第29回厚生科学審議会がん登録部会	資料３
令和６年１０月７日（月）	

法20条に基づいて提供された情報の研究への利用

金沢医科大学医学部公衆衛生学
西野　善一

がん登録推進法第20条

第二十条

都道府県知事は、当該都道府県の区域内の病院等における院内がん登録その他がんに係る調査研究のため、当該病院等の管理者から、当該病院等から届出がされたがんに係る都道府県がん情報（厚生労働省令で定める生存確認情報及び厚生労働省令で定める当該病院等に係る第五条第二項に規定する附属情報に限る。）の提供の請求を受けたときは、全国がん登録データベースを用いて、その提供を行わなければならない。この場合においては、第十七条第一項ただし書の規定を準用する。

生存確認情報（法第5条第1項第9号）

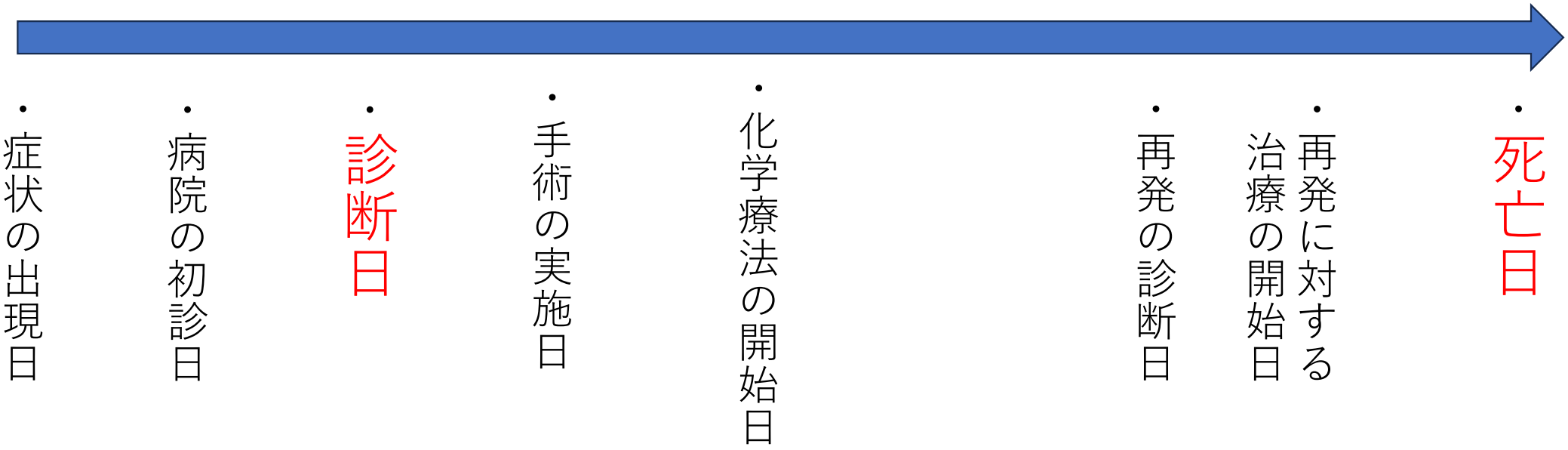
- 生存しているか死亡したかの別及び生存を確認した直近の日として厚生労働省令で定める日
  （生死区分、最終生存確認日）
- 死亡を確認した場合にあっては、その死亡の日及びその死亡の原因に関し厚生労働省令で定める事項
  （死亡日、原死因）

法20条に基づく生存確認情報の提供内容

項目名	詳細
死亡日	届出に記載されている死亡日、または厚労省から入手した死亡情報に基づく死亡日 YYYYMMDD 形式
原死因	厚労省から入手した死亡情報に基づく原死因
最終生存確認日	生存確認調査で得た確認日 YYYYMMDD 形式

がん治療・療養プロセスと研究における生存期間の起算日

- 臨床研究における生存期間の起算日は研究の目的によって異なる
- 研究の実施にあたっては、研究者が生存期間を起算日と死亡日より算出できることが望ましい



診断から治療開始までの期間が予後に与える影響を検討した研究

JAMA Network Open.

Original Investigation | Surgery

Analysis of Delayed Surgical Treatment and Oncologic Outcomes in Clinical Stage I Non-Small Cell Lung Cancer

Brendan T. Heiden, MD; Daniel B. Eaton Jr, MPH; Kathryn E. Engelhardt, MD, MS; Su-Hsin Chang, PhD, SM; Yan Yan, MD, PhD; Mayank R. Patel, MD; Daniel Kreisel, MD, PhD; Ruben G. Nava, MD; Bryan F. Meyers, MD, MPH; Benjamin D. Kozower, MD, MPH; Varun Puri, MD, MSCI

Abstract

IMPORTANCE The association between delayed surgical treatment and oncologic outcomes in patients with non–small cell lung cancer (NSCLC) is poorly understood given that prior studies have used imprecise definitions for the date of cancer diagnosis.

OBJECTIVE To use a uniform method to quantify surgical treatment delay and to examine its association with several oncologic outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted using a novel data set from the Veterans Health Administration (VHA) system. Included patients had clinical stage I NSCLC and were undergoing resection from 2006 to 2016 within the VHA system. Time to surgical treatment (TTS) was defined as the time between preoperative diagnostic computed tomography imaging and surgical treatment. We evaluated the association between TTS and several delay-associated outcomes using restricted cubic spline functions. Data analyses were performed in November 2021.

EXPOSURE Wait time between cancer diagnosis and surgical treatment (ie, TTS).

MAIN OUTCOMES AND MEASURES Several delay-associated oncologic outcomes, including pathologic upstaging, resection with positive margins, and recurrence, were assessed. We also assessed overall survival.

RESULTS Among 9904 patients who underwent surgical treatment for clinical stage I NSCLC, 9539 (96.3%) were men, 4972 individuals (50.5%) were currently smoking, and the mean (SD) age was 67.7 (7.9) years. The mean (SD) TTS was 70.1 (38.6) days. TTS was not associated with increased risk of pathologic upstaging or positive margins. Recurrence was detected in 4158 patients (42.0%) with median (interquartile range) follow-up of 6.15 (2.51-11.51) years. Factors associated with increased risk of recurrence included younger age (hazard ratio [HR] for every 1-year increase in age, 0.992; 95% CI, 0.987-0.997; $P = .003$), higher Charlson Comorbidity Index score (HR for every 1-unit increase in composite score, 1.055; 95% CI, 1.037-1.073; $P < .001$), segmentectomy (HR vs lobectomy, 1.352; 95% CI, 1.179-1.551; $P < .001$) or wedge resection (HR vs lobectomy, 1.282; 95% CI, 1.179-1.394; $P < .001$), larger tumor size (eg, 31-40 mm vs <10 mm; HR, 1.209; 95% CI, 1.051-1.390; $P = .008$), higher tumor grade (eg, II vs I; HR, 1.210; 95% CI, 1.085-1.349; $P < .001$), lower number of lymph nodes examined (eg, ≥10 vs <10; HR, 0.866; 95% CI, 0.803-0.933; $P < .001$), higher pathologic stage (III vs I; HR, 1.571; 95% CI, 1.351-1.837; $P < .001$), and longer TTS, with increasing risk after 12 weeks. For each week of surgical delay beyond 12 weeks, the hazard for recurrence increased by 0.4% (HR, 1.004; 95% CI, 1.001-1.006; $P = .002$). Factors associated with delayed surgical treatment included African American race (odds ratio [OR] vs White race, 1.267; 95% CI, 1.112-1.444; $P < .001$), higher area deprivation index (ADI) score (OR for every 1 unit increase in ADI score, 1.005; 95% CI,

(continued)

Key Points

Question What is the association between delayed surgical treatment and oncologic outcomes among patients with non–small cell lung cancer (NSCLC)?

Findings In this retrospective cohort study of 9904 patients with clinical stage I NSCLC using data from the Veterans Health Administration, surgical procedures that were delayed more than 12 weeks from the date of radiographic diagnosis were associated with increased risk of recurrence and worse overall survival.

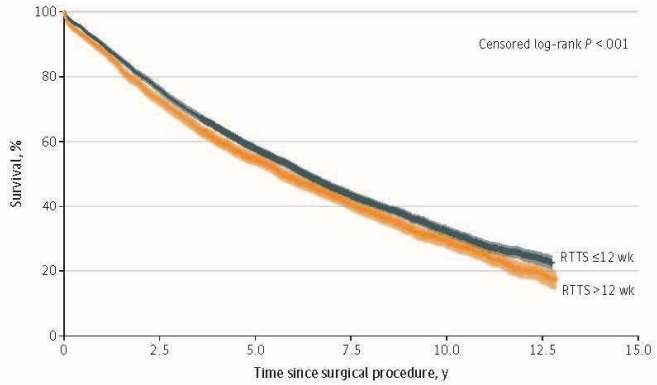
Meaning These findings suggest that patients with clinical stage I NSCLC should receive surgical treatment within at least 12 weeks of radiographic diagnosis.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

非小細胞肺癌について診断から手術実施までの待機期間と再発、死亡リスクとの関連を検討した米国の研究

Figure 3. Overall Survival Following Delayed Surgical Treatment



This Kaplan-Meier curve shows patients with clinical stage I non–small cell lung cancer with delayed (ie, >12 weeks radiological time to surgical treatment [RTTS]) vs nondelayed (≤12 weeks RTTS) surgical treatment.

Heiden BT et al. JAMA Network Open 2021; 4: e2111613

再発例を対象とした臨床研究の例

Taxanes versus S-1 as the first-line chemotherapy for metastatic breast cancer (SELECT BC): an open-label, non-inferiority, randomised phase 3 trial

Tsutomu Takashima, Hirofumi Mukai, Fumikata Hara, Nobuaki Matsubara, Tsuyoshi Saito, Toshimi Takano, Youngjin Park, Tatsuya Toyama, Yasuo Hozumi, Junji Tsurutani, Shigeru Imoto, Takanori Watanabe, Yoshiaki Sagara, Reiki Nishimura, Kojiro Shimozuma, Yasuo Ohashi, for the SELECT BC study group

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See Comment page 11

Osaka City University Graduate School of Medicine, Osaka, Japan (T Takashima MD); **National Cancer Center Hospital East, Kashiwa, Japan** (H Mukai MD, N Matsubara MD); **National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan** (F Hara MD); **Saitama Red Cross Hospital, Saitama, Japan** (T Saito MD); **Toranomon Hospital, Tokyo, Japan** (T Takano MD); **Tohoku Pharmaceutical University Hospital, Sendai, Japan** (Prof Y Park MD); **Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan** (Prof T Toyama MD); **Jichi Medical University, Tochigi, Japan** (Y Hozumi MD); **Kinki University Faculty of Medicine, Osakasayama, Japan** (J Tsurutani MD); **School of Medicine Kyorin University, Mitaka, Japan** (Prof S Imoto MD); **National Hospital Organization Sendai Medical Center, Sendai, Japan** (T Watanabe MD); **Hakuaikai Medical Corp Sagara Hospital, Kagoshima, Japan** (Y Sagara MD); **Kumamoto Shinto General Hospital, Kumamoto, Japan** (R Nishimura MD); **Ritsumeikan University, Kusatsu, Japan** (Prof K Shimozuma MD); **and Chuo University, Tokyo, Japan** (Prof Y Ohashi PhD)
Correspondence to: Dr Hirofumi Mukai, Department of Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwanoha, Kashiwa-shi, Chiba, Japan
hrmukai@east.ncc.go.jp

Summary

Background Oral fluoropyrimidines are used for the first-line treatment of metastatic breast cancer to avoid severe adverse effects, although firm supporting evidence is lacking. We aimed to establish whether S-1 is non-inferior to taxanes in this setting.

Methods We did an open-label, non-inferiority, phase 3 trial at 154 hospitals in Japan. We enrolled individuals who had HER2-negative metastatic breast cancer who had received no chemotherapy for advanced disease, and who were resistant to endocrine treatment. Patients were randomly assigned (1:1) either to taxane (docetaxel 60–75 mg/m² at intervals of 3–4 weeks; paclitaxel 80–100 mg/m² weekly for 3 of 4 weeks; or paclitaxel 175 mg/m² at intervals of 3–4 weeks) or to S-1 (40–60 mg twice daily for 28 consecutive days, followed by a 14-day break). Randomisation was done centrally with the minimisation method, with stratification by institution, liver metastasis, oestrogen and progesterone receptor status, previous treatment with taxanes or oral fluorouracil, and time from surgery to recurrence. The primary endpoint was overall survival, with a prespecified non-inferiority margin of 1·333 for the hazard ratio (HR). The primary efficacy analysis was done in the full analysis set, which consisted of all patients who took at least one study treatment and who had all data after randomisation. This trial is registered with the University Hospital Medical Information Network, Japan (protocol ID C000000416).

Findings Between Oct 27, 2006, and July 30, 2010, we enrolled 618 patients (309 assigned to taxane; 309 assigned to S-1). The full analysis set consisted of 286 patients in the taxane group and 306 in the S-1 group. Median follow-up was 34·6 months (IQR 17·9–44·4). Median overall survival was 35·0 months (95% CI 31·1–39·0) in the S-1 group and 37·2 months (33·0–40·1) in the taxane group (HR 1·05 [95% CI 0·86–1·27]; $p_{non\text{-}inferiority}$=0·015). The most common grade 3 or worse adverse events were neutropenia (20 [7%] of 307 patients in the S-1 group *vs* nine [3%] of 290 patients in the taxane group), fatigue (ten [3%] *vs* 12 [4%]), and oedema (one [<1%] *vs* 12 [4%]). Treatment-related deaths were reported in two patients in the taxane group.

Interpretation S-1 is non-inferior to taxane with respect to overall survival as a first-line treatment for metastatic breast cancer. S-1 should be considered a new option for first-line chemotherapy for patients with HER2-negative metastatic breast cancer.

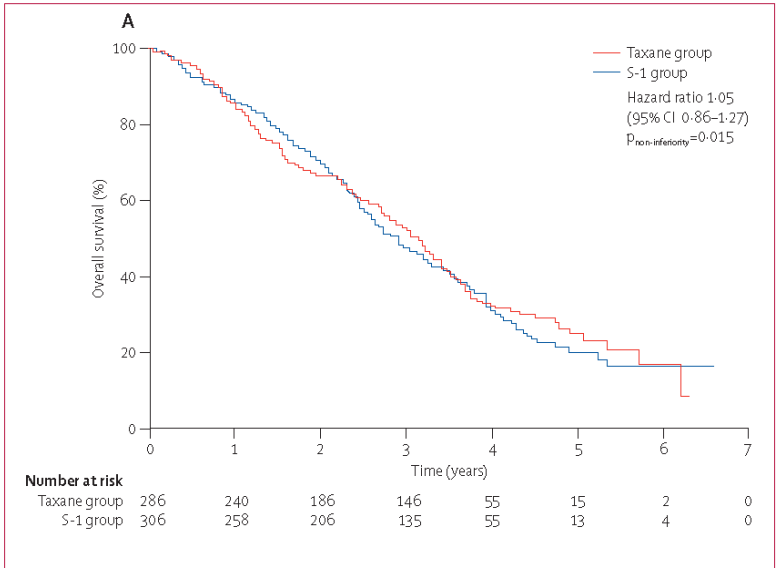
Funding Comprehensive Support Project for Oncology Research of the Public Health Research Foundation, Japan; Taiho.

Introduction

The vast majority of metastatic breast cancers are incurable.[1–3] Less toxic treatments are therefore preferred, and endocrine treatment is recommended for patients with oestrogen receptor-positive tumours whenever appropriate. Patients with oestrogen receptor-negative tumours or endocrine refractory disease receive cytotoxic chemotherapy. In such patients, regimens including anthracycline or taxanes are advised because they improve overall survival.[4–6] However, they often cause severe adverse effects.

Orally administered drugs are generally more convenient than intravenous drugs.[7] S-1 and capecitabine are both oral fluorouracil derivatives widely used in Japan. S-1 is a combination drug, based on a biochemical modification of fluorouracil, containing tegafur, gimeracil, and oteracil in a molar ratio of 1:0·4:1.[8] This combination enables the fluorouracil concentration to be increased while avoiding gastrointestinal toxic effects. It has been used to treat various solid tumours, including stomach cancer,[9,10] colorectal cancer,[11,12] pancreatic cancer,[13] non-small-cell lung cancer,[14,15] and breast cancer.[16] Two phase 2 studies of S-1 in previously treated and untreated patients with metastatic breast cancer have been done in Japan. 42·0% of treated patients and 40·7% of untreated patients had a tumour response, which is similar to the proportion of patients achieving a response when treated with taxane derivatives.[16] We therefore did a phase 3 trial to verify the non-inferiority of S-1 to taxane in terms of overall survival, and its superiority in terms of health-related quality of life, when given as first-line chemotherapy for metastatic breast cancer.

Her2タンパク質陰性の転移・再発乳癌患者を対象として、フッ化ピリミジン系抗悪性腫瘍剤（S-1）とタキサン系薬剤の効果を比較したランダム化比較試験（非劣性試験）



Takashima T et al. Lancet Oncol 2016; 17: 90-98

臓器別がん登録への生存確認情報の提供

臓器別がん登録

- 学会・研究会が主体となって、協力医療機関からデータ収集することにより臓器別に全国規模で腫瘍登録を行うがん登録
- 専門医のいる医療機関が対象
- 詳細な臨床情報が収集されているため、がんの臨床病理学的特徴と進行度の正確な把握に基づく適切な治療指針の確立、進行度分類のあり方などを検討することが可能
- 手術症例データベースであるNational Clinical Database（NCD）との連携で実施されるタイプ（NCD連携型）とそれ以外の学会独立型（日本産婦人科学会など）とがある

National Clinical Database（NCD）

- 2010年に外科系10学会が参画して設立された手術症例データベース（現在は14学会*が参加）
- 登録施設数 5,679、診療科数14,920（2024年4月現在）
- 基本項目と患者属性、術前、手術、術後に関する数十項目から数百項目の医療水準評価項目の登録を実施
- 外科手術レジストリ（消化器外科、呼吸器外科、乳癌）
  - 該当領域手術の95％以上が登録されており、領域のがんが含まれる。外科専門医制度と連携しているため悉皆性が高い
  - 消化器外科、呼吸器外科は短期予後（30日、90日以内死亡など）の把握に限られる
- 外科手術レジストリ以外のがん登録データベース（上記以外）
  - すべての施設が登録を行っているわけではなく、悉皆ではない

* 日本外科学会、日本消化器外科学会、日本小児外科学会、日本胸部外科学会、日本心臓血管外科学会、日本血管外科学会、日本呼吸器外科学会、日本内分泌外科学会、日本乳癌学会、日本脳神経外科学会、日本病理学会、日本泌尿器科学会、日本形成外科学会、日本内視鏡外科学会

臓器別がん登録における予後情報利用の現状

- 学会独立型やNCD連携型でも乳癌学会の乳癌登録は長期予後（5年）の把握を行っているが、7～8割程度の把握にとどまっている
- 長期予後の把握が十分にできていない医療機関は、生存率の分析対象から外して分析しており、一部の施設の情報に基づいて生存率が算出されている可能性がある（選択バイアス*による影響）

- 全国がん登録からの生存確認情報の提供を受けることができれば、臓器別がん登録全体の長期予後の精度が大きく改善する

*本来対象としたい集団ではない偏った集団による分析によるバイアス

日本乳癌学会乳癌登録を利用した臨床研究の例

Breast Cancer Research and Treatment (2022) 196:635–645
https://doi.org/10.1007/s10549-022-06749-3

EPIDEMIOLOGY

Prognosis and effectiveness of chemotherapy for medullary breast carcinoma

Tomohiko Aihara[1] · Hiraku Kumamaru[2] · Makoto Ishitobi[3] · Minoru Miyashita[4] · Hiroaki Miyata[2] · Kenji Tamura[5] · Masayuki Yoshida[6] · Etsuyo Ogo[7] · Masayuki Nagahashi[8] · Sota Asaga[9] · Yasuyuki Kojima[10] · Takayuki Kadoya[11] · Kenjiro Aogi[12] · Naoki Niikura[13] · Kotaro Iijima[14] · Naoki Hayashi[15] · Makoto Kubo[16] · Yutaka Yamamoto[17] · Yoshinori Takeuchi[18] · Shigeru Imoto[9] · Hiromitsu Jinno[19]

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Abstract

Purpose We aimed to determine the prognosis and potential benefit of postoperative chemotherapy according to subtype of medullary breast carcinoma (MedBC), a very rare invasive breast cancer.

Methods A cohort of 1518 female patients with unilateral MedBC and 284,544 invasive ductal carcinoma (IDC) cases were enrolled from the Japanese Breast Cancer Registry. Prognosis of MedBC was compared to IDC among patients with estrogen receptor (ER)-negative and HER2-negative subtype (553 exact-matched patients) and ER-positive and HER2-negative subtype (163 MedBC and 489 IDC patients via Cox regression). Disease free-survival (DFS) and overall survival (OS) were compared between propensity score-matched adjuvant chemotherapy users and non-users with ER-negative and HER2-negative MedBC.

Results Among ER-negative and HER2-negative subtype patients, DFS (hazard ratio (HR) 0.45; 95% confidence interval (95% CI), 0.30–0.68; log-rank $P < 0.001$) and OS (HR 0.51; 95% CI 0.32–0.83; log-rank $P = 0.004$) were significantly better in MedBC than IDC. Patients treated with postoperative chemotherapy showed better DFS (HR 0.27; 95% CI 0.09–0.80; log-rank $P = 0.02$) and OS (HR 0.27; 95% CI 0.09–0.80; log-rank $P = 0.02$) compared to those without. For the ER-positive and HER2-negative subtype, the point estimate for HR for DFS was 0.60 (95% CI 0.24–1.22) while that for OS was 0.98 (95% CI 0.46–1.84) for MedBC.

Conclusion In ER-negative and HER2-negative MedBC, the risk of recurrence and death was significantly lower than that of IDC, about half. Postoperative chemotherapy reduced recurrence and mortality. ER-positive and HER2-negative MedBC may have a lower risk of recurrence compared to IDC.

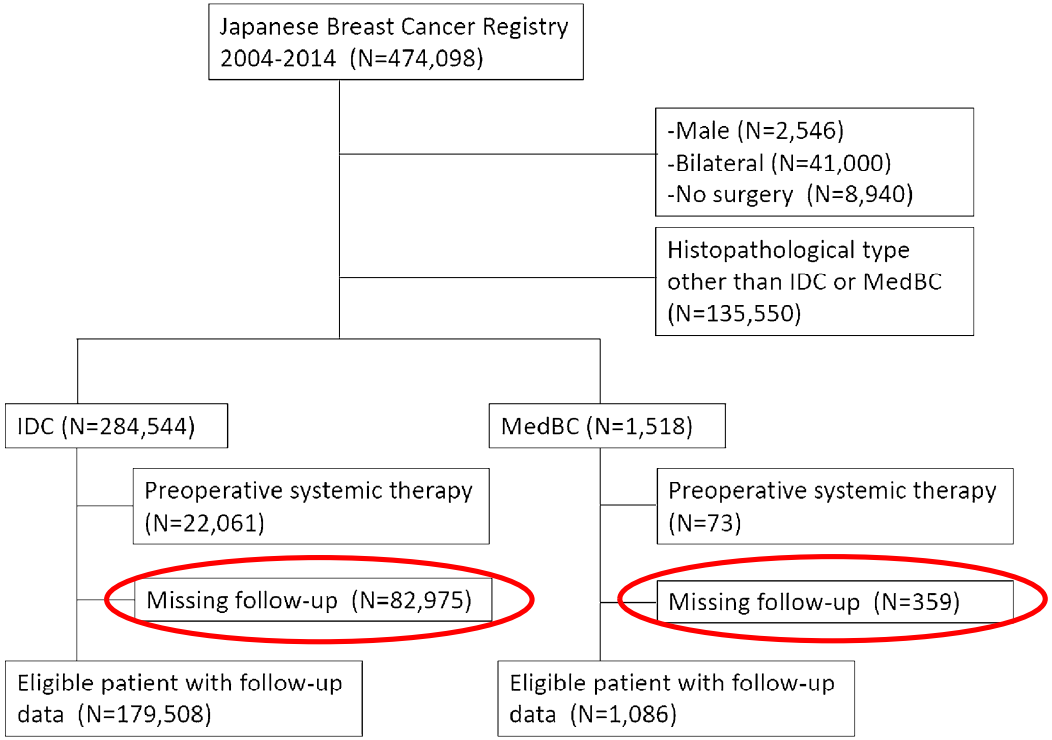
Keywords Medullary breast carcinoma · Prognosis · Adjuvant chemotherapy

Introduction

Primary breast cancer (BC) comprises heterogenous pathological subtypes. Medullary breast carcinoma (MedBC) is a rare subtype of invasive BC, accounting for less than 1% of primary BC. The Ridolfi criteria are generally applied for histopathologic diagnosis [1], which include: a predominantly syncytial growth pattern; microscopically completely circumscribed; absence of intraductal component; moderate to marked diffuse mononuclear stromal infiltrate; nuclear pleomorphism; and absence of microglandular features.

Most MedBC exhibit the triple-negative subtype defined by negative expression of estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) [2], and prognosis is generally poor. Despite such pathological features of MedBC, some studies reported more favorable prognosis of MedBC than invasive ductal carcinoma (IDC) [3, 4], while others reported similar survival [5–7]. Probably because

乳房のmedullary carcinomaとinvasive ductal carcinomaの化学療法の効果をエストロゲン受容体の有無とHer2タンパク質の陽性陰性により層別化して比較を行った研究



Aihara T et al. Breast Cancer Res Treat 2022; 196: 635-645

臓器別がん登録等における全国がん登録情報の利用

- 死亡日：臓器別がん登録が保有している起算日（診断日、治療開始日、手術日）からの生存期間の算出に使用

- 原死因：
  - ✓臨床研究での当該疾患死亡と他死亡を識別することにより疾患特異的生存率（cause-specific survival）の算出に使用
  - ✓他疾患による死亡の影響を考慮した当該疾患の生存率を算出することが可能
  - ✓ICD-10コードが得られれば他疾患死亡の影響の検討が可能

死亡情報の診療録への転記の必要性：臓器別がん登録

- 各診療科から臓器別がん登録に診療録に転記された死亡情報が提供されることによって、全国がん登録では得られない詳細な臨床情報を有する臓器別がん登録のデータによる正確な生存率の把握が可能になる

↓

- 予後に応じたステージ分類や治療法の評価を正確に行うことができ、患者の状況に応じた適切な医療の提供が可能になる
- 施設間・地域間の医療の質評価を行うことができる

↓

- 患者がどこに住んでいても質の高い医療を受けられる（がん医療の均てん化）

死亡情報の診療録への転記の必要性：医療機関での活用

- 医療機関が収集する多様な医療情報（診療内容、主観的アウトカム、苦痛のスクリーニング）と合わせて予後情報を利用することで診療の質評価を行えるデータベースが各医療機関に構築できる

都道府県がん対策推進協議会や学会等が運営する登録システムなどへの第三者提供が可能となれば

- 各都道府県で行う都道府県がん対策推進協議会において、各地域の実情に合わせた医療の質評価やがんとの共生に関する指標の評価を行うことができる
- 学会等が運営する登録システムへの詳細なデータの提供により最新の診断・治療の効果が検討できる

- 誰一人取り残さないがん対策の実現

法20条提供情報の利活用による社会への貢献

- 臓器別がん登録や医療機関の診療情報にある詳細な臨床情報と正確な予後情報を保有するデータベース（リアルワールドデータ）を用いると、希少がんの新規治療開発において、「サンプルサイズの設計」、「対照群としてのヒストリカルコホートとしての活用」に使用ができる

- 開発が遅れがちな希少がんや再発・進行がん、難治性がんなどの新規治療法開発のスピードアップができ、全体的な死亡率改善に寄与する