わが国の大腸がん治療成績は世界でも高い水準を示している。わが国においては、「大腸癌治療ガイドライン」[2]に沿った系統的リンパ節郭清を伴う手術が標準的治療として広く普及しており、そのため、一般に治癒切除可能であるStage0～StageⅢの大腸がんにおいては、今後は手術手技そのものによる治療成績の大幅な改善はないものと予想される。一方で、高度な診断技術や手術技術をもってしても、治癒切除後であっても残念ながら一定の割合で再発を伴うことは避けられず、約30%の症例に再発が起こるのが現状である。

再発大腸がんの治療としては、再発巣の完全切除(治癒切除)が可能であれば、切除後には約40%の5年生存率が期待できるため、切除が推奨される。切除不能進行・再発大腸がんにおいても、新規抗がん剤や分子標的治療薬の登場と、それに伴う新しい多剤併用レジメンの開発により、生存期間中央値は20ヵ月を超える時代に突入している。しかし、化学療法を主とした非手術治療のみでは、根治に至る再発大腸がん症例は今なお非常にまれである。

そこで、重要となるのは"再発の抑制"であり、その手段として、術後補助化学療法のさらなる発展が期待される。

わが国における大腸がん術後補助化学療法の現状と課題

従来わが国では、大腸がん術後補助化学療法として、経口フッ化ピリミジン(FU)系薬剤の1～2年間投与が行われてきたが、1990年代に欧米において、5-FU＋ロイコボリン(LV)静注療法の結腸がん術後補助化学療法としての有効性が確立され、1999年にわが国でLVが保険承認されると、「エビデンスに基づいた補助化学療法」の考え方が浸透し、5-FU＋LVによる術後補助化学療法が広く行われるようになった。その後、5-FU＋LV療法(RPMI法)とUFT＋LV療法、5-FU＋LV療法(Mayo法)とカペシタビン療法の非劣性が証明され[3,4]、併せて、経口抗がん剤としての利便性、医療経済性の高さも報告された[5,6]。

現在わが国では、5-FU＋LV静注療法(RPMI法)、UFT＋LV療法、カペシタビン療法の3レジメンが、結腸がん術後補助化学療法の「標準治療」として「大腸癌治療ガイドライン(医師用・2009年版)」[2]に記載されている。加えて、現在わが国では、UFT＋LVとS-1の非劣性を検証する大規模比較試験(ACTS-CC trial)が進行中であり、S-1とカペシタビンの非劣性を検証する臨床試験も開始予定である。さらに、2009年9月頃には、オキサリプラチンの大腸がん術後補助化学療法としての適応拡大が予定されており、大腸がん術後補助化学療法における選択肢が広がってきている(図1)。

治療法の選択にあたって考慮すべきことは、第一にその有効性(効果)と安全性(副作用)であり、さらにそれらに加えて、患者の利便性やQOL、医療経済性がある。そこで今後は、これらの要素をすべて満たすべく、①適切な対象に、②適切な薬剤・レジメンを、③適切な期間投与することを追求した、適切な治療の選別－「治療の個別化」が課題である(図2)。

対象の個別化 ～再発リスクによる対象の選別～

効率的な術後補助化学療法を行うには、その治療によって予後の改善というメリットを得ることができる可能性が高い対象を選ぶことが重要である。その方法として一般的なのは、再発リスクを分別することである。

1. StageⅡハイリスク群の抽出

「大腸癌治療ガイドライン(医師用・2009年版)」[2]では、補助化学療法の「適応の原則」を「R0切除が行われたStageⅢ大腸癌(結腸癌・直腸癌)」としている。大腸癌研究会プロジェクト研究におけるStage別再発率は、StageⅡでは13.3%、StageⅢでは30.8%であり[2,7](Stage分類は大腸癌取扱い規約【第6版】による)、StageⅢの再発率はStageⅡに比し2倍以上と高く、また、StageⅢに対する術後補助化学療法の有用性は国際的にコンセンサスが得られている(図3、図4)。

一方、わが国におけるStageⅡ症例の予後は、5年生存率が約80%と非常に良好であり、StageⅡに対する補助化学療法の必要性については「大腸癌治療ガイドライン」[2]でも、「再発リスクが高いStageⅡ大腸癌には、適切なインフォームド・コンセントのもとに、補助化学療法の適応を考慮する」、加

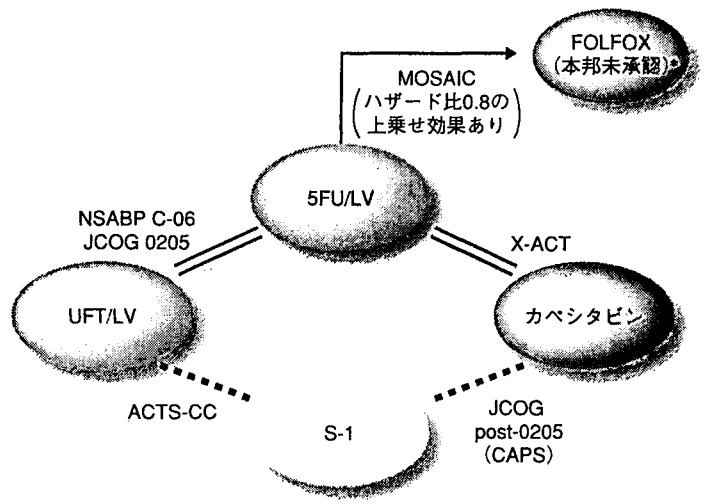

図1　結腸がん術後補助化学療法の選択肢
＊：2009年8月現在。

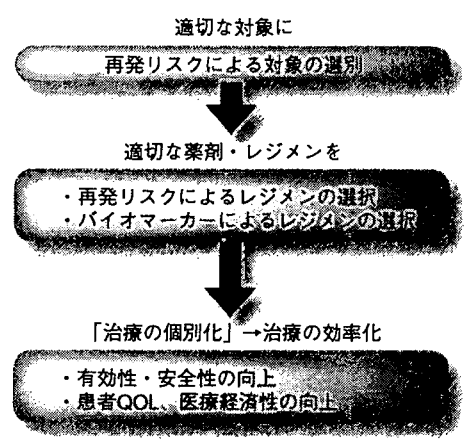

図2　治療法の選択にあたって
～治療の個別化～

えてClinical Questionとして「Stage Ⅱ大腸癌に対する術後補助化学療法の有用性は確立しておらず、すべてのStage Ⅱ大腸癌に対して一律に補助化学療法を適応することは妥当ではない」としている。

しかしその一方で、Stage Ⅱのなかに、Stage Ⅲに勝る再発高危険群が存在することも指摘されている。Petersenら[8]はDukes' B症例の予後不良因子として漿膜浸潤、脈管侵襲、断端陽性、穿孔の4つをあげてスコア化し、スコア別の予後をDukes' C症例と比較した。その結果、リンパ節転移が1個のみのDukes' C症例に比し、このスコアにより分別された「ハイリスクStage Ⅱ」症例では有意に予後が不良であった。米国の代表的なガイドラインであるNCCNガイドライン[9]では、結腸がん術後補助化学療法の対象を、リンパ節転移のある症例(大腸癌取扱

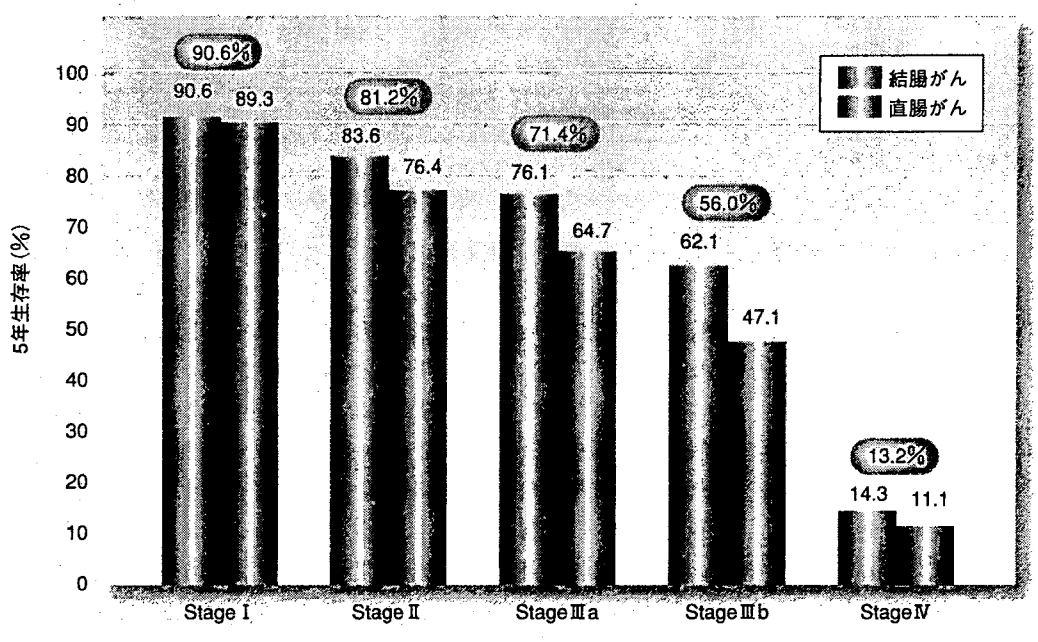

図3　Stage別5年生存率(文献2より改変引用)(大腸癌研究会・大腸癌全国登録 1991～1994年度症例)
注)Stage分類は「大腸癌取扱い規約」[第6版]による。

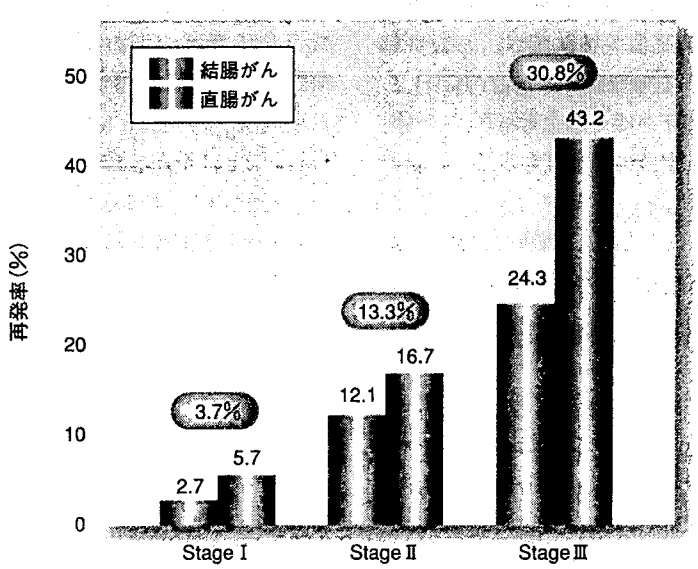

図4　Stage別再発率(文献2,7より改変引用)
(大腸癌研究会プロジェクト研究 1991～1996年症例)
注)Stage分類は「大腸癌取扱い規約」[第6版]による。

表1 StageⅡ大腸がん「ハイリスク因子」の候補

臨床病理学的因子
深達度T4、漿膜浸潤、低分化な組織型、脈管侵襲、簇出、穿孔、腸閉塞、検索リンパ節個数(12個未満)など
分子生物学的因子
MSI (microsatellite instability)、18qLOHなど

い規約【第7版】のStageⅢにあたる)および、リスク因子のあるTNM-StageⅡ症例(同規約【第7版】StageⅡにあたる)としており、リスク因子として、T4、穿孔、腸閉塞、脈管侵襲、閉塞、低分化な組織型、検索リンパ節個数12個未満、などをあげている。その他のガイドラインなどにおいても、この「ハイリスクStageⅡ」という表現はしばしば用いられ、ほぼ同様の因子がリスク因子としてあげられているが、明確な定義はなされておらず、いまだ統一したコンセンサスが得られていない状況である(表1)。

今後は、より効率的かつ可能な限り簡便な方法で「ハイリスクStageⅡ」症例を抽出し、補助化学療法の対象に含め、これらの症例における予後の向上を目指すことが、早急な課題であろう。わが国では、StageⅡ結腸がんに対する術後補助化学療法の有用性、および「ハイリスクStageⅡ」症例を抽出する因子の探索を目的とした大規模比較試験(SACURA trial)が進行中であり、その結果が待たれる。

2. 転移・再発巣切除後の補助化学療法の有用性の検証

大腸がんにおいては、前述の如く、転移・再発巣の治癒切除により予後の改善が得られることが明らかとなっており、積極的に切除が行われている。約40%の症例では根治も期待できるが、一方でその再々発率は高い。そこで、再々発予防のための、転移・再発巣切除後の補助化学療法が考慮されるが、その有用性はいまだ確立されていない。

現在わが国において、大腸がんの転移・再発として最も頻度の高い肝転移について、肝切除後の補助化学療法としてのFOLFOX療法の有用性が検討されている(JCOG0603)。肝臓や肺などの主要臓器の切除後は、有害事象が強く出る可能性や、患者のQOLを著しく低下させる懸念もあり、有効性と併せて安全性の検証も非常に重要である。

治療法(レジメン)の個別化～何を基準に選択すべきか～

レジメンの選択にあたっては、その治療によって対象とする患者群にどれだけの予後改善が見込めるか、また、補助化学療法であるという性格上、予想される効果に対して許容できる範囲の副作用であるか、患者のQOLを極力損ねないものであるか、また費用に見合う効果が得られるか、などを総合的に判断し、対象に見合ったレジメンを選択することが望まれる。その選択が的中する"精度"を上げるためには、一般的な方法として、再発リスクによる治療intensityの個別化があり、今後の発展が期待される方法として、バイオマーカーによる薬剤の個別化がある。

1. 再発リスクによるレジメンの選択

Stageは単純で分別能の高い有用な予後予測因子である。StageⅡ、StageⅢa、Ⅲbの5年生存率はそれぞれ81.2%、71.4%、56.0%であり[2]、StageⅢbは予後不良群であるといえる。また、結腸がんと直腸がんを比較した場合、直腸がんの再発率は有意に高率であり、5年生存率においてもStageによっては5～15%程度の開きがある[2]。このような予後の異なる患者群に対して、画一的に同じレジメンによる補助化学療法を行うのは非効率的である。StageⅢbのような、再発率が30%を超えるいわゆる「再発高危険群」に対しては、現在のわが国における標準レジメンである5-FU＋LVな

どよりもさらに強力な治療として、FOLFOXなどのオキサリプラチン併用レジメンを考慮する余地がある。

MOSAIC[10]では、FOLFOX4と5-FU＋LVとのStageⅡ・Ⅲ症例に対する補助化学療法としての有効性を比較し、StageⅢ症例において5年無病生存割合で5.9％(73.3％：67.4％、ハザード比0.80)、6年全生存割合で2.5％(78.5％：76.0％、ハザード比0.84)のオキサリプラチンによる上乗せ効果が示された。ただし、わが国と欧米ではそもそも治療成績が異なり、5年生存率において10～20％の差が存在する。そのため、わが国においては、すべてのStageⅢ症例に術後補助化学療法としてFOLFOXを行うことは大いに議論の余地のあるところである。しかし、いくつかのリスク因子によりさらに症例を絞り込めば、「ハイリスクStageⅢ」症例の治療成績を向上させる強力な手段となる可能性も高く、期待がもたれる。

また、同試験においては、StageⅡ症例におけるオキサリプラチンの上乗せ効果は認められなかった。もともと再発率が15％程度のStageⅡ症例に対して、一律にFOLFOXのようなintensiveかつ高価な治療を行うことは、効果がないばかりか、患者QOLおよび医療経済的な観点においてむしろマイナスである。

いずれにせよ、わが国と欧米では手術成績も異なり、また医療保険制度も大きく異なるため、術後補助化学療法に関しては、欧米のエビデンスをそのまま外挿することには慎重にならねばならない。また、同じStageであっても、その臨床病理学的因子によって、特に予後良好な群、平均的な予後を辿る群、特に予後不良な群が存在することは、常に感じるところである。Stageのみによる分別ではなく、より効率的なリスク因子の同定を含めた、わが国におけるエビデンスを積極的に構築していく必要がある。

2. バイオマーカーによるレジメンの選択

前述のごとく、結腸がん術後補助化学療法として、わが国で使用できるレジメンには複数の選択肢がある。非劣性とされている複数のレジメンのなかから、何を基準に、どのレジメンを選択すべきかが、今後解決すべき課題である。

そもそもFU系薬剤の歴史は長く、FU系薬剤の感受性に関する研究はこれまでに数多く行われてきた。これらの結果から、その有効性・安全性は、TS、DPD、TP、OPRTなどのFU系代謝関連酵素の発現に影響を受けることが報告されている(**図5**)。Salongaら[11]は、高TS、高DPD、高TPの腫瘍は5-FU＋LVに抵抗性であることを示し、市川ら[12]は、低TS、低DPD、高OPRTの腫瘍でUFT/LVの効果が高いことを報告した。また、西村ら[13]は、カペシタビン投与症例において、腫瘍内TPが高値の症例群ではTP低値群に比し有意に無再発生存率が高いことを示した。これらと同様の内容の報告は複数あり、すでにコンセンサスを得ていると考えられるが、個々の報告における検討症例数は少なく、いまだ臨床応用には至っていない。

また、個々のFU系経口抗がん剤には、創薬コンセプトともいうべき薬剤の特性がある。UFTは、5-FUのプロドラッグであるテガフールに、5-FUを分解代謝するDPDを阻害するウラシルを配合することにより、5-FUの血中濃度を維持する。さらに、葉酸であるLVを併用することにより、TSと強固なternary complexを形成し、5-FUの抗腫瘍効果を高めている。カペシタビンは、3つの代謝酵素により段階的に代謝を受け、腫瘍内に発現の多いTPで選択的に5-FUに変換され、腫瘍内5-FU濃度を選択的に高めるとともに、消化管毒性を軽減させる工夫がなされている。

今後の大腸がん術後補助化学療法は、これらFU系代謝関連酵素などを<バイオマーカー>として、個々の腫瘍プロファイルと薬剤の特性に応じて、理論的に薬剤を選択する「個別化治療」の臨床応用の実現を目指す方向へ進むものと予想される。現在わが国では、腫瘍内のFU系代謝関連酵素の発現と補助化学療法の有効性・安全性との関連を検討し、個別化治療の可能性を検討する大規模コホート研究(B-CAST)が進行中である。

術後補助化学療法の至適期間の検証

1990年代の欧米の無作為比較試験において、間接的ではあるが、5-FU＋LVの6ヵ月投与は5-FU＋LEVや5-FU＋LVの1年間投与と同等の有効性があることが示された。これに準じて、その後の経口抗がん剤と5-FU＋LVと

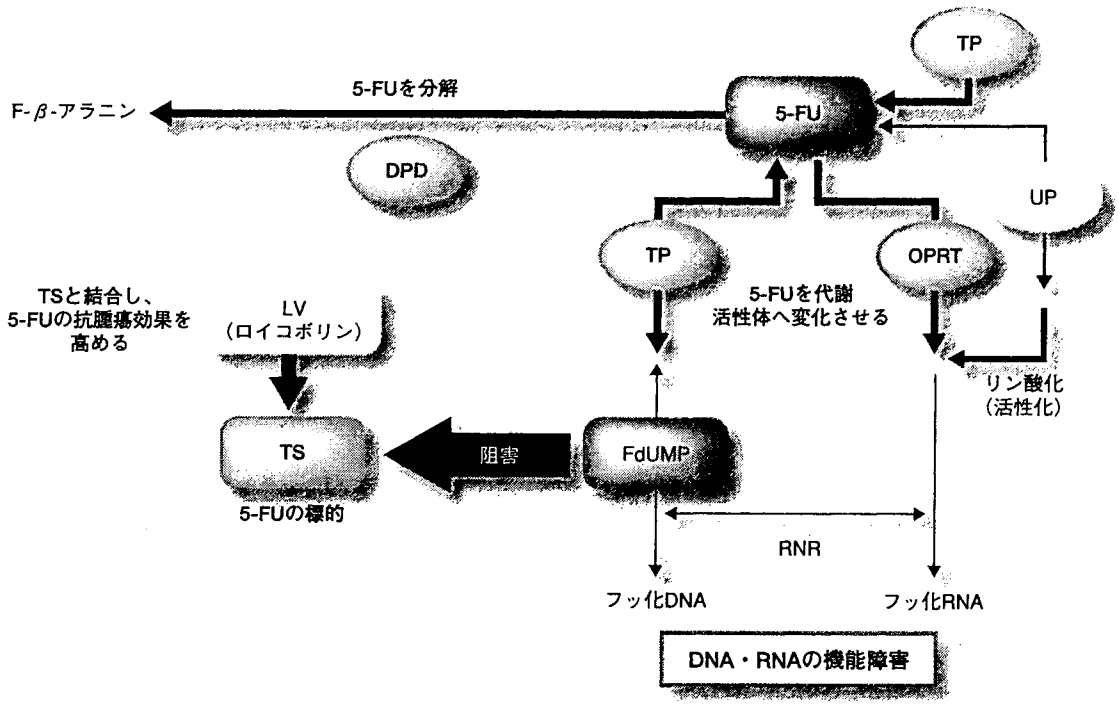

図5　5-FUの作用・代謝経路

DPD：dihydropyrimidine dehydrogenase、FdUMP：fluorodeoxyuridine monophosphate、OPRT：orotate phosphoribosyl transferase、RNR：ribonucleotide reductase、TP：thymidine phosphorylase、TS：thymidylate synthetase、UP：uridine phosphorylase。

の比較試験においても、6ヵ月投与によるエビデンスが集積され[3,4]、現在、術後補助化学療法は「6ヵ月間」が標準とみなされている。しかし、補助化学療法としての経口抗がん剤の投与期間に関しては、いまだ明確な検証はなされていない。治療期間の長短による効果の差異が証明されれば、再発リスクに応じて治療期間を決定するという、新たな「治療の個別化」の可能性も生じてくる。

現在、わが国では経口抗がん剤（UFT、カペシタビン）、海外ではFOLFOX4の至適投与期間を検討する比較試験が行われている。補助化学療法の投与期間は、その有効性のみならず、患者のQOLおよび経済的負担に直結する重要な問題であり、検証の結果が待たれる。

おわりに

大腸がん術後の補助化学療法は、治療の選択肢が広がった現在、新たな方向性である「個別化治療」を目指す時代に入っている。具体的には、

・再発リスクの層別化と、リスクに応じた治療intensityの選択
・腫瘍プロファイル（バイオマーカー）による、より有効かつ安全なレジメンの選択

が当面の課題である。適切な「個別化」を図ることによって、有効性・安全性の向上のみならず、治療の効率化による患者QOL・医療経済性の向上も期待できる。わが国の治療成績に基づいた、わが国独自のエビデンスを発信することが強く望まれる。

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ORIGINAL ARTICLE

Apocrine metaplasia of breast cancer: clinicopathological features and predicting response

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Abstract
Background Tailor-made therapies are currently gaining prominence, and the clarification of predictive markers for anticancer agents represents an important research issue. From our institutional neoadjuvant experience, apocrine carcinoma showed a high correlation with therapeutic effect against breast cancer. We thus considered that apocrine metaplasia (AM) might represent a predictive marker for breast cancer.
Methods A total of 210 primary invasive breast cancers from Japanese patients were scored according to the size of cytoplasmic granules and abundance of cytoplasm, then classified into three categories: non-AM, incomplete AM and complete AM. Clinicopathological features were evaluated based on these classifications.
Results Distribution according to the classification of AM was: non-AM, 61%; incomplete AM, 36%; and complete AM, 3%. No significant differences with regard to estrogen receptor, progesterone receptor, human epidermal growth factor receptor type 2, androgen receptor or bcl-2 were observed among the three groups. Gross cystic fluid protein-15 showed a high positive rate (83%) for complete AM. Cases of incomplete AM and complete AM were combined to form the AM group. Among lymph node-positive patients without chemotherapy, the 10-year recurrence-free survival (RFS) rate was 85% for non-AM and 44% for AM ($p < 0.05$). Conversely, among the lymph node-positive group with chemotherapy, the 10-year RFS rate was 45% for non-AM and 75% for AM ($p < 0.05$). Prognoses for non-AM and AM were turned around by chemotherapy. Lymph node metastasis was related to prognosis in multivariate analysis, although AM did not remain an independent prognosticator.
Conclusions Apocrine metaplasia appears to offer an effective predictive marker for anticancer therapy.

Keywords Breast cancer · Apocrine metaplasia · Chemotherapy · Predictive marker

Abbreviations

AM	Apocrine metaplasia
IDC-NST	Invasive ductal carcinoma of no special type
RFS	Recurrence-free survival
ER	Estrogen receptor
PgR	Progesterone receptor
HER2	Human epidermal growth factor receptor type 2
AR	Androgen receptor
CMF	Cyclophosphamide, methotrexate and fluorouracil
GCDFP-15	Gross cystic disease fluid protein-15

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Introduction

Apocrine metaplasia (AM) is a common pathological change in breast epithelial cells and is seen in association with normal ducts and lobules, benign lesions such as cyst and papilloma, in situ carcinoma and invasive carcinoma [1–3]. Apocrine carcinoma demonstrates the same architectural growth pattern as invasive ductal carcinoma of no special type (IDC-NST), differing only in cytological appearance. Carcinoma showing cytological features of apocrine cells in most of the tumor cells is diagnosed as apocrine carcinoma [1, 4, 5]. The prevalence of apocrine carcinoma is reportedly 0.3–4% [2, 6–8]. AM is not reflected in the diagnosis if the association with breast cancer is focal or incomplete, but these kinds of AM are not uncommon and can be seen in 12–63% of IDC-NST [7, 9, 10].

Breast cancer is classified into numerous histological types according to morphology. Recently, in addition to the classification of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor type 2 (HER2), classification by gene profiling using DNA microarray analysis has been established and has opened a new era of histological classification for the breast cancer. Conversely, to achieve optimal systematization for chemotherapy, there is a continual drive to identify markers that will aid in predicting prognosis and response to therapy [11–15]. Breast cancer is a morphologically and biologically heterogeneous disease that shows individual responses to the same treatment. Valid predictors of the efficacy of chemotherapy would allow the selection of candidates who will respond well to treatment and would also help to exclude poor candidates who are likely to experience undesirable side effects rather than the benefits of treatment. Over the last decade, several efforts have been made to identify predictors of response to anticancer agents. ER and PgR status has been used for many years to help determine the suitability of patients for endocrine therapy. More recently, testing for HER2 has been included in routine patient workups, in recognition of the value of this parameter as both a prognostic marker and, more particularly, a predictor of response to trastuzumab. In addition, numerous studies have investigated prognostic factors in breast cancer, such as histopathological features [16] and, at the molecular level, proliferation indices (Ki67, S-phase fraction) and p53 mutations to predict response to general anticancer agents. Evaluations have likewise been conducted for dihydropyrimidine dehydrogenase and thymidylate synthase levels in tumor to predict response to 5-fluorouracil [17, 18] and HER2 and topoisomerase IIα levels in tumor to predict response to anthracycline [19, 20]. Such predictive biomarkers remain under development.

At the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, neoadjuvant chemotherapy was performed for 473 patients between January 2000 and June 2006 [21]. The rate of complete response according to histological therapeutic efficacy criteria in Breast Cancer Management was 7% (10/141) for solid-tubular carcinoma, which was the most effective therapeutic effect among IDC-NST. With respect to special types, few cases of apocrine carcinoma were seen, and the rate of complete response was 25% (2/8), representing the highest therapeutic effect among the histological types of invasive carcinoma. This result suggests AM as a good candidate for a predictive marker.

AM is also interesting at the level of basic research. Farmer et al. [22] reported the identification of a group of breast tumors with increased androgen signaling and a "molecular apocrine" gene expression profile using cDNA expression arrays. All tumors in this group were ER-negative and were non-basal tumors as defined by the intrinsic gene set in the Stanford array studies [23]. Pathological review of these tumors showed that all demonstrated marked apocrine features, so the tumors were referred to as "molecular apocrine." Molecular apocrine tumors overlapped significantly with the HER2 group, for which anthracycline regimens show high efficacy [24, 25], suggesting a link between AM and chemosensitivity at the molecular level. Associations between therapeutic effect and "molecular apocrine" have yet to be studied, and the clinical value of "molecular apocrine" remains unclear. Further studies are required to confirm associations between "molecular apocrine" and therapeutic effect.

The present study hypothesized that AM offers a useful predictive marker for therapeutic efficacy and proceeded to analyze our institutional data retrospectively.

Patients and methods

Patients

We retrospectively examined data from 483 Japanese patients who had been surgically treated for primary invasive breast cancer in 1996 at the Cancer Institute Hospital, Tokyo, Japan. Patients with bilateral breast cancer, unilateral multiple breast cancers, unknown cause of death, double cancers, neoadjuvant therapy, post-excisional biopsy, stage IV cancer, unmeasurable cancer (tremendous lymphatic permeation or mucocele-like tumor) or death due to reasons other than breast cancer were excluded from analysis. A total of 210 cases (43%) with tumors showing a diameter of 1.1–3.0 cm were selected. Median duration of follow-up was 124 months (range 43–129 months).

In 1996, no guidelines had been set for adjuvant therapy, and the individual doctor made the decision as to whether adjuvant therapy would be performed for a patient. Hormone therapy was considered to have been performed if duration of this therapy was >2 years. At that time, 92% of adjuvant hormonal therapy was tamoxifen and 70% of adjuvant chemotherapy was cyclophosphamide, methotrexate and fluorouracil (CMF).

Scoring

A representative slide was stained using hematoxylin and eosin. Based on the characteristics of AM, we scored the size of cytoplasmic granules and the abundance of cytoplasm into three categories each. Abundance of cytoplasm was defined as the ratio of cytoplasmic area to nuclear area. Cytoplasmic granule score was: 1, no cytoplasmic granules; 2, fine cytoplasmic granules; 3, coarse cytoplasmic granules (Fig. 1). Abundance of cytoplasm score was: 1, ratio <2; 2, ratio ≥2 but <3; 3, ratio ≥3 (Fig. 2). Total score was then classified as follows: total score 2 or 3, non-AM; 4 or 5, incomplete AM; 6, complete AM.

Immunohistochemistry

Staining for ER, PgR, HER2, gross cystic disease fluid protein (GCDFP)-15, AR and bcl-2 were performed immunohistochemically. All immunohistochemical studies were performed using formalin-fixed, paraffin-embedded specimens. Representative slides were selected for immunohistochemistry. Antigen retrieval was performed by boiling sections to be immunostained for ER, PgR or bcl-2 for 2 min in 10 mM citrate buffer (pH 6) utilizing a pressure cooker. For AR immunohistochemistry, sections were boiled in Target Retrieval Solution High pH (Dako, Carpinteria, CA) for 40 min. Antigen retrieval was not needed for GCDFP-15 staining. Sections were incubated with the following antibodies: anti-GCDFP-15 mouse monoclonal (clone D6, diluted 1:100; Signet Laboratories, Dedham, MA), anti-AR mouse monoclonal (clone AR27, diluted 1:100; Novocastra Laboratories, Newcastle, UK), prediluted anti-ER mouse monoclonal (clone 1D5; Dako), prediluted anti-PgR mouse monoclonal (clone 1A6; Dako) and anti-bcl-2 oncoprotein mouse monoclonal (clone 124, diluted 1:20; Dako). Incubation for anti-GCDFP-15, -ER, -PgR and -bcl-2 antibodies was for 60 min at room temperature, while that for anti-AR antibody was overnight at 4°C. ChemMate Envision (Dako) was used for all immunohistochemical reactions. Appropriate negative and positive controls were included in each batch. HER2 immunohistochemistry was performed using a Dako Herceptest kit (Dako) according to the designated procedure.

Immunoreactivities for ER, PgR, AR, GCDFP-15 and bcl-2 were scored independently by evaluating the percentage of positively stained cancer cells, with nuclear immunoreactivity to steroid hormone receptors in ≥10% of cancer cells and cytoplasmic immunoreactivity to GCDFP-15 and bcl-2 in ≥10% of cancer cells considered as positive results. Tumors were considered HER2-positive if ≥10% of tumor cells showed distinct circumferential membrane staining. HER2 was scored with a system that has recently come into clinical use (scores: 0; 1+, >10% cells weakly positive; 2+, moderate homogeneous staining; 3+, strong homogeneous staining).

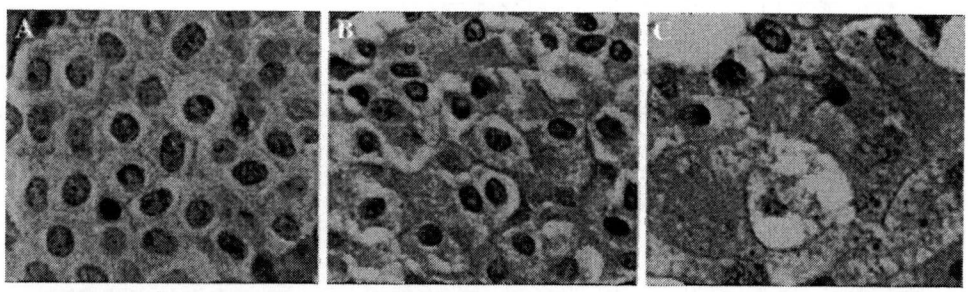

Fig. 1 Cytoplasmic granule score (H&E). **a** Score 1, no cytoplasmic granules. **b** Score 2, fine cytoplasmic granules. **c** Score 3, coarse cytoplasmic granules

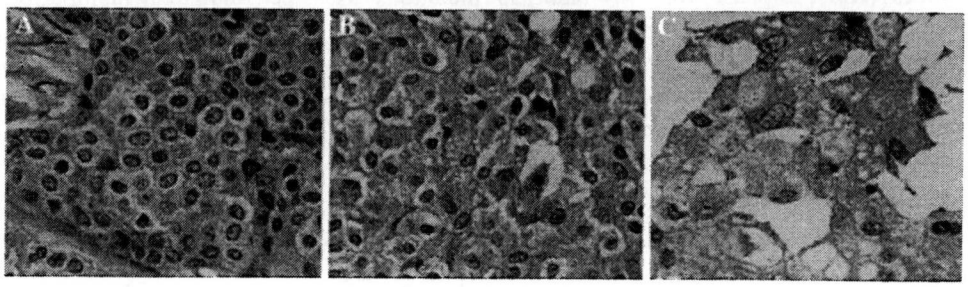

Fig. 2 Abundance of cytoplasm score (H&E). **a** Score 1, cytoplasmic area/nuclear area <2. **b** Score 2, cytoplasmic area/nuclear area ≥2 but <3. **c** Score 3, cytoplasmic area/nuclear area ≥3

Statistical analysis

Recurrence-free survival (RFS) and overall survival were calculated using Kaplan–Meier methods and compared using log-rank testing. Statistical differences were analyzed using the χ^2 test, or Fisher's exact test when indicated. Values of $p < 0.05$ were considered statistically significant.

Results

Relationship between classification of apocrine metaplasia and clinicopathological characteristics

For the 210 patients, the distribution according to the classification of AM was: non-AM, 61%; incomplete AM, 36%; and complete AM, 3%. In 1996, only three cases of breast cancers were diagnosed as apocrine carcinoma, with incomplete AM in two cases and complete AM in the remaining case according to our scoring system. Mean age was 52 years for non-AM, 56 years for incomplete AM and 61 years for complete AM. Age tended to be higher for patients with complete AM than for the other groups, but no significant difference was identified. The rate of positive lymph node metastasis was comparable among the three groups. According to the architectural growth pattern, non-AM was mostly scirrhous carcinoma that invaded diffusely, while incomplete AM and AM appeared as solid-tubular carcinoma that invaded expansively. This difference was significant ($p < 0.05$) (Table 1).

Classification of apocrine metaplasia and immunohistochemical characteristics

No significant differences with regard to ER, PgR, HER2, AR or bcl-2 were observed between groups. For complete AM, rates of ER and PgR double-negative and bcl-2-negative were both 67% (4/6), respectively, tending to be higher than in the other groups. The AR-positive rate was 64% in all cases, and no significant difference in AR was seen between groups. The positive rate for GCDFP-15 was 83% for complete AM, 37% for incomplete AM and 25% for non-AM ($p < 0.05$) (Table 2).

Correlations to clinical outcome

To investigate whether the three different groups identified by the scoring system represented clinically distinct subgroups of patients, univariate survival analyses were performed to compare groups in terms of overall survival and RFS (Fig. 3). No significant differences in RFS or overall survival were apparent between groups. Cases of incomplete and complete AM were combined to form an AM group, then therapeutic effects were compared between AM and non-AM groups. No significant differences in RFS were observed between groups either with or without chemotherapy. However, in the with-chemotherapy group, AM showed better prognosis than non-AM in terms of 10-year RFS rates (non-AM, 60%; AM, 74%) (Fig. 4). We also examined the RFS of patients stratified according to nodal status. In the lymph node-negative group, no significant differences in RFS were observed between

Table 1 Clinicopathological characteristics of classification of apocrine metaplasia

	All ($n = 210$)	Non-apocrine metaplasia ($n = 129$)	Incomplete apocrine metaplasia ($n = 75$)	Complete apocrine metaplasia ($n = 6$)	p value
Distribution		61%	36%	3%	
Median age (range, years)	54 (24–80)	52 (24–79)	56 (36–74)	61 (49–80)	0.17
Tumor size (cm)	1.8	1.8	1.9	1.7	0.93
Lymph node metastasis					
Negative	124	82	39	3	0.14
Positive	86	47	36	3	
Architectural growth pattern					
Papillotubular	15	10	4	1	<0.05
Solid-tubular	91	34	53	4	
Scirrhous	104	85	18	1	
Hormonal therapy					
No	147	97	47	3	0.09
Yes	63	32	28	3	
Chemotherapy					
No	124	76	43	5	0.46
Yes	86	53	32	1	

Table 2 Immunohistochemical characteristics of classification of apocrine metaplasia

	All ($n = 210$)	Non-apocrine metaplasia ($n = 129$)	Incomplete apocrine metaplasia ($n = 75$)	Complete apocrine metaplasia ($n = 6$)	p value
ER, PgR					
ER (−) PgR (−)	67	37	26	4	0.13
ER (+) PgR (+)	102	64	37	1	
ER (+) PgR (−)	32	19	12	1	
ER (−) PgR (+)	9	9	0	0	
HER2					
0	150	95	50	5	0.55
1+	13	7	6	0	
2+	10	6	3	1	
3+	37	21	16	0	
AR					
Negative	75	46	26	3	0.75
Positive	135	83	49	3	
bcl-2					
Negative	63	37	22	4	0.14
Positive	147	92	53	2	
GCDFP-15					
Negative	145	97	47	1	<0.05
Positive	65	32	28	5	

ER Estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor type 2, *AR* androgen receptor, *GCDFP-15* gross cystic disease fluid protein-15

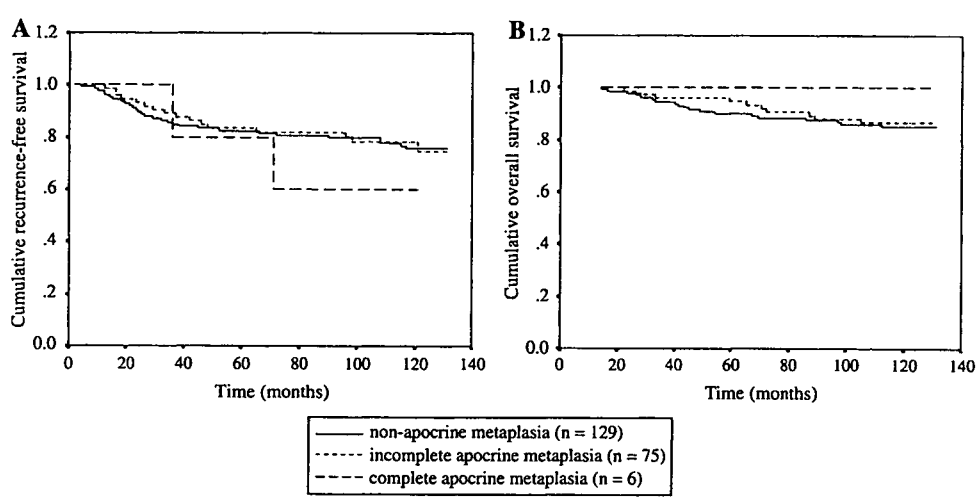

Fig. 3 Recurrence-free survival (**a**) and overall survival (**b**) of patients with non-apocrine metaplasia (*full line*), incomplete apocrine metaplasia (*short dotted line*) and complete apocrine metaplasia (*long dotted line*). No significant differences were seen among the three groups for either recurrence-free survival or overall survival

patients with or without chemotherapy (Fig. 5). However, in the lymph node-positive group without chemotherapy, the 10-year RFS rate in patients with non-AM was 85% compared to 44% in patients with AM ($p < 0.05$) (Fig. 6). The AM group thus showed worse prognosis than the non-AM group. Conversely, in the lymph node-positive group with chemotherapy, the 10-year RFS rate was 45% in patients with non-AM and 75% in patients with AM ($p < 0.05$) (Fig. 7). The AM group thus showed better prognosis than the non-AM group. We also examined RFS excluding cases with metastasis to >10 lymph node. In the group without chemotherapy, AM was still associated with significantly worse outcomes than non-AM (10-year RFS rate: AM, 44%; non-AM, 85%; $p < 0.05$), while in the group with chemotherapy, no significant difference was apparent in RFS rate between non-apocrine and AM. No significant differences, except in architectural growth pattern, were noted when the various clinical and pathological parameters (including age, tumor size, lymph node metastasis, HER2 and hormonal therapy) were compared

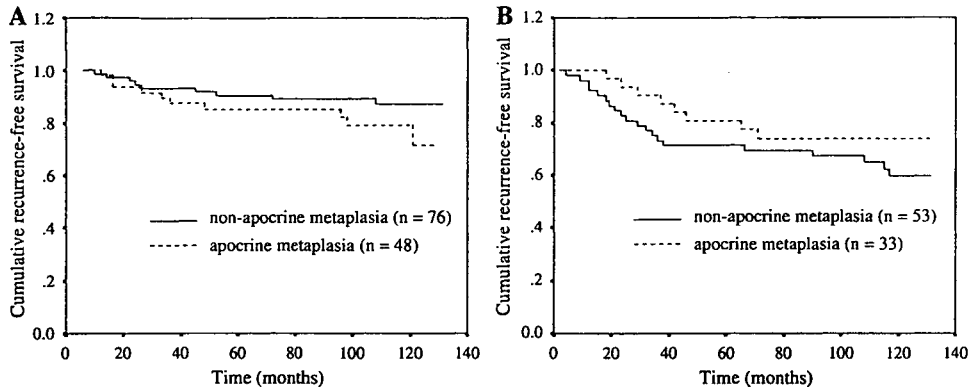

Fig. 4 Recurrence-free survival in patients with non-apocrine metaplasia (*full line*) and apocrine metaplasia (*short dotted line*). **a** Without chemotherapy ($p = 0.14$). **b** With chemotherapy ($p = 0.21$)

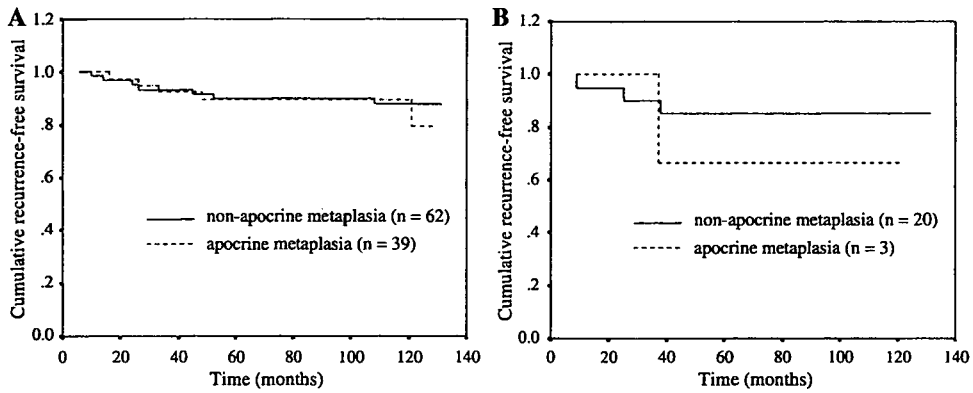

Fig. 5 Recurrence-free survival of node-negative patients with non-apocrine metaplasia group (*full line*) and apocrine metaplasia group (*short dotted line*). **a** Without chemotherapy ($p = 0.72$). **b** With chemotherapy ($p = 0.46$)

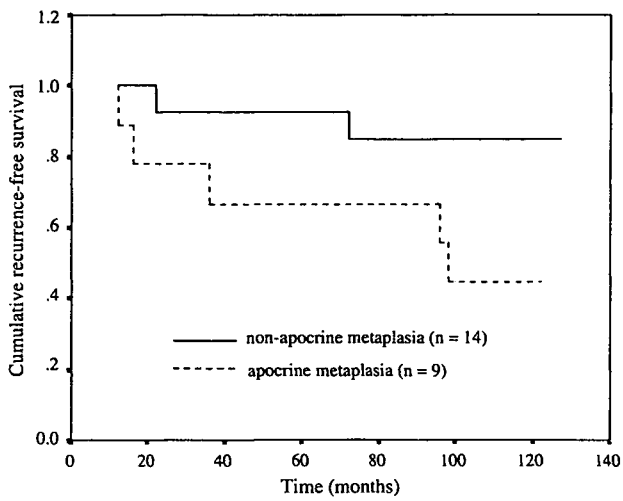

Fig. 6 Recurrence-free survival of node-positive patients without chemotherapy for non-apocrine metaplasia (*full line*) and apocrine metaplasia (*short dotted line*) ($p < 0.05$)

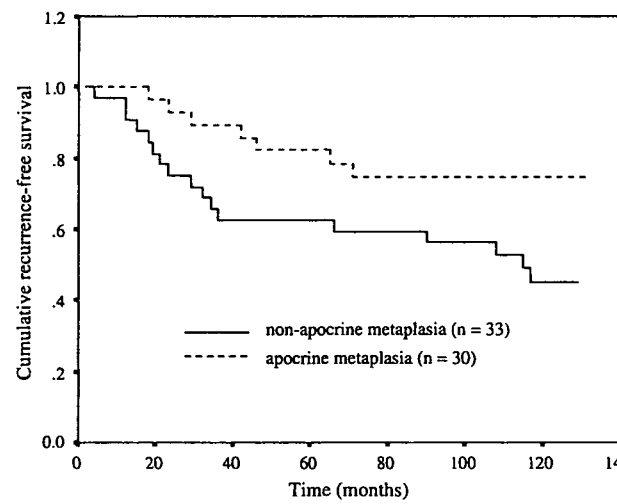

Fig. 7 Recurrence-free survival of node-positive patients with chemotherapy for non-apocrine metaplasia (*full line*) and apocrine metaplasia (*short dotted line*) ($p < 0.05$)

between non-AM and AM groups whether with presence or absence of chemotherapy. Using Cox multiple-regression analysis including tumor size, age, lymph node metastasis, hormonal status, HER2 status and AM, the persistence of lymph node metastasis was the only predictor of outcome. No associations between AM and prognosis were observed.

Discussion

The present study set up the hypothesis based on our institutional experience of neoadjuvant therapy that AM is useful as a predictive factor for therapeutic efficacy of chemotherapy. We then analyzed our institutional data retrospectively. We selected cases with invasive tumors 1.1–3.0 cm in diameter to ensure that all tumors had a measurable invasive size and to investigate lesions of comparable size. As the morphologic diagnostic criteria of AM remain unclear [2, 3, 6, 26], we proceeded with this study based on a definition of AM using our own scoring system with the size of cytoplasmic granules and the abundance of cytoplasm each classified into three categories. As 40% of tumors showing score 2 for abundance of cytoplasm did not exhibit the full characteristics of AM, a total score of three points was classified as incomplete AM. In all tumors including incomplete or complete AM, more than half of the area was occupied by AM, so we did not evaluate the percentage area occupied by AM. Cases of incomplete and complete AM were combined to form an AM group, because only one of six cases of complete AM received chemotherapy, so statistical analyses could not be performed among complete AM, incomplete AM and non-AM receiving chemotherapy. As this study focused on AM rather than apocrine cancer, incomplete and complete AMs were combined.

Some immunohistochemical analyses have reported apocrine carcinomas as ER-negative, PgR-negative, AR-positive, bcl-2-negative and GCDFP-15-positive [1, 7]. We performed these immunohistochemical analyses to improve the accuracy of diagnosis for AM, but no factors other than GCDFP-15 appeared as apocrine characteristics. GCDFP-15 positivity was high in the AM group, so we also analyzed prognoses between GCDFP-15-positive and GCDFP-15-negative tumors, but no significant differences were identified.

Among patients who had undergone chemotherapy, AM tended to be associated with better prognosis than non-AM, but no significant difference was identified. We also examined RFS in patients stratified according to lymph nodal status. In the lymph node-positive group, significant differences were seen in prognosis between AM and non-AM with or without chemotherapy. Recently, all patients identified as lymph node-positive have received chemotherapy as adjuvant therapy, according to the guidelines [27, 28]. However, in 1996, no guidelines regarding adjuvant therapy had been devised, so not all lymph node-positive patients received chemotherapy. We found that among lymph node-positive patients without chemotherapy, AM was associated with significantly worse prognosis than non-AM. Conversely, among lymph node-positive patients who received chemotherapy, patients with AM showed significantly better prognosis than those with non-AM. This suggests that AM responds well to chemotherapy, improving the prognosis of patients with AM.

Among lymph node-positive patients who received chemotherapy, the rate of metastasis to >10 lymph nodes, which is associated with very poor prognosis, was 10% for the AM group and 33% for the non-AM group. No significant difference in the distribution of the number of lymph node metastases was seen between AM and non-AM groups, but the possibility remains that the prognosis for patients with metastasis to >10 lymph nodes is so poor that the prognosis for non-AM group RFS is markedly skewed. We therefore excluded cases with metastasis to >10 lymph nodes and compared prognosis between AM and non-AM groups. No significant difference was observed between these groups if chemotherapy had been administered. However, in the absence of chemotherapy, the AM group showed clearly worse prognosis than the non-AM group. The AM group might thus have achieved comparable prognosis to the non-AM group largely due to the markedly good response to chemotherapy. In multivariate analysis, AM did not remain as an independent prognosticator. However, in lymph node-positive cases, AM without chemotherapy showed worse prognosis than non-AM, while AM with chemotherapy showed the same or better prognosis than non-AM. This suggests AM as a factor influencing therapeutic effect.

The two factors of structural and morphological features are important when considering histological classification of breast cancer. Recent histological classifications have mixed the histologic names based on structural features and morphologic features. IDC-NST, which comprises a majority of breast cancers, is diagnosed based on the structural features. Conversely, apocrine carcinoma is diagnosed based on the cytologic features of AM. The association of focal or incomplete AM is ignored and is not reflected in the diagnosis. Thus, the ultimate type of breast cancer with AM is diagnosed as apocrine cancer. With the increasing importance of pharmacotherapies, histological classifications that include predictors of response to therapy are needed. The present results indicate that AM could represent a useful predictive factor. We therefore suggest a reconstruction of the histological classification system based on structural classifications with the addition of cytological appearances, such as "scirrhous carcinoma

with complete AM," "solid-tubular carcinoma without AM" and so on. This classification extinguishes the existence of apocrine carcinoma, which is named based only on morphologic features. These new histological classifications of breast cancer could make pathological diagnosis more clinically useful and meet the demands of the times.

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ORIGINAL ARTICLE

Malignant transformation of breast fibroadenoma to malignant phyllodes tumor: long-term outcome of 36 malignant phyllodes tumors

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Abstract
Background Malignant phyllodes tumor of the breast is a rare neoplasm for which clinical findings remain insufficient for determination of optimal management. We examined the clinical behavior of these lesions in an attempt to determine appropriate management. We evaluated long-term outcome and clinical characteristics of malignant phyllodes tumors arising from fibroadenomas of the breast.
Methods A total of 173 patients were given a diagnosis of phyllodes tumor and underwent surgery at the Cancer Institute Hospital in Japan between January 1980 and December 1999. Of these patients, 39 (22.5%) were given a diagnosis of malignant phyllodes tumor; in three of these cases, detailed medical records were lost. Malignant phyllodes tumors were classified into two groups based on history of malignant transformation. Of the 36 malignant cases, 11 (30.6%) were primary and were given a diagnosis of fibroadenoma, experienced recurrence during the follow-up period, and were diagnosed with malignant phyllodes tumor (cases with a history of fibroadenoma). The other group was defined as cases without history of fibroadenoma and in whom lesions initially occurred as malignant phyllodes tumors. Based on differences between the two groups, overall survival curves were plotted using the Kaplan–Meier method, and statistical comparisons were performed using the log-rank test and Peto and Peto's test.
Results The outcome of cases with history of fibroadenoma was significantly better than that of cases without history of fibroadenoma.
Conclusions Patients with malignant phyllodes tumors but without prior history of malignant transformation who exhibit rapid growth within 6 months require aggressive treatment.

Keywords Malignant phyllodes tumor · Fibroadenoma · Malignant transformation · Breast tumor · Cohort study

Introduction

Phyllodes tumor of the breast is an uncommon fibroepithelial breast neoplasm that accounts for 0.3–1.0% of cases of female breast carcinoma [1]. On the other hand, fibroadenomas are the most frequent benign tumors of the breast after fibrocystic disease. The histogeneses of fibroadenoma and phyllodes tumor of the breast appear to be closely related. Because of the similarity of the epithelial cells in phyllodes tumors to cells in fibroadenomas, many believe phyllodes tumors to arise from a preexisting fibroadenoma [2, 3]. Whether all phyllodes tumors originate as fibroadenomas or whether they can arise de novo without a preexisting fibroadenoma is a matter of ongoing debate. In a study in 1995, Noguchi et al. [3] reported three

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cases of fibroadenoma that were diagnosed by excisional biopsy and recurred as benign phyllodes. Clonal analysis showed that all three fibroadenomas were monoclonal in origin. It was speculated that phyllodes tumors begin as fibroadenomas, and that subsequently a single stromal cell undergoes mutation and develops into a phyllodes tumor composed mainly of monoclonal stromal cells but partially of monoclonal epithelial cells. Kuijper et al. [4] studied clonal progression in fibroadenomas and phyllodes tumors and concluded that fibroadenomas can progress in an epithelial direction to carcinoma in situ or in a stromal direction to phyllodes tumors. The incidence of monoclonal fibroadenoma is quite low, and this tumor can subsequently progress to phyllodes tumor. Valdes et al. [5] presented a case of malignant transformation of a fibroadenoma to cystosarcoma phyllodes after 5 years of radiologic stability, and demonstrated that monoclonal fibroadenomas can progress to phyllodes tumors by clonal analysis performed on fine-needle aspiration (FNA) sample. However, performing clonal analysis on all fibroadenomas is time consuming and not cost effective. Malignant phyllodes tumors are very uncommon. Successful management of them will require determination of their clinical characteristics. In this study, we specifically, evaluated the outcomes of and prognostic factors for the malignant transformation from fibroadenomas to malignant phyllodes tumors.

Patients and methods

Patient population

We treated 173 patients with the diagnosis of phyllodes tumors between 1980 and 1999 at the Department of Breast Surgery, Cancer Institute Hospital in Japan and classified the tumors as benign, borderline or malignant using the histological classification (Table 1) proposed by the Japanese Breast Cancer Society, which is similar to that proposed by Pietruszka and Barnes [6]. In total, 39 patients were diagnosed with malignant phyllodes tumors, though three of these patients were excluded because their medical records had been lost. The clinical features of 36 patients with malignant phyllodes tumors were retrospectively reviewed and collated.

Classification of cases

"Malignant transformation" was considered to have occurred when a fibroadenoma became a benign phyllodes tumor, or when a benign phyllodes tumor became a malignant phyllodes tumor. Eleven patients (30.6%) had been diagnosed as having fibroadenoma previously. Ten patients underwent excisional biopsy, exhibited recurrence in the region near the scar, and were diagnosed with malignant phyllodes tumors, while in one patient the tumor was demonstrated histopathologically (Fig. 1). These 11 cases were classified as cases with history of fibroadenoma. Another 25 patients (69.4%) were initially diagnosed with malignant phyllodes tumors. We compared findings for these two groups of patients.

Table 1 Histologic features used in classification of phyllodes tumors subtypes [1, 6]

Histologic features	Benign	Borderline	Malignant
Stromal cellular atypia	Mild	Marked	Marked
Mitotic activity	<4/10 HPF	4–9/10 HPF	≧10/10 HPF
Stromal overgrowth	Absent	Absent	Present
Tumor margins	Circumscribed	Circumscribed or infiltrative	Infiltrative

HPF high-power field

Statistical analysis

For this study, the two groups were compared with respect to age, tumor size, surgical treatment, surgical margins, duration of signs and symptoms, local recurrence, metastases, and survival. Overall survival curves were plotted using the Kaplan–Meier method, and statistical comparisons were performed using the log-rank test and Peto and Peto's test [7]. Comparisons of clinical background factors were made between those two groups using Welch's *t*-test and Fisher's exact test.

Result

Patient demographics

There were 36 patients diagnosed with malignant phyllodes tumors between the years 1980 and 1999. All were female, with a median age of 43.6 (range 16–88) years. The median size was 91.4 (range 15–320) mm. The median duration of follow-up was 68.5 (range 2–287) months. Of 36 patients, nine (25%) had local recurrence and 14 (39%) had hematogenous metastases.

Outcomes of groups with or without history of fibroadenoma

In the group with history of fibroadenoma, four of 11 (36.4%) patients developed generalized hematogenous

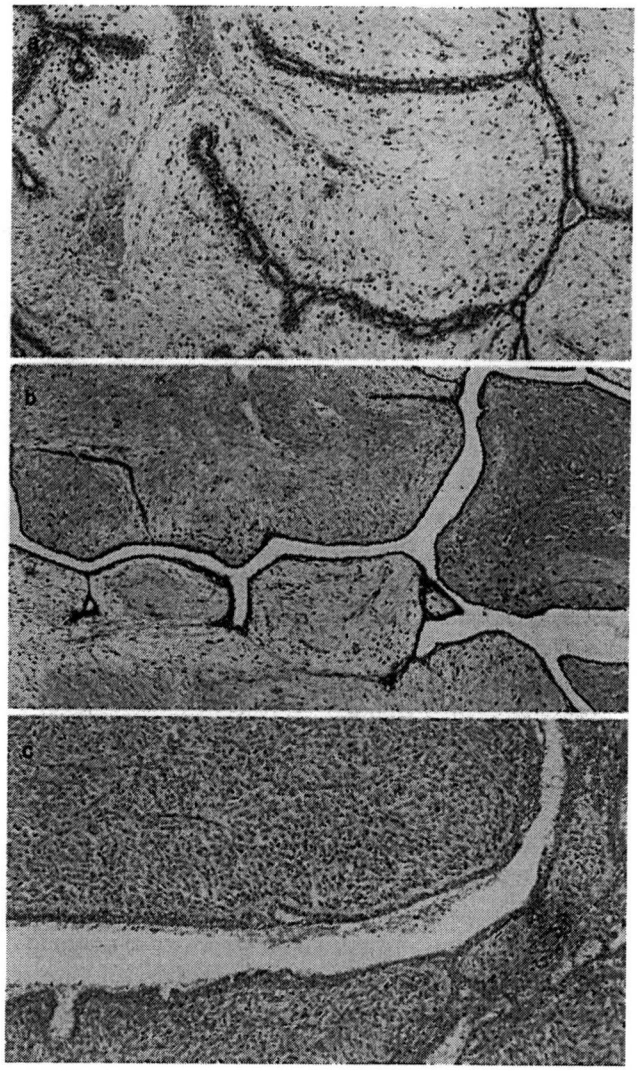

Fig. 1 Histologic features of typical tumor of fibroadenoma; benign and malignant phyllodes tumors are demonstrated. **a** Fibroadenoma. **b** Benign phyllodes tumor. **c** Malignant phyllodes tumor. Hematoxylin and eosin (H&E, ×400)

metastases. Three of the four died, and the remaining patient underwent three partial resections of lung metastases and remains alive 137 months after mastectomy.

However, in the group without history of fibroadenoma, 13 of 25 (52%) patients died. Ten patients developed generalized hematogenous metastases; nine of these 10 patients died early (at 2–27 months after diagnosis), and only one patient died later, at 134 months after final mastectomy, with pleural effusion and ascites. The other three patients died of other diseases. Moreover, some of the patients without history of fibroadenoma exhibited aggressive tumor growth, and died despite surgical resection. However, these were no early deaths among patients without history of fibroadenoma. The overall 20-year survivals of the two groups are shown in Fig. 2. The outcome

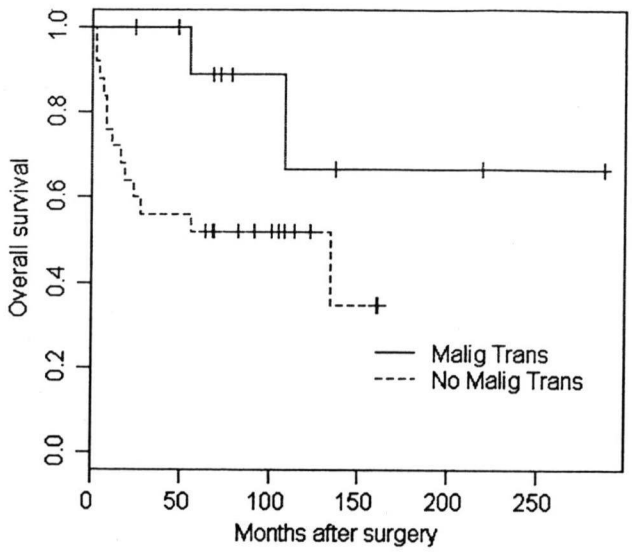

Fig. 2 Twenty-year survival of patients treated for primary malignant phyllodes tumors. *Malig trans* malignant transformation group (cases with history of fibroadenoma); *no malig trans* group without malignant transformation (cases without history of fibroadenoma)

of cases with history of fibroadenoma was significantly better than that of cases without history of fibroadenoma (log-rank test $p = 0.0551$, Peto and Peto's test [7] $p = 0.0409$). Multivariate analysis using the Cox model was used for stepwise regression to select the best subset of predictors from candidate covariates, yielding the following statistically significant variables as effective predictors of survival: tumor size, tumor growth rate in duration of symptoms (SIZE/DOS), surgical treatment, and malignancy (Table 2).

Table 3 summarizes tumor-related characteristics according to malignant transformation. The difference between the two groups in DOS was significant (Welch's t-test $p = 0.01437$). The cases without history of fibroadenoma had shorter DOS than the cases with history of fibroadenoma. There were no differences in age, tumor size, surgical treatment, surgical margins, local recurrence, metastasis or survival outcome between the two groups.

Discussion

Phyllodes tumor of the breast is a rare fibroepithelial lesion that accounts for less than 1% of all primary breast neoplasms [1]. The majority of phyllodes tumors have been described as benign (35–64%), with the remainder divided between borderline and malignant subtypes. The malignant subtype is found in approximately 25–30% of resected phyllodes tumors [1, 2]. Malignant phyllodes tumor sometimes metastasizes to the lungs. The median rate of metastasis reported after surgery for malignant phyllodes

Table 2 Multivariate analysis of Cox proportional-hazards model

Variable	Coefficient	Hazard ratio (95% CI)	*p* Value
Malignant transformation	1.545	4.69 (0.998–22.036)	0.05
Tumor size	0.00504	1.01 (0.999–1.011)	0.093
SIZE/DOS	0.0749	1.08 (1.023–1.136)	0.005
Surgical treatment	2.546	12.76 (1.054–154.426)	0.045

SIZE/DOS tumor growth rate in duration of symptoms, *SIZE* tumor size, *DOS* duration of symptoms

Table 3 Patients and tumor-related characteristics by malignant transformation

	Malig trans	No malig trans	*p*-Value
Age (mean, years)	42.5	44.1	0.721
Tumor size (cm)	8.2	9.5	0.5372
<5	4	7	
5–10	2	11	0.3226
>10	5	7	
Treatment			
Mastectomy	11	19	0.1479
Lumpectomy	0	6	
Surgical margins (cm)			
<0.5	1	1	0.5238095
≧0.5	10	24	
DOS (months)	33.6	34.6	0.9471
0–6	1	12	
6.1–12	2	0	0.01437
>12	8	11	
Unknown	0	2	
Local recurrence			
Yes	3	6	≧0.999
No	8	19	
Metastasis			
Yes	4	10	≧0.999
No	7	15	
Follow-up			
Alive	8	12	0.2767
Dead	3	13	0.4559
Died of disease	3	10	

DOS duration of symptoms; *malig trans* malignant transformation group (cases with history of fibroadenoma); *no malig trans* group without malignant transformation (cases without history of fibroadenoma)

tumors is 25–35% [2]. A report [8] from the M.D. Anderson Cancer Center on a subset of 30 women with the malignant histological subtype estimated that 5- and 10-year overall survival rates were 79% and 42%, respectively. Recently, Macdonald et al. [9] reviewed data on primary nonmetastatic malignant phyllodes tumors ($n = 821$) obtained from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results program and reported that predicted cause-specific survival rates were 91%, 89%, and 89%, at 5, 10, and 15 years, respectively, with median follow-up of 5.7 years. Another recent report [10] noted that the relative cumulative survival of malignant phyllodes patients was 87.4% at 10 years. In our study, the overall survival rates were 65%, 60%, and 52%, at 5, 10, and 20 years.

Previously reports [9] in the literature have suggested that stromal overgrowth, tumor size, surgical margin status, and types of surgery were predictive of local or distant recurrence after primary surgery. Patients with stromal overgrowth, tumor size >5 cm [8], and positive margins of excision [11] were found to have a high rate of distant failure. In the present series, the outcome of cases with history of fibroadenoma was significantly better than that of those without history of fibroadenoma. Multivariate analysis using the Cox model was used for stepwise regression technique to select the best subset of predictors, and revealed that size, SIZE/DOS, surgical treatment, and malignancy were effective predictors of survival. Nonmalignant transformation, large size, rapid growth, and mastectomy were significantly correlated with poor survival.

The course from fibroadenoma to phyllodes tumor was slow, but these tumors became histologically more malignant with every local recurrence. Recurrence was perhaps due to residual tumor secondary to inadequate excision of initial fibroadenoma, which can progress to phyllodes tumor. Chen et al. [12] reported that 22 of 172 phyllodes tumors patients had previously undergone fibroadenoma excisions, but that none of them had metastases. All 19 of these 22 patients had a first local recurrence of benign phyllodes tumor. According to his study of recurrent phyllodes tumors, the majority of recurrent tumors were histologically similar to the initial tumors; however, seven patients (19%) developed a malignant recurrence from an initially benign or borderline tumor [13]. Moreover, preoperative diagnosis of phyllodes tumors is difficult. Rapid growth and/or large size of apparent fibroadenomas may be the only imaging finding suggestive of phyllodes tumor. Whole-breast ultrasound showed that nearly one-third of women with phyllodes tumors had concurrent fibroadenoma [14]. It is important to examine most fibroadenomas with ultrasound, and to assess their rate of growth, if any. Rapid tumor growth or sudden increase in size is the most important clinical characteristic for prediction of progression. It is, however, difficult to assess the reliability of this observation, since no objective measurements of tumor growth rate were performed [1, 9]. Some reports notes that phyllodes tumors begin as fibroadenoma, and that subsequently a single stromal cell undergoes mutation and

develops into a phyllodes tumor composed mainly of monoclonal stromal cells and partially of monoclonal epithelial cells. The results of monoclonal analysis of our excisional biopsy samples would thus be of great interest.

To our knowledge, this is the first report on the frequency and prognosis of malignant transformation from fibroadenoma to malignant phyllodes tumor. About 20–30% of cases of malignant phyllodes tumors begin as fibroadenomas, and these have better prognosis than those that do not.

Conclusions

The prognosis of malignant phyllodes tumor arising from a preexisting fibroadenoma is relatively good. Patients with malignant phyllodes tumors but without prior history of malignant transformation who exhibit rapid growth within 6 months require aggressive treatment.

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