Clinical characteristics of patients

No. lesions	4
Stage before CRT (stage I/II)	3/1
Days after CRT (median)	749 (range 217-1377)
Residual/recurrent	2/2
Tumor depth (m/sm)	2/2
Tumor size (mean [SD]) (mm)	35 ± 15 (range 15-50)
Procedure time (mean [SD]) (min)	58 ± 42
En bloc resection rate	100% (4/4)
Tumor-free lateral margin rate	75% (3/4)
Local recurrence rate	0% (0/4)
Complication (perforation)	0 (0%)

DISCUSSION

The ESD technique, by using a B-knife[21-24] and an IT-knife,[17,23,24] enhanced the en bloc resection rate, thereby increasing the likelihood of curative results for local residual or recurrent tumors. In fact, ESDs with a B-knife and an IT-knife are performed to treat superficial neoplastic lesions, such as gastric and colonic neoplasms, at the NCCH.[17,22-24] ESD has enabled us to treat recurrent gastric cancers after EMR. As indicated in our previous reports,[26] about 5% of such cases involved perforations, although virtually all of the perforation cases were successfully treated by means of endoscopic clipping, without the need for additional surgery.

The esophagus is located in the mediastinum, so the risks of ESD are further enhanced, and perforations must be avoided. The newly developed B-knife results in a safer ESD, because the electric current is localized at the needle tip.[21] The IT-knife [17,23,24] also decreases the risk of perforation as a result of the insulated tip attached to the end of the needle. A B-knife was mainly used for the dissection of fibrosis caused by CRT. The combined use of these two instruments has enabled us to safely perform ESDs even for local recurrence of residual tumors after CRT with successful results similar to our experience in the colorectum.[23,24] Although the number of patients who underwent ESD in our series was limited and the follow-up periods were short, there were no cases of recurrence after ESD during any of the follow-up periods. Further follow-up data are required, however, for meaningful recurrence and survival analyses.

For comparison, 17 local recurrent or residual tumors (10 recurrent tumors, 7 residual tumors) in 14 patients treated at the NCCH between January 2005 and December

2005 by conventional strip biopsy (EMR) were included as historical controls. Ten of the EMR lesions were stage I treated by CRT, and the other 7 were stage II lesions. The 17 EMRs were performed from 134 days to 636 days after the initial CRT.

Analysis showed a significant difference between the 2 treatment groups in terms of en bloc resection rates, with 100% (4/4) in the ESD group compared with 47% (8/17) in the EMR group ($P = .05$), despite the tumor size being significantly larger in the ESD group. Further analysis showed a difference between the 2 groups in terms of resection margin involvement, with 25% (1/4) in the ESD group and 65% (11/17) in the EMR group (not significant). The higher en bloc resection rate and lower incidence of margin involvement in the ESD group compared with the EMR group resulted in a higher curability rate.

It is recognized that ESD for local recurrent or residual tumors is difficult because of fibrosis, which results after CRT. Although it is still not technically feasible to perform either EMR or ESD for an invasive SCC deeper than sm2 (close to the muscle layer), ESD enables us to resect invasive SCC for both sm1 and sm2. Surgical treatment for esophageal SCC is difficult, with a poor quality-of-life reported for patients after surgery, whereas a higher recurrence rate has been reported after CRT treatment. ESD or EMR should be performed initially, therefore, followed by CRT to treat possible lymph node metastasis when EUS or magnifying endoscopy examinations reveal no evidence of deeper invasion to the muscle layer as previously reported.[27]

In conclusion, ESD for recurrent or residual superficial esophageal tumors after CRT with a B-knife or an IT-knife achieves the goal of an en bloc resection with a low rate of incomplete treatment without greater risk than the EMR technique. ESD should be the reference procedure, therefore, for treating such lesions.

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DISCLOSURES

The authors report that there are no disclosures relevant to this publication.

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Endoscopic submucosal dissection for cancers of the remnant stomach after distal gastrectomy

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Background: Endoscopic submucosal dissection (ESD) of early gastric cancer is less invasive than surgical resection, and if technically feasible, it may result in less long-term morbidity than does incisional surgery. However, ESD is technically difficult in patients who have had a previous distal gastrectomy.

Objective: Our purpose was to retrospectively assess the results of ESD of early gastric cancer in the remnant stomach.

Design: Case series.

Setting and Patients: A total of 31 lesions in 30 patients with early remnant gastric cancer were treated with ESD at Okayama University Hospital, Tsuyama Central Hospital, Hiroshima City Hospital, Kagawa Prefectural Central Hospital, and Mitoyo General Hospital from March 2001 to January 2007.

Intervention: ESD.

Main Outcome Measurements: En bloc resection rate, complete resection rate, operation time, and complications.

Results: En bloc resection and complete resection were achieved in 30 (97%) and in 23 (74%) lesions, respectively. The median operation time required for ESD in the remnant stomach was 113 minutes (range 45-450 minutes). Perforation occurred in 4 (13%). The incidence of delayed bleeding requiring blood transfusion was 0%.

Limitation: Short duration of follow-up.

Conclusions: ESD is feasible in the remnant stomach but has a relatively high complication rate and should only be performed by experienced endoscopists.

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

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Distal gastrectomy for benign disease appears to lead to an increased risk for the development of gastric cancer.[1,2] Although remnant gastric cancers are usually detected at an advanced stage and surgical resection of the total remnant stomach has been accepted for a long time,

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腫瘍外科治療の最前線

A. 食道の腫瘍性疾患
胸部早期食道癌

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永井書店

A. 食道の腫瘍性疾患

15. 胸部早期食道癌

Early thoracic esophageal cancer

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早期食道癌は粘膜内に限局した食道癌でリンパ節転移を問わないものと定義される．粘膜病変の診断は食道造影，色素内視鏡，超音波内視鏡，拡大内視鏡さらにはNarrow band imageにて行う．治療はm1～m2であれば内視鏡的粘膜切除(EMR)が適応である．相対的EMRの適応であるm3は，まずEMRを行い，脈管侵襲の有無にて追加治療の必要性を検討する．追加治療では化学放射線療法(CRT)または食道切除を行う．リンパ節転移のあるm癌の場合は外科的切除またはCRTが行われる．2次癌に対する予防(禁煙禁酒)および早期発見が重要で，患者教育と定期的な長期にわたる検診が不可欠である．

key word 早期食道癌/リンパ節転移/内視鏡下粘膜切除/化学放射線療法/食道切除術

はじめに

食道癌は男性に多く，中部胸部食道に好発し，発癌因子として喫煙，飲酒，刺激物の摂取，低栄養などが示唆されている．欧米では消化液逆流と関連があるBarrett腺癌が半数以上を占めているが本邦ではまだ目立った増加はきたしていない．食道癌は胃癌や大腸癌と異なり粘膜下層に癌が浸潤すると高頻度にリンパ節転移を生じ，またリンパ節転移は頸部，胸部，腹部の3領域にまたがって生じる特徴がある．したがって，他の消化管癌と異なり，早期食道癌は浸潤が粘膜部分にとどまる癌に限られる．しかしながら，従来の色素内視鏡，超音波内視鏡に加えて近年の拡大内視鏡検査さらにはNarrow band image(NBI)により，その診断検出能は向上し，内視鏡的粘膜切除(EMR)の治療成績は良好である．また，m3，sm1に対する化学放射線治療(CRT)による食道温存治療の成績も良好で手術の役割は限定されるものとなってきている．

MEMO 1 NBI

狭帯域画像システム(narrow band imaging：NBI)は内視鏡観察光の分光特性を変更することで粘膜表面の血管や粘膜の微細模様を強調表示する技術であり，ヘモグロビン吸収波長である415 nmで臓器表面を観察すると微細な血管構造が明瞭に認識される．

本稿では，現時点での早期食道癌の診断，治療について概説する．

早期食道癌(扁平上皮癌)の定義

第10版食道がん取り扱い規約(2007発刊予定)では早期食道癌は粘膜内に限局した癌であるがリンパ節転移を問わないものと定義される．

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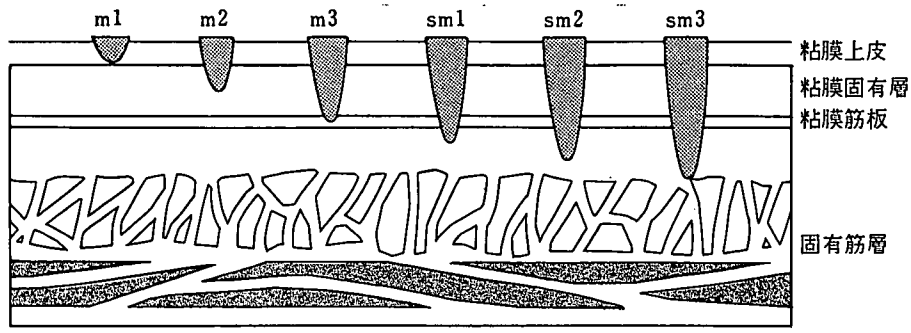

図1 食道表在癌の深達度亜分類(食道疾患研究会，臨床病型分類検討委員会，一部改変)

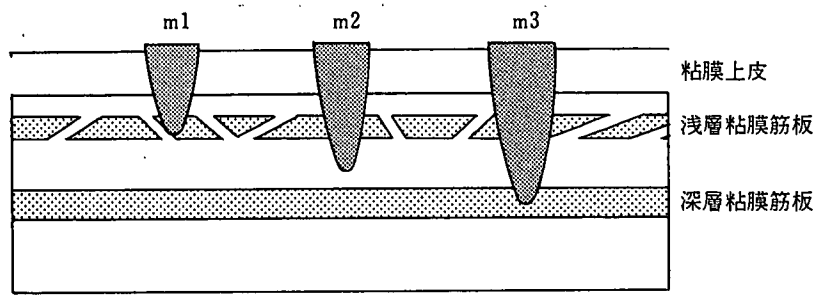

図2 Barrett腺癌深達度分類

T1a 癌腫が粘膜内にとどまる病変
T1a-EP 癌腫が粘膜上皮内にとどまる病変(Tis)
T1a-LPM 癌腫が粘膜固有層内にとどまる病変
T1a-MM 癌腫が粘膜筋板に達する病変

従来一般的に使用されてきた深達度亜分類はほぼ以下のごとく対応する．

m1：T1a-EP，m2：T1a-LPM，m3：T1a-MM(図1)．以下 m1～m3 で表記する．

早期 Barrett 食道癌の定義

胃から連続性に食道にのびる円柱上皮を Barrett 粘膜と言い，腸上皮化成の有無を問わないものと定義される．この Barrett 粘膜に生じた腺癌を Barrett 食道癌とよび，Barrett 食道では本来の粘膜筋板のほか円柱上皮深部に新たな粘膜筋板形成が認められ，本来の粘膜筋板を深層粘膜筋板(deep muscularis mucosa)，新生されたものは浅層粘膜筋板(superficial muscularis mucosa(SMM))と定義される．早期 Barrett腺癌の壁深達度は図2のごとく定義される．

T1a 癌腫が従来の粘膜筋板を越えない病変
T1a-SMM 癌腫が円柱上皮層または浅層粘膜筋板にとどまる病変
T1a-LPM 癌腫が浅層粘膜筋板を越えるが，深層粘膜筋板に達しない病変
T1a-MM 深層粘膜筋板に浸潤する病変

診　　断

食道造影，通常内視鏡検査，色素内視鏡，超音波内視鏡，拡大内視鏡を組み合わせた NBI による検査で食道原発巣の診断を行い，CT，MRI，PET でリンパ節転移，遠隔臓器転移を診断する．m1～m2 までの深達度診断は容易である．早期癌の別れ目となる m3 と sm1 の鑑別，および前癌病変と癌との鑑別は困難である場合がある．多発癌，重複癌の診断にも心配りが必要である．

1．食道造影

食道壁の硬化，顆粒状変化が描出できれば m3，sm1 とされるが，m1，m2 病変の描出は困難である．明らかに描出可能な病変は sm2 以深であり，粘膜病変の対象からははずれる．

2．通常内視鏡観察と色素内視鏡

通常内視鏡観察が基本であるがIIb病変の拾い出しは通常観察だけでは困難である．ヨード染色を併用する内視鏡検査で扁平上皮癌では100%に近い拾い出し能がある．しかしながらヨード不染を示す部分がすべて癌とは言えない．上皮内腫瘍(intraepithelial neoplasia，従来のdysplasia)や炎症との鑑別は最終的には生検にてなされる．Barrett食道癌ではメチレンブルー，インジゴカルミン，クリスタルバイオレットなどの青色系色素が用いられるがヨード染色の診断能より格段落ちる．

3．超音波内視鏡

通常描出される9層構造のうち第3層(粘膜筋板)の断裂の有無を観察し判断する．気管の陰がブラインドになる欠点があるが円形の腫大したリンパ節の拾い上げ，リンパ節構造の読影から高い正診率が得られている．さらにfine needle aspiration biopsy (FNA)により診断能が向上している．

4．拡大内視鏡とNBI

拡大観察によって得られる粘膜・粘膜下層の血管網の乱れを指標に診断を行う．とくに上皮乳頭内毛細血管ループintra-papillary capillary loop (IPCL)の形態変化により質的診断および深達度診断が可能となる[1]．さらに新しく開発されたNBIにてよりコントラストが鮮明になり診断しやすくなっている．ヨード染色に向いていない下咽頭癌の診断，ならびに色素内視鏡の診断能が低いBarrett腺癌の早期癌の検出に威力を発揮する．さらにはヨード染色でのいわゆる“まだら食道”でも拡大内視鏡やNBIが有用であると期待されている．

MEMO 2 IPCL

食道扁平上皮の樹枝状血管網から垂直に立ち上がってくる血管がループ状となっており上皮乳頭内毛細血管ループintra-papillary capillary loop (IPCL)と呼称される．このIPCLは通常観察ではほとんど観察できないが，拡大内視鏡により同定され，この血管ループにおける「拡張，蛇行，口径不同，形状不均一」の4要素の変化で病変の質的診断および深達度診断が行われる．

5．病理診断の変更点

従来，異型成と呼称していたdysplasiaは上皮内腫瘍intraepitheilal neoplasiaと呼び，低異型度上皮内腫瘍(low grade intraepithelial neoplasia)および高異型度上皮内腫瘍(high grade intraepithelial neoplasia)に分類される．病変によっては炎症，癌との鑑別が困難である場合がある．また，癌の導管内進展はT1aで，導管外に浸潤している場合は，浸潤している層をもってその深達度とすると定義されることとなった．

6．重複癌・多発癌の診断

食道癌症例ではその20%近くが他臓器重複癌を有している．頭頸部癌が最も多く40%を占め，胃癌，大腸，肺癌などがあげられる．またEMR症例でも20%に食道内多発癌が認められる．治療に当たってはこれらの精査が不可欠である．

早期食道癌におけるリンパ節転移頻度

食道疾患研究会の集計結果に基づくリンパ節転移頻度はm1で0%，m2で3.3%，m3で12.2%と報告されている．したがって，m2とm3には大きな隔たりがある．しかもm3ではly(+)が23.1%と報告されており，潜在的なリンパ節転移可能性は症例の1/4に存在する．sm1では26.5%にリンパ節転移が認められ，ly(+)は40.7%，v(+)が12.9%に存在し，すでに進行癌である[2]．m3，sm1の中でリンパ節転移を起こしやすい症例は脈管侵襲陽性，inf γ，低分化癌であり，病変の長径が50 mm以上であることと関連が認められている[3]．

治　　療

1．早期胸部食道癌の治療

現時点で治療のアルゴリズムを図3に示す．m1とm2はリンパ節転移のない病変であり，EMRまたはESDの適応である[4]．m3には可及的にEMRを行い，リンパ節転移の可能性のあるものには外科的根治術またはCRTを行う．リンパ節転移のあるm癌の場合は外科的切除またはCRTが行われる．再発時の対応は前治療により対処が異なる．EMR可能病変に対

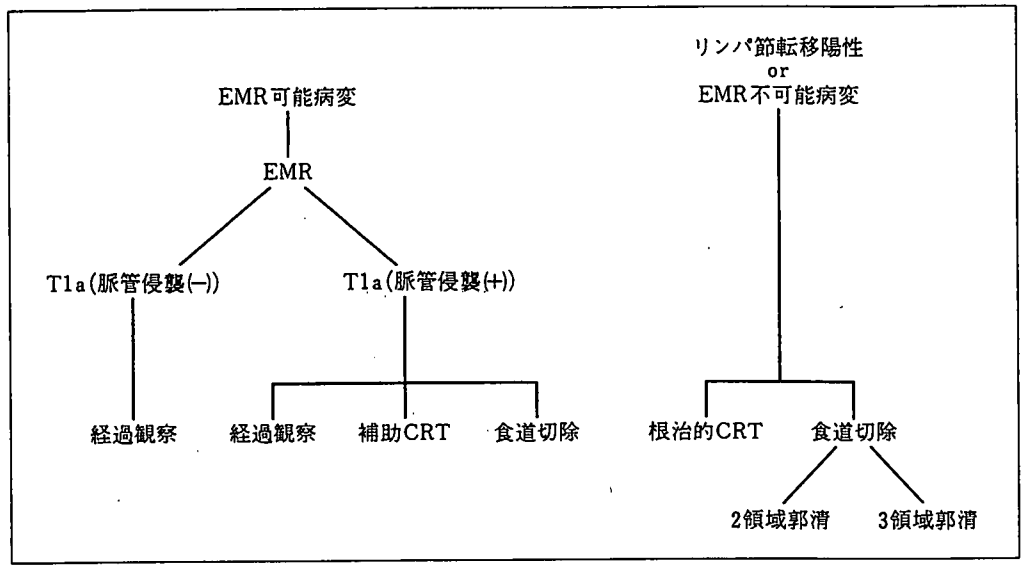

図3 早期食道癌に対する治療アルゴリズム

してはEMR，表在性病変であれば，光線力学的療法(PDT)やアルゴンプラズマ凝固療法(APC)も選択枝となるが，手術適応が有れば食道切除または転移リンパ節切除が行われる．CRT後でなければCRTも選択枝となる．以下，治療法別に概説する．

2．内視鏡摘粘膜切除(EMR)

EMRには2チャンネル法，EMR-C法，EEMR-tube法，ESD法があり病変および各施設の状況に応じて施行されている．2 cm以上であればESD以外は分割切除となる．また周在性2/3以上であると食道狭窄のリスクが高まる．小山らの提唱するESD法は大きな病変も一括切除でき，分割切除での局所再発の危険性を減らすことができる[5]．m3や周在性2/3以上の病変は相対的適応とされる．EMRで脈管侵襲陽性，inf γ，低分化癌，m3浸潤部が大きい場合は，追加治療を考慮する．EMRの合併症としては出血，穿孔，縦郭気腫などの急性期合併症と潰瘍治癒過程で生じる狭窄などの晩期合併症がある．粘膜内癌のEMRの5年生存率は90%以上である．内視鏡治療の適応とならない，全周性病変や長径5 cm以上の病変は外科治療または根治的CRTが行われる．

Barrett食道癌では2 cm以下のUL(−)の分化癌でm癌と診断された場合にはEMRの適応とされ，sm浸潤がなければEMR後は経過観察される．m癌であれば予後は悪くない．しかしながら症例数が少なく明確なEMR規準はまだない[6]．

MEMO 3 APC

APC (Argon plasma coagulation)は内視鏡的にアルゴンガスを噴出し，高周波電流を放電させ，熱凝固により，組織を焼灼する治療．高周波電流は抵抗性の低い部分に向かう特性を有し，凝固が進むと組織の抵抗が高まり同一部の凝固は進展しない．したがって，粘膜や粘膜下層浅層の組織破壊に限定される．

3．治療の実際

症例は74歳男性．通常観察で中部食道の後壁中心に存在する，約半周に及ぶ発赤した浅い陥凹性病変を認める(図4a)．病変に一致してヨード不染帯として病変が認識でき，不染領域内には正常食道粘膜の取り残しと考えられるヨードに染まる部位が存在する(図4b)．送気量を変えると縦ひだ・畳み目模様が描出され，粘膜内病変が示唆される(図4c)．NBI通常観察で病変は淡い褐色の領域として認識でき，同部位では正常な食道血管影が消失している．NBI拡大では井上分類type V-1，有馬分類type 3bのIPCLを認める(図4d)．術前診断は0-IIc SCC深達度m1/m2でESDを施行．病変をマーキング後，フックナイフとITナイフで全周切開してフックナイフで剝離して終了した(図4e)．最終病理診断は0-IIc SCC m1で術後は穿孔・出血なく，術後4ヵ月の時点で狭窄症状を認めていない．