Appendix

1. What is your disease?

_____

2. When was your disease diagnosed?

Year _____ month _____

3. How old are you?

_____ Years old

4. Please indicate your sex.

Male/Female

5. What about your present daily activity? Please tick the number below.

1) not limited at all, 2) somewhat limited with slight symptoms

3) bed rest more than 50% of the day, 4) bed rest all day

6. Please indicate your level of education.

1) junior high school, 2) high school, 3) college, 4) university, 5) other ( )

7. Are you committed to any religion?

Yes / No

8. Please indicate all treatments that you have received.

1) surgery, 2) chemotherapy, 3) hormonal therapy, 4) radiation, 5) palliative care

6) others ( )

9. Please indicate all treatments that you are currently receiving or will receive.

1) surgery, 2) chemotherapy, 3) hormonal therapy, 4) radiation, 5) palliative care

6) others ( )

10. Has your outlook on life been changed by suffering from this disease?

Yes / No (if yes, how?)

11. Did (Do) the treatments you received meet your needs?

Yes / No

12. Have you ever used complementary and alternative medicines (CAM)?

(*CAM includes various therapies as follows: Chinese herbal medicine, other CAM products such as Agaricus, Propolis, Chitosan, and shark cartilage, acupuncture, chiropractic, aromatherapy, homeopathy, imagery, yoga, thalassotherapy, hypnosis, etc.)

Yes / No

If 'yes', please continue to answer the questions below.

If 'no', the questions are finished here. Thank you very much for your cooperation.

---

13. When did you start CAM?

Year _____ month _____

14. Are you using CAM now?

Yes / No (if no, when did you stop? Year _____ month _____)

15. What kind of CAM do (did) you use?

(continued on following page)

Appendix (continued)

Please state all the names of cancer CAM you use (used), referring to cancer CAM notes*.

. _____ . _____

. _____ . _____

. _____ . _____

16. Why did you start CAM? Please tick the number below.

1) recommended by family members or friends, 2) your own free will,

3) recommended from a physician, 4) other ( )

17. Did you obtain enough information about the efficacy and safety of CAM before you started it?

Yes / No

18. What did (do) you expect by using CAM? Multiple choices are allowed in this question.

1) cure, 2) suppress the progression, 3) improve the symptoms, 4) complementary effects to the present medicine, 5) other ( )

19. Did it work?

Yes / No / difficult to judge

20. If 'yes', how effective was it?

_____

21. Did you experience any detrimental effects from CAM?

Yes / No / difficult to judge

22. If 'yes', how detrimental was it?

_____

23. What was the cost to you? Please indicate the mean expenditure per month.

_____ Yen

24. Did your doctor or other medical professionals ask about CAM use?

Yes / No

25. Have you mentioned CAM use to your doctor?

Yes / No

26. If 'yes', how did your doctor respond?

1) encouraged you to continue using, 2) advised you to stop using,

3) was neutral about using (neither encouraged nor discouraged),

4) other ( )

27. If 'no', why did you not mention it to your doctor?

1) Because my doctor never asked me about the topic, 2) Because I thought my doctor would not understand, 3) Because I thought my doctor would disapprove of CAM use, 4) other ( )

28. Please answer the next question, if you have received or are receiving chemotherapy.

Have you ever used CAM products and anticancer drugs at the same time? CAM products include Chinese herbs, mushrooms, shark cartilage, etc. which are sold over the counter.

Yes / No

Thank you very much for your cooperation.

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(2) 臨床評価指標の設定と評価

−がん診療について−

栗田 啓　高嶋成光

(2) SETTING AND EVALUATION OF A CLINICAL INDICATOR

Akira KURITA and Shigemitsu TAKASHIMA

臨床評価指標（以下指標）の基本理念として，安全な医療の確保，政策医療の提供，医療の質が掲げられている．独法化後は各施設で特化した機能を表看板にたてるところが多いと思われ，評価する視点が多少異なると思われる．当施設は，がん診療に特化した施設であり，またがん診療にかかわる指標の設定の試案に当初からかかわってきたので，指標設定の経緯を述べ，実際に運用する上での問題点に関し考察した．

指標決定の経緯

がん診療に関する指標の設定には，国立がんセンター中央病院の笹子充先生を委員長として，全国13施設のがん診療を看板とする施設の代表が集まって案を練った．当初，代表的ながん腫として，胃癌，大腸癌，子宮癌，乳癌，肺癌，前立腺癌が候補にあがったが，肺癌は施設がかたよっているとして除かれた．残りの5種で，患者数，手術例数，術後5年あるいは10年生存率，治療関連死率を評価項目としてあげ，さらに消化管の癌では，EMR施行数が，前立腺癌，子宮癌では放射線治療例数が加えられた．放射線治療を全体的に評価しようということで，放射線治療の3項目が加えられた．さらに，治験とその達成率，治験，公的臨床試験での治療関連死率，実働しているCRCの数が盛り込まれ，原案の合計項目数は52にのぼった（表1）．子宮癌においては，頸癌と

表 1　臨床評価指標（がん政策医療分野）原案

胃癌の臨床実績	胃癌患者総数，胃癌手術患者数，胃癌治療関連死亡数および率，胃癌切除例の5年生存率（当該年より5−7年前の3年間の症例数とその5年生存率（KM法））；stage Ⅰ，stage Ⅱ，stage Ⅲ，stageⅣ，EMR施行症例数
子宮癌の臨床実績	子宮癌症例数と体癌の割合，子宮頸癌における放射線治療割合，子宮頸癌における手術治療割合，子宮頸癌手術治療関連死亡率，子宮頸癌放射線治療関連死亡率，子宮体癌における手術治療割合，子宮頸癌の5年生存率（当該年より5−7年前の3年間の症例数とその5年生存率（KM法））；stage Ⅰ，stage Ⅱ，stage Ⅲ，stageⅣ，子宮体癌の5年生存率（当該年より5−7年前の3年間の症例数とその5年生存率（KM法））；stage Ⅰ，stage Ⅱ，stage Ⅲ，stageⅣ
乳癌の臨床実績	乳癌全患者数，乳癌手術患者数，乳癌の乳房温存手術率，乳癌治療関連死亡率，乳癌切除例の10年生存率（当該年より10−12年前の3年間の症例数とその10年生存率（KM法））；stage Ⅰ，stage Ⅱ，stage Ⅲ，stageⅣ
大腸癌の臨床実績	大腸癌全症例数（全入院治療例），大腸癌全手術患者数，大腸癌治療関連死亡率，大腸癌の5年生存率（当該年より5−7年前の3年間の症例数とその5年生存率（KM法））；stage Ⅰ，stage Ⅱ，stage Ⅲ，stageⅣ，大腸癌ポリペクトミー数
前立腺癌の臨床実績	前立腺癌全治療症例数，前立腺手術症例数，前立腺放射線根治照射症例数，前立腺癌手術症例治療関連死亡率，前立腺癌切除例の10年生存率（当該年より10−12年前の3年間の症例数とその5年生存率（KM法））；stage Ⅰ，stage Ⅱ，stage Ⅲ，stageⅣ
放射線治療の臨床実績	放射線治療実施症例総数，根治照射実施率，複雑・特殊照射施行症例数
臨床試験を内包する臨床実績	施設に働くCRC（P）数，治験・公的臨床試験での治療関連死率，治験契約達成率

国立病院機構四国がんセンター National Hospital Organization Shikoku Cancer Center 外科
Address for reprints：Akira Kurita, Department of Surgery, 13 Horinouchi, Matsuyama, Ehime 790-0007 JAPAN
e-mail：akurita@shikoku-cc.go.jp
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体癌で治療戦略が違うという理由で別個に扱うこととされた．大腸癌における腹腔鏡下手術の件数を評価項目に加えるとした意見があったが，まだ一般的な治療法ではないとする意見もあって見送られた．

医療の質の評価としてあげられた生存率は，各癌腫ごとの学会による病期分類ごと，すなわち stage Ⅰ から stage Ⅳまで，それぞれを期間を限定してあげることとした．また，安全な医療としての指標である治療関連死の定義が問題となったが，結局，治療終了から30日以内の全死亡例と治療によって生じた有害事象による死亡例とし，治療後の日数は問わないということで意見の一致をみた．

その後，第3回臨床評価指標検討会が平成15年1月30日に開催され，データの収集率を高めるためにも指標数を20までにすること，診断に関する指標を加えること，生存率は医療の質を最も反映するもの1つとすること，ターミナルケアーに関する指標を加えることとの指摘があった．また，治験やCRCに関する指標は病院共通の指標の中に含むので削除すること，データの収集可能性を詰めるようにとの指示があった．再検討の結果，日本人に最も代表的な，胃癌，大腸癌，乳癌，子宮頸癌，さらに全般を通しての放射線治療の項目に落ち着いた．生存率の算定では，胃癌，大腸癌，子宮頸癌ではⅢ期，乳癌ではⅡ期を選択した．ターミナルケアーに関する指標の決定には難渋したようであるが，結局，オピオイド使用に対する服薬指導件数が採用された．診断に関する指標については，診断は各施設が保有している機器に大いに依存することとなるので，評価項目には採用しないことで委員のコンセンサスが得られた．

暫定案と回答

暫定案が決定し，全17項目でがんネットワークに登録されている全国61施設へデータ収集の依頼がなされた（表2）．すべての項目の検討は，限られた紙面では不可能なので，いくつかを選んで検討した．各項目に対し，考察も加えた．

全体の提出率は，55施設で90.2%であったが，値の記載のないものが2施設あり，実際の回答率は86.9%であった．細かい内訳を見てみると愕然とした気持ちを禁じ得なかった．5年生存率を例にとってみてみると，全体の回答率では，63.2%と低率であった．癌腫別では，胃癌において63.2%，大腸癌；68.4%，乳癌；61.4%，子宮癌；59.6%であった．それぞれの実際の値をみてみると，胃癌では0－76.6%，大腸癌で0－87.5%，乳癌で0－100%，子宮癌で0－100%と大きな開きがあった．0%といった記載は，記載間違いとしか思えない．医師の目を通さず，事務レベルで記入されたものと思われるが，数値としてだされると，それが一人歩きをしてしまう．次に，治療関連死を取り上げてみる．回答率は，全体で91.2%．実際の数値は，胃癌では0－64.3%，大腸癌で0－32.0%，乳癌で0－45.0%，子宮癌で0－48.0%と施設間でこれまた大きな開きがあった．治療関連死が64.3%とは医師にとっては誰が考えてもありえない値と思うが，実際に数値としてあがってきているのである．5年生存率と間違えているとも思える値でもある．明らかに医師サイドの目を通していないと思われた．はたして，この値をそのまま鵜呑みにしてよいものだろうか．とうてい思えないというのが結論であろうが，数値として世に出ると，それで評価されるのであるから，慎重の上にも慎重であらねばならないであろう．

最　終　案

その後，最終の検討会を経て，暫定案の4つの癌腫に加えて肺癌，肝細胞癌が加わり，合計24項目で最終案が決定された（表3）．

考　　察

これら評価項目の問題点に関し，考察してみたい．

まず，先述したように，医師サイド，事務サイドの協力で出されたとはとうてい思えない数値があげられていることが問題である．5年生存率を例にとってみると，回答が得られたものが63.2%と非常に低率であった点に

表 2　臨床評価指標（がん政策医療分野）第1回調査項目

胃癌の臨床実績	胃癌患者総数，胃癌治療関連死亡数および率，胃癌切除例の5年生存率（平成7－9年の症例の生存率）；stageⅢ，EMR 施行症例数
乳癌の臨床実績	乳癌全患者数，乳癌の乳房温存手術率，乳癌治療関連死亡率，乳癌切除例の10年生存率（平成2－4年の症例の生存率）；stageⅡ
大腸癌の臨床実績	大腸癌全患者数（全入院治療例），大腸癌治療関連死亡率，大腸癌の5年生存率（平成7－9年の症例の生存率）；stageⅢ，大腸癌ポリペクトミー数
放射線治療の臨床実績	放射線治療実施症例総数，根治照射実施率
子宮癌の臨床実績	子宮頸癌手術治療関連死亡率，子宮頸癌の5年生存率（平成7－9年の症例の生存率）；stageⅢ
緩和医療の臨床実績	オピオイド使用例に対する服薬指導件数および率

表 3 臨床評価指標（がん政策医療分野）最終確定案

胃癌の臨床実績	胃癌患者総数，胃癌治療関連死亡数および率，胃癌切除例の5年生存率（平成7−9年の症例の生存率）；stageⅢ，EMR 施行症例数
乳癌の臨床実績	乳癌全患者数，乳癌の乳房温存手術率，乳癌治療関連死亡数および率，乳癌切除例の10年生存率（平成2−4年の症例の生存率）；stageⅡ
大腸癌の臨床実績	大腸癌全症例数（全入院治療例），大腸癌治療関連死亡数および率，大腸癌切除例の5年生存率（平成7−9年の症例の生存率）；stageⅢ，大腸癌ポリペクトミー数
放射線治療の臨床実績	放射線治療実施症例総数，根治照射実施率
子宮癌の臨床実績	子宮癌患者総数，子宮癌手術治療関連死亡数および率，子宮頸癌切除例の5年生存率（平成7−9年の症例の生存率）；stageⅢ
肺癌の臨床実績	肺癌患者総数，肺癌治療関連死亡数および率，肺癌切除例の5年生存率（平成7−9年の症例の生存率）；stageⅡ
肝細胞癌の臨床実績	肝細胞癌患者総数，肝細胞癌治療関連死亡数および率，肝細胞癌切除例の5年生存率（平成7−9年の症例の生存率）；stageⅡ
穏和医療の臨床実績	オピオイド使用例に対する服薬指導件数および率

ある．施設内のデータベースが整っていれば短時間で出せるはずの基本的な指標である．各施設が，この評価項目をみて，施設ごとにデータベースを整えておく必要性をひしひしと感じたと思われる．近い将来，国立病院機構以外の病院と比較されるときに，データベースを整えておくことは必須の事項と思われた．また，事務サイドと医師サイドの連絡，協力がいかに大切かということも理解できたと思われる．その意味でも，この調査は意義があったと考えている．

次に，施設間の格差がある点である．これには，各施設の診療自体に問題があることもあるであろうが，各施設がある地域の人口構成，疾患構成が考慮されていないこともあげられるだろう．Fujii らは，全国18の癌診療拠点病院における5年生存率を第71回胃癌学会の発表に基づいて紹介している[1]．Stage Ⅲb 期を例にとると，7.8%から57.0%までの開きがあったのである．これには，地域の年齢構成が大いに関係していると思われるが，数値だけを出されると一人歩きしてしまい，施設の真の評価にはほど遠いものとなってしまう可能性があるのではないか．その疾患の年齢構成も同時に記載することである程度，正しい評価が得られるのではないだろうか．

治療関連死亡を公にすることが求められた．とかく埋もれてしまいがちな，というよりも隠されがちな数値を表に出すことで，施設が取り組む安全な医療を評価しようとするものである．前項で述べた実際に上がってきた数値は別として，これからの医療を評価する大切な指標となると考えられる．しかし，ここでも，扱われる癌腫の病期によるバイアスがかかってくると思われる．進行した治療困難な症例が多いところの治療関連死率がある程度高くなるのは大いに考えられるところである．施設ごとに，扱う癌腫の症例構成を併記した方が，より理解しやすくなると思われる．

最　後　に

癌関連指標の大きな特徴は，そのほとんどが診療科におけるデータベースの存在を念頭に置いていることであろう．これは，独立行政法人化後に他施設と競合していくためにもデータベースを整えておくべきだとする意味合いが込められている．この成績が公表されることで，さらに施設ごとの疾患に対する取り組みがシュアになっていくのではないかと思っている．

文　　献

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Evaluation of endoscopic mucosal resection and nodal micrometastasis in pN0 submucosal gastric cancer

KAZUYA ENDO[1], SHUNJI KOHNOE[1], TAKESHI OKAMURA[2], MASARU HARAGUCHI[2], KENICHI NISHIYAMA[3], YASUSHI TOH[2], HIDEO BABA[4] and YOSHIHIKO MAEHARA[4]

[1]Department of General Surgery, Fukuoka Dental College Hospital; Departments of [2]Gastroenterologic Surgery and [3]Pathology, National Kyushu Cancer Center; [4]Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

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Abstract. Endoscopic mucosal resection (EMR) is a minimally invasive, standard treatment for intramucosal (early) gastric cancers, but is not standard for submucosal gastric cancers based on existing criteria. We evaluated the possibility of extending EMR as a therapy for submucosal gastric cancers by analyzing nodal micrometastasis through immunohistochemical staining in patients with apparent node-negative submucosal gastric cancer, the patients for whom EMR might be appropriate. We used anti-cytokeratin (AE1/AE3) antibody to immunohistochemically detect nodal micrometastasis that was not identified by routine pathological examination in 162 patients (total, 2048 lymph nodes) with apparent node-negative submucosal gastric cancer. The relationship between the incidence of nodal micrometastasis and clinicopathological factors was analyzed. Micrometastasis was detected in 45 of 2048 nodes (2.2%), representing 31 of 162 patients (19%). A significantly high incidence of nodal micrometastasis was found with submucosal cancers of large size (>2 cm), as well as with tumors that showed lymphatic or venous invasion and deeper submucosal invasion ($p<0.0001$). Nodal micrometastasis was also recognized in 2 cases of histologically well-differentiated tumors with focal submucosal invasion without venous or lymphatic invasion. Of the 162 patients, only 2 died of recurrent disease regardless of nodal involvement. Based on the present results, risk factors for nodal micrometastasis are tumor size, presence of lymphatic-vascular invasion, and depth of tumor, which are nearly the same as those established in previous pathological studies that used hematoxylin and eosin staining. We conclude that EMR is not recommended for patients with submucosal gastric cancer.

Correspondence to: Dr Kazuya Endo, Department of General Surgery, Fukuoka Dental College Hospital, 2-15-1 Tamura, Sawara-ku, Fukuoka 814-0193, Japan
E-mail: kendo@college.fdcnet.ac.jp

Key words: endoscopic mucosal resection, indication, submucosal gastric cancer, micrometastasis

Introduction

Gastric cancer has been a major cause of cancer deaths in Japan, and early gastric cancer (EGC), defined as disease confined to the mucosa or submucosa regardless of regional lymph node metastasis, has been increasing in incidence. The 5-year survival rate of patients with EGC is >90% following gastrectomy with complete removal of primary and secondary lymph nodes; the incidence of nodal metastasis with mucosal EGC has been reported to be only 3% (1-6). In the last decade, it has been thought that less invasive treatments, which avoid major surgery, may be more appropriate for these patients (1-6).

Endoscopic mucosal resection (EMR) has been accepted by most clinicians as the standard and least invasive treatment for the majority of mucosal early gastric cancers, namely those tumors that satisfy criteria regarding diameter, macroscopic appearance, and histological differentiation. More than 15 years have passed since EMR was first introduced to Japan (2), at which time criteria had been already established that EMR is effective for mucosal gastric cancer. However, the procedure was not standard for submucosal cancer due to the higher incidence of lymph node metastasis (3,4).

Although EMR has been frequently performed for mucosal gastric cancer according to the criteria, it has sometimes been performed for submucosal gastric cancer (that is, beyond the criteria) in two settings: intentional EMR for tumors invading the superficial submucosa in proportion to mucosal cancer, and cases of submucosal invasion by tumor that has been identified only after treatment has been given. In the latter case, additional surgical treatment has been recommended. Because of the increasing number of patients with early submucosal gastric cancer who want to be treated by EMR, the question whether radical resection by EMR may be possible for submucosal gastric cancer under complete prediction of lymph node metastasis has been presented in a few reports (5,6). On the other hand, many studies have revealed that the presence of nodal micrometastasis in histologically node-negative lymph nodes is a prognostic factor that reflects the malignant potential in gastric cancers (7-10).

In this study, we addressed whether EMR can be extended to patients with submucosal early gastric cancer by using

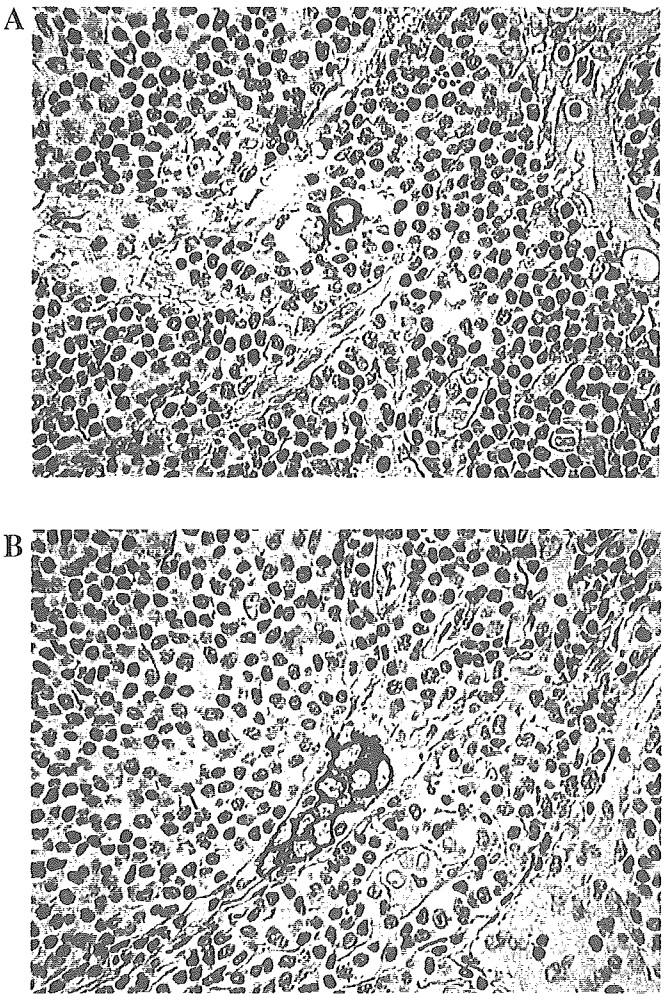

Figure 1. Cytokeratin immunostaining in lymph nodes. (A) Micrometastasis in the form of a single cancer cell. (B) Micrometastasis in the form of clustered cancer cells.

immunohistochemical means to detect nodal micrometastasis in patients with pN0 submucosal disease, and hypothesized that a very low frequency of micrometastasis might be balanced by the benefits of the non-invasive surgical procedure for at least some patients.

Patients and methods

Patients. A total of 162 consecutive patients with pN0 submucosal gastric carcinoma who underwent curative gastrectomy with lymphadenectomy at the Department of Gastroenterologic Surgery, National Kyushu Cancer Center, between 1994 and 2002, were eligible for this study. None had received pre-operative chemotherapy. All 162 patients underwent a D2 lymphadenectomy based on the Japanese classification of gastric carcinoma (11). Pathologic examination revealed that all patients were judged to have no residual disease, yielding a high probability that the resection was curative. The patients consisted of 112 men and 50 women (average age, 65 years).

Total gastrectomy was performed in 26 patients. Distal gastrectomy or subtotal gastrectomy was done for the rest of the patients. Three lesion sites in the stomach were designated as U (upper third), M (middle third), and L (lower third). Tumors were classified into two histologic subgroups. Differentiated type tumors included papillary, well differentiated, and moderately differentiated tubular adenocarcinomas. Undifferentiated type tumors consisted of poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma. Depth of tumor was divided into three grades: submucosal (sm)1, sm2, and sm3. We defined sm1 as slight invasion limited to the upper submucosa. Grade sm2 tumors showed moderate invasion into the middle of the submucosa, and sm3 tumors showed deep and massive submucosal invasion close to the muscular layer. Tumor size was determined on the basis of the superficial maximum diameter of the lesion. Tumors were classified into three macroscopic types: elevated, flat, and depressed. Clinical stage, including lymph node groups, was assigned according to the Japanese classification

Table I: Comparison of clinicopathological characteristics of pN0 submucosal gastric cancer patients with or without the presence of nodal micrometastasis

Characteristics	Total	Nodal micrometastases: Positive (n=31)	Nodal micrometastases: Negative (n=131)	p-value
Sex				NS
Male	112	19 (17%)	93 (83%)	
Female	50	12 (24%)	38 (76%)	
Age	65.3±13.0	61.0±13.7	65.8 ±9.2	NS
Tumor size				<0.05
≤2 cm	50	5 (10%)	45 (90%)	
>2 cm	112	26 (23%)	86 (77%)	
Macroscopic type				NS
Elevated	40	8 (20%)	32 (80%)	
Flat	7	0 (0%)	7 (100%)	
Depressed	115	23 (20%)	92 (80%)	
Location				NS
Upper third	30	7 (23%)	23 (77%)	
Middle third	77	13 (19%)	64 (81%)	
Lower third	55	11 (20%)	44 (80%)	
Tumor depth				<0.0001
sm1	76	5 (7%)	71 (93%)	
sm2	67	15 (22%)	52 (78%)	
sm3	19	11 (58%)	8 (42%)	
Histology				NS
Differentiated	103	17 (17%)	85 (83%)	
Undifferentiated	59	14 (24%)	45 (76%)	
Lymphatic invasion				<0.0001
Positive	42	18 (43%)	24 (57%)	
Negative	120	13 (11%)	107 (89%)	
Venous invasion				<0.0010
Positive	15	8 (53%)	7 (47%)	
Negative	147	23 (16%)	124 (84%)	

NS, not significant.

Table II. Patients with nodal micrometastasis without lymphatic-vascular invasion in histologically differentiated carcinoma invading up to sm2.

Patient	Age	Gender	Tumor size	Mac. type[a]	Depth of tumor	Hist. type[b]	Station of LNM[c]
1	62	M	30 mm	IIc	sm1	Tubl	No. 7
2	53	M	15 mm	IIc	sm2	Tubl	No. 7
3	65	M	18 mm	IIa + IIc	sm1	Tubl	No. 7
4	64	M	95 mm	IIc + III	sm2	Tubl	No. 4d

[a]Macroscopic and [b]histological type, according to reference (11). [c]Station of lymph node micrometastasis.

Table III. Details of deceased patients in pN0 submucosal gastric cancer.

Patient	Age	Gender	Tumor size	Mac. type[a]	Depth	Hist. type[b]	Ly[c]	Cytokeratin	Cause of death
1	65	M	50 mm	IIb + IIc	sm2	Tubl	(-)	(-)	Another cancer
2	77	M	19 mm	IIc	sm2	Tubl	(+)	(-)	Pneumonia
3	70	M	48 mm	IIc	sm1	Tubl	(-)	(-)	Another disease
4	72	M	65 mm	IIc	sm1	Tub2	(+)	(-)	Liver metastasis
5	78	M	106 mm	IIa + IIc	sm3	Por2	(+)	(+)	Peritoneal disseimination
6	49	M	30 mm	IIa	sm1	Porl	(+)	(-)	Tongue cancer
7	81	M	36 mm	IIc	sm1	Tubl	(+)	(-)	Another disease
8	66	M	12 mm	IIa + IIc	sm2	Porl	(+)	(+)	Myeloma
9	80	M	25 mm	IIc	sm3	Porl	(-)	(-)	Another disease
10	73	M	30 mm	IIc + III	sm3	Porl	(-)	(-)	Pneumonia
11	71	M	30 mm	IIc + III	sm1	Tub2	(-)	(-)	Heart failure
12	86	F	30 mm	IIc	sm2	Tubl	(-)	(-)	Old age
13	70	F	40 mm	IIa	sm2	Tubl	(-)	(-)	SMA[d] embolism
14	65	M	85 mm	IIc	sm1	Tubl	(+)	(+)	Post-operative complication

[a]Macroscopic and [b]histological type, according to reference (11). [c]Lymphatic invasion and [d]super mesenteric artery.

of gastric carcinoma (11). Tumors and their regional lymph nodes, fixed in formalin and embedded in paraffin, were examined by immunohistochemical techniques. As many perigastric lymph nodes as possible were collected by means of careful manual palpation.

Immunohistochemical staining. A total of 2048 lymph nodes were collected from the 162 patients. The mean number of investigated lymph nodes per patient was 12.6. Two consecutive sections of 4-μm-thickness were prepared from each sample. One section was stained with hematoxylin and eosin (H&E). The other was subjected to specific immunostaining with anti-cytokeratin antibody (20:1 mixture of AE1 to AE3; Boehringer, Mannheim, Germany), a monoclonal antibody cocktail that is reactive with a broad spectrum of human cytokeratin (7-9,17). All sections were incubated at 60°C overnight. Tissue sections were then deparaffinized in xylene and rehydrated with a series of graded ethanols. After cooking the slides in citrate buffer solution (pH 6.0) for 6 min in a pressure cooker, sections were incubated with the AE1/AE3 mixture at a 1:100 dilution. The reactions for cytokeratin were developed using an alkaline phosphatase technique. Normal and carcinomatous gastric tissues were used as positive controls.

Evaluation of micrometastasis in lymph nodes. First, the H&E-stained slides were assessed by a pathologist for the presence of metastasis although all lymph nodes used for the current study had already been diagnosed as having no metastasis (pN0). Then, AE1/AE3-positive cells in the lymph node were examined and compared with the same sections as those stained with H&E. Micrometastasis was confirmed by the presence of AE1/AE3-positive cells in the lymph node without evidence of pathological lymph node metastasis. Any tumor cells, single or in groups, detected by AE1/AE3 staining were considered to be positive (Fig. 1). The reviewing pathologist was blind to corresponding clinical data and outcome.

Statistical analysis. We divided the 162 patients into two groups depending on whether lymph nodes were AE1/AE3-positive or -negative and compared clinicopathological characteristics using the Chi-square and Mann-Whitney tests. A p-value <0.05 was considered statistically significant.

Results

Immunohistological staining revealed single tumor cells or clusters located at the marginal sinus of the lymph node

(Fig. 1). Initially, 164 patients were considered eligible and enrolled in the present study. However, 2 patients were excluded due to positive results of re-examination of H&E stained sections prior to AE1/AE3 staining. Thus, a total of 162 patients were analyzed for this study.

Based on results of immunohistochemical staining, 31 of 162 patients (19%) and 45 of 2048 lymph nodes (2.2%) were positive for nodal micrometastasis. We compared clinicopathological factors for micrometastasis-positive and -negative groups (Table I). Nodal micrometastasis was more frequent with large primary tumors (superficial diameter >2 cm) and increased with increasing depth of invasion: 5 of 76 patients (6.6%) in sm1 had nodal micrometastasis compared with 15 of 67 (22%) sm2 cases and 11 of 19 (58%) sm3 cases (Table I) ($p<0.001$). We also recognized nodal micrometastasis in 2 patients with sm1 histologically differentiated tumors that showed no evidence of lymphatic or venous invasion (Table II). Regarding other factors, the micrometastasis-positive group had a greater incidence of lymphatic or venous invasion ($p<0.001$), which was detected in 14 of 76 sm1 patients (18%), 30 of 67 sm2 patients (45%), and 6 of 19 sm3 patients (30%), (data not shown). No significant differences were noted between the two groups with respect to gender, age, tumor location, or histological differentiation (Table I).

Of 162 patients, 14 have died at the time of this writing. Specifically, 2 micrometastasis-negative patients died of recurrent disease with liver metastasis and peritoneal dissemination, 4 patients died of another cancer, and the rest of the patients died from pneumonia, old age, or post-operative complications other than recurrent gastric cancer (Table III). No differences in survival were recognized, based on nodal status for the 87 patients who have been followed for >5 years after their surgery (data not shown).

Discussion

It has been 15 years since EMR was first introduced to Japan. Although the number of patients undergoing EMR is increasing due to its low invasiveness compared with other surgical treatments, there are still problems to be solved regarding its indications, technique, evaluation of curability, and follow-up (1,12,13). Along with developments in EMR technique, instruments related to EMR have also been improved or introduced (e.g. the insulation-tipped diathermy knife), and both have simplified the procedure and expanded its indications (1,12,13). Despite the expansion of indications, EMR is basically still considered a treatment for early mucosal gastric cancers that satisfy original criteria and not a treatment for submucosal gastric cancer. EMR for submucosal gastric cancer has been limited to those cases with microinvasion to the submucosal layer that satisfy criteria other than tumor depth (5,6,12,13). Although the number of patients requesting EMR for early gastric cancer is increasing, there is no consensus of opinion on further expansion of indications for EMR, including the possibility of being an additional surgical treatment after the initial EMR procedure.

The barrier to extending indications for EMR is the higher incidence of lymph nodes metastasis in submucosal cases compared with mucosal cases (3,4). According to previous studies, tumor size >30 mm, tumor depth greater than sm2, and lymphatic-vascular involvement are risk factors for lymph node metastasis with submucosal early gastric cancers (3,4). Thus, we formed the hypothesis that the extension of EMR indications is possible under complete prediction of lymph node metastasis based on the above risk factors (5,6,12,13).

In the current study, we examined possible nodal micrometastasis in submucosal gastric cancer cases that were histologically node-negative (pN0), thus investigating indications for EMR retrospectively. Our data show that the incidence of nodal micrometastasis increased depending on depth of tumor (6.5% of sm1 patients, 22% of sm2 patients, and 63% of sm3 patients), and it was identified in 58% of patients whose tumors showed lymphatic invasion.

All sm2 and sm3 patients with both lymphatic and vascular invasion were positive for immunohistochemical signs of micrometastasis. Of 31 patients with nodal involvement, 26 (81%) had large tumors with a superficial diameter of >2 cm. These data indicate that lymphatic-vascular invasion and tumor size are also significant risk factors for micrometastasis in histologically negative nodes per H&E staining (3,4). Furthermore, we recognized micrometastasis in 2 patients with sm1 histologically well differentiated tumors without venous and lymphatic invasion. Superficial tumor diameter in the 2 micrometastasis-positive patients just described was <2 cm, which satisfied an EMR criterion (Table II) (1,5,6,12,13).

Many studies (7-10,15) have reported that the incidence of nodal micrometastasis is a potent prognostic factor in pN0 gastric cancer, but this is of little prognostic value in submucosal gastric cancer (16,17). Cai and colleagues (14) reported that tumor size, macroscopic type, lymphatic invasion, and tumor depth were strongly associated with lymph node involvement including micrometastasis, findings that are similar to ours. Nodal micrometastasis in submucosal gastric cancer appears to be less effective as a predictor of prognosis, but it may indicate some malignant potential through the clinical factors empirically related to prognosis (16,17).

In conclusion, our data support current EMR criteria. EMR is probably not appropriate as an additional surgical treatment for patients with tumors >2 cm in diameter or invading past the sm2 level, regardless of lymphatic-vascular invasion status. However, the clinical impact of nodal micrometastasis in cases of submucosal gastric cancer is controversial, and our results do not completely rule out the possibility of extending EMR indications. Further studies and progression of techniques for prediction of lymph node metastasis are required.

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