ULTRASOUND GUIDED INTRA-ARTERIAL CHEMOTHERAPY IN BREAST CANCER

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Purpose
Induction treatment using chemotherapy or radiation is used to treat locally advanced breast cancer (LABC), but we have developed a simple and safe method, intra-arterial infusion chemotherapy, which is less invasive than the conventional method. For the purpose of simplification in intra-arterial chemotherapy for locally advanced breast cancer, we developed an ultrasonically guided intra-arterial infusion method. With this method, a fine injection needle is inserted into the subclavicular artery on the central side of the truncus thyrocervicalis and on the peripheral side of the vertebral artery under ultrasonic guidance, and the breast, axillary lymph nodes and subclavicular lymph nodes are selectively infused with high concentrations of anticancer drugs. This method controls the localized breast cancer and should also be effective against systemic micrometastasis, which makes it useful for the treatment of LABC.

Materials
After chest X-rays, bone scintigraphy and liver ultrasound were conducted to screen for metastasis, the cancer was confirmed by the needle core biopsy. This treatment is indicated for cases of locally advanced breast cancer, stage IIIA and IIIB.

Methods
The dosing schedule was as follows:

- Cyclophosphamide: 65 mg/day p.o. days 1 to 7
- Adriamycin: 40 mg i.a. day 1
- 5-FU: 300 mg i.a. day 1

Repeated every 3 or 4 weeks, 3 to 6 times.

The intra-arterial infusion procedure is described below.

1. Adriamycin is dissolved at a dose of 40 mg and placed in a 20 cc syringe; 5-FU at 300 mg placed in a 10 cc syringe.
2. An extension tube for pediatric use is attached to a 23G Ueno needle, and connected
to the syringes containing the anticancer drugs and isotonic sodium chloride solution using a three-way stopcock.
(3) To prevent virus or bacterial infection, the ultrasonic transducer is covered with a condom, which is disinfected with alcohol.
(4) The patient is told to lie in a supine position on a special bed for angiography.
(5) The supraclavicular fossa is disinfected with alcohol and coated with sterilized ultrasound transmission gel.
(6) The thyro-cervical trunk is confirmed by ultrasound, and the skin and fascia are anesthetized with 1% Xylocaine.
(7) The 23G Ueno needle is inserted into the subclavicular artery via the anterior scalenus anterior muscle under ultrasound guidance, and arterial reflux is confirmed. The tip of the needle is about 2 mm proximal from the branching part of the truncus thyrocervicalis.
(8) After injecting contrast medium to confirm by fluoroscopy that it flow into the internal mammary artery and subclavicular artery, not into the vertebral artery, the DSA is imaged and the flow conditions into the subclavicular artery are again confirmed.
(9) If no contrast medium flows into the vertebral artery, the anticancer agents are injected.
(10) A tourniquet is wrapped around the upper arm of the patient and a pressure of 180 mmHg is applied, and pressure is applied beneath the costal arch manually to the superior epigastric artery to prevent the anticancer agents from entering the arms and abdominal wall.
(11) First, 5-FU is injected, followed by injection of adriamycin. When the injection is performed, reflux is observed for every 2 cc injected and it is confirmed that the tip of the needle is in the artery.
(12) The Ueno needle is removed and pressure to stop blood flow is no longer applied.
(13) The injection site is confirmed by the redness of the skin.

Results and Conclusion
This method has been performed to date more than total of 54 times on 10 patients. The details are shown in Table 1. Eight of the patients underwent modified radical mastectomy and two breast conserving treatment. CR was achieved in three patients and PR in six. The CR and PR mean tumor shrinkage rates were 80.3%. The tumors showed marked shrinkage and cancer cells could not be detected histologically in
the primary lesion in three patients. No cancer cells were found in the regional lymph nodes in one patient.

Severe headache and vomiting were observed in the first patient who had a injection with Cathelin needle and did not had a confirmation of flow by angiography. After angiography and Ueno needle were used concomitantly there after, the incidence of nausea and vomiting has decreased. Two patients had pain in the shoulder joint. Leukopenia occurred with WBC nadir of 1300 to 2300.

In intra-arterial treatment performed so far, infusion was performed after implantation of a catheter and infusion port, but this procedure presented various problems, including the high degree of invasiveness and the time required until the start of treatment. With this method, the patient can be treated as an outpatient without being admitted to the hospital since the intra-arterial injection is Table 1.Reduction rate by USGIAC for LABC completed safety in a short time immediately after diagnosis. The dose has still not be established, but it is considered best if the blood levels are the same as those with intravenous infusion and high concentrations of the anticancer agents enter the breast. In this way, if local control is achieved, systemic chemotherapy can be performed at the same
time. The advantages are more rapid effects than with radiation therapy and simultaneous systemic therapy. Transient pigmentation occurs, but there is no edema and skin injuries are milder than with radiation.

From histological findings, breast conserving treatment appears possible by down-staging of the advanced breast cancer.

References
Recently, there have been important advances in the chemotherapy for breast cancer. A number of new agents have shown promising results in the treatment of metastatic breast cancer. In ER-positive breast cancer, the addition of chemotherapy to tamoxifen improves disease-free survival. The addition of sequential paclitaxel to Adriamycin plus cyclophosphamide appears to improve disease-free and overall survival in operable, node-positive breast cancer.

CHEMOTHERAPY FOR METASTATIC DISEASE

Taxanes
Paclitaxel or docetaxel has a response rate of 30-40% in anthracycline-resistant metastatic breast cancer. In a recent intergroup trial, patients with metastatic breast cancer were randomly assigned to doxorubicin, paclitaxel, or combination of paclitaxel and doxorubicin (1). Combined treatment produced a higher response rate and 2 months longer time to disease progression. However, there was no survival benefit.

Capecitabine
Capecitabine is a new oral fluoropyrimidine carbamate which is converted to 5-fluorouracil by thymidine phosphorylase selectively in tumors. This drug has been shown to be effective in patients with paclitaxel-resistant metastatic breast cancer (2).

Anti-HER2 antibody
A number of studies have shown that overexpression of HER-2 oncogene is associated with poor prognosis and drug resistance. Two trials tested the efficacy of the humanized anti-HER2 antibody (Herceptin) in patients with HER-2 overexpressing metastatic breast cancer. In one trial, 222 patients with prior chemotherapy were treated with Herceptin alone (3). Overall response rate was 15% with median survival of 13 months. In the other trial, patients were randomized to chemotherapy alone or chemotherapy plus Herceptin (4). Combined treatment resulted in higher response rate (62% vs. 36%).
ADJUVANT CHEMOTHERAPY

Combined chemoendocrine therapy

In NSABP B20 trial, 2,306 patients with node-negative, ER-positive breast cancer were randomized to tamoxifene alone (T), T plus MF, or T plus CMF (5). Addition of chemotherapy resulted in the improvement of disease-free and overall survival. An intergroup trial compared T vs. CAF plus T in node-positive, ER-positive patients (6). This trial reported benefit in disease-free survival for patients who received combined treatment without advantage in overall survival.

Taxanes

In CALGB 9344, 3,170 patients with 4 positive nodes were treated with AC for 4 cycles with or without paclitaxel for 4 cycles (7). Patients with ER-positive disease received tamoxifen for 5 years. The addition of paclitaxel increases in disease-free survival (90% vs. 86%) and overall survival (97% vs. 86%).

REFERENCES

6. Albain K, Green S, Osborne K, et al: Tamoxifen (T) versus cyclophosphamide, Adriamycin, and 5-FU plus either concurrent or sequential T in postmenopausal, receptor(+), node(+) breast cancer. a Southwest Oncology Group phase III intergroup trial.
CONSERVATIVE TREATMENT FOR BREAST CANCER

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Content of Lecture
1. History of Surgical Treatment of Breast
2. Background of BCT
3. Randomized Trials of BCT
4. Current Issues of BCT

A. History of Surgical Treatment

1. Radical mastectomy
   • 1884, William Halsted
     • An Anatomic and Mechanistic perception of tumor spread - Lymphatic spread
     • En bloc Resection
   • Long term Result
     13% survived 30 yrs free of cancer
     57% dying of breast cancer
     24% dying of other causes
     6% lost to follow-up

2. Extended Radical Mastectomy
   • Internal mammary lymph node
     Failed to show any difference in disease-free or overall survival between SRM and ERM
   • The overall survival rate - 10 yrs
     • SRM 60.7%
     • ERM 57.0%
3. Modified Radical Mastectomy
- 1960s, most common operative treatment
- D.H. Patey
- Consensus Development Conference on the treatment of breast cancer in 1979
- MRM was standard Tx for stage I and II breast cancer

4. Total mastectomy
- B.Fisher of the NSABP
- better understanding of the biology of metastasis
- cancer is a systemic disease involving a complex spectrum of host-tumor interrelations
- variations in local-regional therapy are unlikely to substantially affect survival.

Radical vs. Total mastectomy (NSABP B04)
LN(-):radical mastectomy or TM c/s RT
LN(+):radical mastectomy or TM c RT

No significant difference in overall survival or disease free survival

5. Breast Conserving Treatment (BST)
1. Backgrounds
   - Earlier detection of cancer
     Better education
     More extensive information
     More refined diagnostic tools
     Diffuse screening campaigns
   - Radiotherapeutic advance
   - Cosmesis
   - Quality of life
2. Randomized Clinical Trials
- Institut Gustave-Roussy (1972-1979)
- NSABP-B06 (1976-1984)
- EORTC (1980-1986)

3. NSABP-06 lumpectomy trial
   Tumor recurrence
   - Lumpectomy + radiotherapy: 90% free of tumor
   - Lumpectomy alone: 61% tumor free

   Survival
   - no significant difference in DFS, distant disease free survival or overall survival

   Conclusions: Lumpectomy and radiotherapy are appropriate for stage I and II breast cancer

4. Goal of BCT
   - Provide survival equivalent to mastectomy
   - Preservation of the cosmetic outcome
   - Low rate of recurrence in the treated breast

5. Local recurrence
   - undesirable consequences of
     - Inappropriate patient selection or
     - Inadequate surgery.
   - rate of less than 5% at 5 years is commonplace.
   - Low local recurrence rates
     - adequate wide local excision on appropriately selected patients.
     - a standard regime of post-operative radiotherapy
   - What is affecting on Local Recurrence after BCT?

1) Patients Risk Factors: age
2) Tumor Risk Factors
   - Tumor Size
   - Involvement of LN
   - Extensive Intraductal Component (EIC)
   - Lymphatic Vessel Invasion
   - Histologic Tumor Type
3) Marginal Status

<table>
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<th>Investigator</th>
<th>Interval(y)</th>
<th>Positive</th>
<th>Negative</th>
<th>Close</th>
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<td></td>
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<tr>
<td>Veronesi</td>
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<tr>
<td>Schnitt</td>
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<td>15</td>
<td>3</td>
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<td>Schmidt-Ullrich</td>
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<tr>
<td>Solin*</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>11</td>
<td>7</td>
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</tbody>
</table>

* The dose of radiation was adjusted in relation to margin status

4) Treatment Factors
   a. Extent of Breast Resection
   b. Technical Details of the Radiotherapy
   c. The Use of Adjuvant Systemic Therapy

5) Questions to Treatment Factors
   a. How much should I remove the tissues?
   b. How do I evaluate the Marginal Status?
      a) Specimen-inking Method (SIM)
      b) Cavity Shavings Method (CSM)
c) Bed Biopsy

c. Which patients can be omitted the Radiation Therapy?
d. Who must be performed the Mastectomy?

- Malik HZ, Macmillan RD et al. - In press.
  Margin assessment by cavity shaving after breast-conserving surgery. analysis and follow-up of 543 patients
  - Cancer was found in the cavity shavings in 37
  - A total of 15% of patients underwent further surgery (10% mastectomy)
  - 5-year rate of local recurrence - 2%
  - Risk factor: Tumor Grade and EIC

- Which Patients can be omitted the RTx
  - Role of RTx
    - Reduction of recurrence:
      85% (range, 75% to 97%)
    - Overall survival: not show a significant survival benefit

Controversies in DCIS

1. DCIS: A Changing Disease

<table>
<thead>
<tr>
<th></th>
<th>Before 1985</th>
<th>After 1985</th>
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<tbody>
<tr>
<td>Frequency</td>
<td>Unusual</td>
<td>Common</td>
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<tr>
<td>Presentation</td>
<td>Palpable</td>
<td>Nonpalpable</td>
</tr>
<tr>
<td>Classification</td>
<td>Architectural</td>
<td>Biological</td>
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<tr>
<td>Treatment</td>
<td>Mastectomy</td>
<td>Breast Conservation</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>None/delayed</td>
<td>Immediate</td>
</tr>
</tbody>
</table>

- Why
  1) Increased mammographic utilization
  2) The improvement in mammographic technique
  3) The acceptance of breast-conservation therapy for invasive breast cancer

2. Architectural Classification of DCIS
  - Non-comedo type
    - Papillary
3. Problem in architectural classification
   - Not uncommon for high nuclear grade noncomedo lesions
   - Mixtures of various architectural subtypes within a single biopsy specimen are common
   - No uniform agreement how much comedo DCIS needs to be present to consider the lesion a comedo DCIS

4. Six prognostic factors

<table>
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<tr>
<th></th>
<th>Univariate p Value</th>
<th>Multivariate p Value</th>
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<tbody>
<tr>
<td>Nuclear grade</td>
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<td>0.0001</td>
</tr>
<tr>
<td>Margin width</td>
<td>0.004</td>
<td>0.01</td>
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<tr>
<td>Tumor size</td>
<td>0.005</td>
<td>0.01</td>
</tr>
<tr>
<td>Presence of necrosis</td>
<td>0.009</td>
<td>0.09</td>
</tr>
<tr>
<td>Comedo architecture</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>HER2 neu(erbB2)</td>
<td>0.02</td>
<td>NS</td>
</tr>
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</table>

NS = not significant

5. Diagnostic and Surgical Pretreatment Issues

   1) Mammography
      - High quality mammography is needed
      - About 85% of DCIS: not palpable
      - Calcifications do not always map out the entire extent of the DCIS lesion (esp. low grade)
      - Palpable vs Non-palpable

   2) Biopsy
      - FNA
      - Stereotactic core biopsy
      - Surgical biopsy
      - Localization method
Hooked wire(multiple or single)
Dye
- Clear margin or cosmesis

3) Histological Excision Margins
- Definition of Clear margin
  • Silverstein: 1mm in all direction
  • Solin: 2mm in all direction
  • NSABP: not transected tumor
  • Holland: normal breast structure between tumor and inked margin
  • Nottingham group: 10mm in all direction

6. Treatment of DCIS
- Mastectomy
- Breast conservation
  - Excision alone
  - Excision and Radiation therapy

1) Why is Local Recurrence Important?
  - Invasive recurrence - about 50%
  - Threat to life
  - Biological worsening of the stage of disease
  - Tx of choice: Mastectomy

2) Role of Radiation
  • NSABP - B17 (1998 update)
    - Patients: 818 cases
    - Median follow up: 90 months
    - RT: 5000 cGy
    |                  | Excision | Excision + RT |
    |------------------|----------|---------------|
    | Local recur rate(8 yr) | 27%      | 12%           |
    | Non-invasive IBT    | 13.4%    | 8.2%          |
    | Invasive IBT        | 13.4     | 3.9%          |

• Criticism of the Protocol(NSABP B17)
  - Lack of size measurement(40% more)
  - Lack of requirement for mammographic-pathologic correlation of specimen radiography
  - No uniform guidelines for tissue processing or size estimation
- No author’s definition of “Clear margin”
- No subgroup

3) Problem in Radiation Therapy
   A. Side effects
      - Cardiac Toxicity
      - Pulmonary fibrosis
   B. Expensive cost
   C. Mammographic follow up - difficult
      - delayed diagnosis of recurrence

4) Subgroups and RTx
   • Factors
     - Pathologic factors
       • Nuclear grade
       • Comedo necrosis
     - Tumor size
     - Margin width
     - Age
     - Past History

A. High grade vs low grade in local recurrence rate
   - 33% vs 2% of recurrent rate after Wide excision (by Lagios et al)
B. Comedo vs Noncomedo type in local recurrence rate
   - 32% vs 3% of local recurrence after Wide excision (by Schwartz et al)
C. Solin et al
   - No significant differences on recurrent rate
   - But Comedo + nuclear grade 3 vs other groups
     \[20\% \text{ vs } 5\% ; P = 0.009\]

D. Van Nuys Prognostic Index (VNPI)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Tumour size (mm)</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Margin width (mm)</td>
<td>≥10</td>
</tr>
<tr>
<td>Pathological classification</td>
<td>Not high grade, no necrosis (nuclear grades 1 and 2)</td>
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</tbody>
</table>

*Scores (1-3) for each of the predictors are totalled to yield an index score ranging from a low of 3 to a high of 9. Reproduced with permission.*
5. Axilla

- General agreement
  - Not be treated
  - Not irradiated
  - No form of axillary sampling or dissection
  - Option: (by Silverstein)
    - For patients with lesions large enough to require mastectomy - Sentinel LN biopsy
SURGICAL MANAGEMENT OF DCIS  
(Overview and The Experiences in Korea Cancer Center Hospital)

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The optimal treatment of patients with ductal carcinoma in situ (DCIS) is of particular intense interest to modern surgeon treating patients with breast cancer. Not long ago, only 1% to 2% of breast cancers were identified as DCIS. Currently, patients with DCIS accounts for approximately 20% to 25% of those with newly diagnosed breast cancer in Western countries (1). In Korea, the incidence of DCIS has also been increasing primarily due to increasing use of screening mammography.

DCIS is defined as a malignancy of epithelial cells that lines the lactiferous ducts in which the malignant cells remains confined within the duct. DICS with microinvasion or microinvasive carcinoma (MIC) has been defined as a predominantly noninvasive lesions accompanied by the presence of malignant cells up to but not more than 100 μ beyond the basement membrane of involved duct (2,3). Despite the fact that any evidence of microinvasion should preclude the diagnosis of DCIS, the differences between DCIS and MIC in terms of biological characteristics and outcome of treatment has not been fully defined yet.

Mastectomy has been considered the appropriate treatment for all patients with DCIS for several decades. The rationale of mastectomy included the significant incidence of multifocality, multicentricity, and the possibility of an occult invasion in association with DCIS. The management of DCIS by lumpectomy, radiotherapy or both was initially suggested by Bloodgood, who described a case of DCIS in 1917. At that time, the strategy was uniformly rejected by the surgical community, but the success of breast conserving therapy (BCT) for invasive breast carcinoma spawned a renewed interest for BCT in DCIS (4). Because the rate of local recurrence after wide excision alone had been disturbingly high, and of patients who have local recurrence, an average of 50% do so with invasive disease (5), the addition of radiation therapy to wide excision has been performed to reduce the rate of local recurrence.
The NSABP B-17 trials were designed to investigate the role of radiotherapy in the treatment of patients with DCIS. The recurrence rate was 16.4% in the lumpectomy alone group compared with 7% in the group receiving radiotherapy. In addition, this reduction was most apparent for invasive carcinomas (6). Although there are some criticism and difficulties in interpreting the result of this study, NSABP B-17 trials is a landmark study that will influence our understanding of DCIS for years to come (7). Another trials (EORTC-10853) that assesses the value of radiation therapy in the treatment of patients with DCIS is ongoing.

Mastectomy is still the other option to be considered and should be recommended for patients with DCIS of large size, with diffuse microcalcification and in which clear resection margin cannot be achieved by local excision.

Recently, Silverstein et al (8) proposed a guideline to aid in the complex treatment selection process of DCIS. According to this guideline (VNPI score), DCIS patients with score of 3 or 4, can be considered for excision only. Patients with intermediate score (5, 6 or 7) should be treated with excision plus radiotherapy and patients with score 8 or 9 should considered for mastectomy.

Even though there are still many controversies over the surgical treatment for the patients with DCIS, we have learned the followings so far (9).

1. Pure DCIS is local, noninvasive malignancy for which mastectomy yields nearly 100% disease-free survival.
2. There is no role for axillary dissection for pure DCIS.
3. There is no role for cytotoxic chemotherapy for DCIS.
4. If a BCT is selected, complete excision of index lesion under strict margin control is crucial for the reducing the chance of local recurrence. This approach also mandates close clinical and mammographic follow-up.

In order to investigate the incidence, clinicopathologic features and outcome of treatment of DCIS and MIC, authors reviewed the 91 patients with DCIS or MIC who had been treated in Korea Cancer Center Hospital during the period from 1983 to 1996. The results were as follows.

1. the incidence was 2.72% (91/3,343) and had been increasing (2.1% in 1980s and 3.3%
in 1990s
2. The mean age was 44.2 years and the age of peak incidence was fifth decades.
3. The most common clinical manifestation was palpable mass (69%) followed by nipple discharge, MMG abnormality and Paget’s disease in decreasing order of frequency.
4. According to pathologic classification by Schwartz, comedo type was the most common (32%) followed by cribriform (23%), papillary (20%), mixed (11%), solid (9%) and micropapillary (5%) type.
5. There were 58 cases (69%) of pure DCIS and 16 cases (17.5%) of MIC. In 17 cases (18.5%) the presence of microinvasion was equivocal or cannot be assessed.
6. There were no significant differences between DCIS and MIC in terms of mean age (44.5 years vs 43.8 years), mean tumor size (2.15 cm vs 2.25 cm), the frequency of comedo type (29% vs 36%), lymph node metastasis (0% vs 6%) and multicentricity (3.3% vs 3.0%). However, the palpable mass was more common in MIC than DCIS (82% vs 62%, p<0.05).
7. 75 patients (82%) were treated with mastectomy and 16 patients were treated with breast conserving surgery.
8. Besides 2 cases of systemic recurrence among MIC, there was no case of recurrence or disease-associated death during the period of follow-up.

Based on the results of this review, the following conclusions were obtained.
1. Even though the rates of BCT has been increasing, mastectomy was still the most common procedure for the treatment of DCIS and MIC.
2. The outcome of treatment, in terms of recurrence or survival, was very excellent and almost the same for both groups of pure DCIS and MIC. More long-term follow-up and multicenter study seems to be necessary to identify the differences in clinical features and outcome between pure DCIS and MIC in Korea.
References

ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF BREAST CANCER

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Radiation clearly plays an important role in the management of breast cancer and its application is increasing due to general use of breast-conserving treatment and re-appraisal of post-operative radiotherapy. The role of radiation therapy in the management of breast cancer can be defined in four categories as follows; 1) Primary radiation therapy after breast-conserving surgery in early breast cancer (both intraductal and invasive cancer). 2) Post-operative adjuvant radiotherapy after mastectomy for high-risk patients. 3) Radiotherapy for locally advanced breast cancer in combination with neoadjuvant chemotherapy, with or without surgery. 4) Palliative radiation therapy for metastatic breast cancer, mostly bone and brain metastases, and loco-regional recurrences.

Primary Radiation Therapy After Breast-conserving Surgery for Early Breast Cancer

Breast-conserving surgery and irradiation has now been settled as more preferred treatment method than total mastectomy for the patients with stage I and II breast cancer and some patients with intraductal cancer. The need for radiotherapy after local excision has been tested in several randomized prospective studies. A statistically significant reduction in local breast failure from 20-40% to less than 10% was seen. Although one might argue that local failure rates of 20 to 40% after excision alone are acceptable in order to avoid treating all women with radiation. However, many local recurrences require a patient to undergo a mastectomy at the time of recurrence. Furthermore, breast radiotherapy is extremely well tolerated with very low complications. Thus, radiotherapy is necessary after breast-conserving surgery to provide a woman with the greatest chance of having an intact, cosmetically acceptable breast after the conclusion therapy. Any tumor, not more than 5 cm with no grave signs, single focus or multiple foci confined to one
quadrant of breast, and negative or small, mobile low nodes can be eligible for breast-conserving treatment. Breast recurrences following conservative surgery and radiation is most likely related to the presence of a significant residual tumor burden following breast-conserving surgery that cannot be controlled with modest dose of radiation. Therefore, to reduce the local recurrence after conservative treatment, careful patient selection and proper surgical management before radiation are mandatory. The most important steps to select the patients are thorough physical examination of breast, mammographic evaluation before surgery to rule out gross multifocal or multicentric disease, careful review of pathologic material to assess resection margin, and specimen mammography along with post-operative mammography after partial mastectomy to confirm the removal of disease. The purpose of surgery in breast-conserving treatment is to remove the tumor grossly with minimal cosmetic deformity. The purpose of radiotherapy in the breast-conserving treatment is to eradicate the residual microscopic cancer with moderate dose of radiation while preserving the good cosmetic result. Therefore, standardized radiotherapy technique with optimum radiation volume and dose is essential. Total dose of 45 to 50 Gy with daily dose of 180 to 200 cGy to the entire involved breast with or without boost dose to the primary site is generally accepted for control of subclinical disease or microscopic residual disease in the remaining breast tissue. Although, there is a lack of consensus concerning the need for irradiation of regional lymph node bearing area, there is agreement in the need to avoid axillary irradiation after a complete axillary dissection. It is because not only is the rate of axillary node recurrence after axillary dissection negligibly low but axillary irradiation also adds morbidity such as arm edema, breast edema, and brachial plexopathy.

**Post-operative Radiotherapy**

One of the most actively studied and controversial areas in the treatment of breast cancer is the utility of post-operative radiotherapy (RT). The term post-operative RT refers to RT to the chest wall and draining lymph node regions used as an adjuvant treatment after definitive surgery (mastectomy). There are two possible reasons for the use of prophylactic postoperative RT. The first is to reduce the rate of local or regional tumor recurrence (i.e., recurrence on the chest wall or in the axillary, internal mammary, or supraclavicular lymph nodes) by treating residual microscopic disease that has spread beyond the margin of
surgical resection. It has been well documented that in the absence of post-operative RT, there is a substantial risk of local recurrence after modified radical or radical mastectomy. The second rationale for post-operative RT is to improve survival. It is possible that residual local disease after mastectomy may be the only site of persistent cancer and a source of subsequent distant metastases. The addition of post-operative RT to radical mastectomy has been shown to decrease the risk of local recurrences in a number of retrospective studies and prospective randomized trials. Studies performed before the late 1980s failed to show an overall survival benefit for patients treated with radiation. However, there are significant methodological problems in performing such a study properly. The most important problem is the technical aspects of RT. Some of those trials used improper RT volume and RT dose and also used inadequate technique that irradiated large portions of heart resulting in excess late cardiac mortality. Also, many of the studies were very small and randomization was not strict. Furthermore, most post-operative RT studies did not involve the use of adjuvant systemic therapy. Thus, an effective local treatment such as postmastectomy irradiation may have its value diminished by a flood of systemic failures. One might speculate that if systemic chemotherapy were effective in controlling micrometastatic systemic disease, the role of post-operative RT in controlling local disease might become increasingly important. Modern studies in which radiation techniques were optimum and chemotherapy was combined are actually beginning to show a long-term survival advantage for the radiated group. The Danish Cooperative Breast Group trial and British Columbia trial which tested post-operative RT in node-positive pre-menopausal women receiving chemotherapy showed a trend toward survival benefit for the irradiated group. The issue of the utility of post-mastectomy irradiation is still controversial and will likely be the subject of additional clinical trials in the upcoming years. In the meantime, post-operative RT appears indicated in the following cases.

1. Positive margins or gross residual disease
2. Any T4 tumor
3. T3 tumor with positive lymph nodes
4. Gross extracapsular disease in the axilla
5. Patients treated curatively with high-dose chemotherapy and autologous stem cell support
Combined Modality Treatment for Locally Advanced Breast Cancer

Locally advanced breast cancer (LABC) has been defined as all patients with stage III cancer and those with stage IV disease, but with metastases limited to the ipsilateral subclavicular or supraclavicular fossa. The management of patient with these LABC has evolved substantially over the past three decades. As the majority of LABC have already occult distant metastasis, systemic chemotherapy prior to local therapy such as surgery or RT is required. The major clinical advantages of induction chemotherapy include 1) the ability to monitor response to therapy by serial measurements of the primary tumor, and 2) the achievement of downstaging, which often permits breast conservation. The most important aspect of combined modality therapies is the conceptual framework. When patients with LABC were treated with surgical resection or radiation therapy, the surgeon or the radiation oncologist decided on the type and sequence of treatments. For optimal use of all treatment modalities, this practice has changes, so that all interested specialists (radiologist, pathologists, surgeon, radiation and medical oncologists) review the data and examine the patient jointly to evaluate the response to each therapy and determine the optimal type and sequence of therapies. Thus, harmonious teamwork approach is essential for successful treatment of LABC.

Palliative Radiotherapy

Breast cancer can metastasize widely, especially to bone, frequently requiring palliative radiotherapy. The purposes of RT in bone metastases are to relieve pain, to prevent pathologic fracture of weight-bearing bone, and to relieve spinal cord compression. Spinal cord compression by spine metastases or leptomeningeal spread need an emergency radiotherapy to prevent irreversible neurological damage. Standard regimen of 20 Gy in 5 fractions or 30 Gy in 10 fractions is usually successful. Smaller fraction size of 2 – 2.5 Gy is indicated to reduce late soft tissue fibrosis. Similarly, brain metastases are often treated with 30 Gy in 10 fractions with a possible cone-down boost to a solitary metastasis. Late complications following whole-brain RT can be severe and debilitating in some patient. Brain atrophy, necrosis, endocrine dysfunction, leukoencephalopathy with neurocognitive deterioration, and frank dementia have been reported. The incidence of late complication is related to many factors including total dose, fraction size, patient age, extent of CNS
disease, and pre-existing neurologic impairment. For the same total dose, the larger the daily fraction size, the greater the risk of late CNS sequelae. Thus, for patients with favorable prognostic factor and a projected survival of greater than 6 months, it is recommended that smaller daily fraction size (less than 2.5 Gy/d). Alternative fractionation regimen for brain metastases is 30–37.5 Gy in 12–15 fractions.

References


BONE MARROW MICROMETASTASES IN BREAST CANCER

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Department of Surgery, College of Medicine, Yeungnam University, Daegu, Korea

Introduction
Although bone and bone marrow are most frequent sites of metastases in breast cancer, conventional radiologic and scintigraphic techniques can detect bone involvement only when the bone matrix has been destroyed. In 1980, Sloane et al. were the first to use an immunocytochemical approach for the detection of disseminated carcinoma cells in bone marrow aspirates of breast cancer patients and termed them micrometastatic cells. A number of studies have focused on the prognostic impact of the bone marrow micrometastases (BMM) status in breast carcinoma. In some cancer including breast carcinoma, positive BMM status has been identified as an indicator of poor prognosis, and guideline of chemotherapy. Today, BMM status in proposed as an entry in the TNM classification as a facultative prognostic factor indicated M1(i). The aim of this study were to determined incidence BMM as detected by means of MoAb immunofluorescence and to correlated the presence of these micrometastases with prognosis and other clinical and pathological features.

Material and Methods
Micrometastases were identified in bone marrow aspirates collected from both iliac creats in 220 breast cancer patients after surgery between July 1991 and January 1997. A small skin incision was made prior to insertion of the needle and 6 ml of marrow were collected in a heparinized syringe from each other. Aspirates were diluted with RPMI-1640 medium with fetal calf serum. The cells were sedimented onto a Picoll-Hypaque density gradient and centrifuged at 400×g for 20 min. The interface layer were collected and washed three times with RPMI-1640. Air-dried cytopsin slides were fixed with 100% ethanol. The slides were washed three times with PBSA (PBS-0.1% BSA) and incubated with monoclonal antibody AE1/AE3 (Boehringer Manheim Indianapolis, IN) And the slides were washed with PBSA and incubated with fluorescein-conjugated rabbit antimouse antiserum (DAKO, USA). The slides were washed PBSA and coverslipped using glycerol.

Results
Median age of the patients were 46 (range 23-78 years). Seventy one of the 220 patients (32.3%) had MoAb positive bone marrow cells (table 1). Tumor cells were detected in the bone marrow of 41 (34.7%) of 118 lymph node positive patients and in 30 (29.4%) of 102 lymph node negative patients. Twenty seven percent of T1, 34.5% of T2 and 39.1% of
T3 displayed positive micrometastatic cells. Twenty six percent (10 of 38) stage I, 32.1% (45 of 140) stage II, and 41% (16 of 39) stage III patients showed antigen positive cells in the marrow. No association was found between bone marrow positivity and histologic findings such as lymphatic invasion, vascular invasion, neural invasion, histologic grade, nuclear grade, and mitotic index. No association was found between bone marrow positivity and hormonal receptor status. The mean follow up after primary surgery was 41.6 months. Distant metastases occurred in 34 cases (15.4%). Twenty two of these were found among the 71 patients with tumor cells in the bone marrow. In contrast, only 12 of the 149 patients without tumor cells in aspirates developed distant metastases (p<0.05) (table 2). Bone metastases occurred in 16 cases, 14 of these were found among the 24 patients with BMM. In contrast, only 1 of the 12 patients without BMM developed bone metastases (p<0.05) (table 3). No difference in local recurrence was observed in the two group. Thus patients with positive BMM developed distant and bone metastases more frequently than those in the negative BMM. But no difference in DFI between two group.

Table 1. Detection of occult micrometastases in bone marrow aspirates of patients with operable breast cancer.

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Epithelial antigen(BMM*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>220</td>
<td>71(32.3%)</td>
</tr>
<tr>
<td>149</td>
<td>149(67.7%)</td>
</tr>
</tbody>
</table>

*Bone marrow micrometastases

Table 2. Association between the distant metastases and BM

<table>
<thead>
<tr>
<th></th>
<th>DFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMM(+)</td>
<td>22/ 71(30.9%)</td>
</tr>
<tr>
<td>BMM(-)</td>
<td>12/149(8.5%)</td>
</tr>
</tbody>
</table>

Total 34/220(15.5%) 27.3 Mo

BMM : bone marrow micrometastases
DFI : disease free interval
P<0.05

Table 3. Association between bone metastases and BMM

<table>
<thead>
<tr>
<th>No of bone metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMM(+)</td>
</tr>
<tr>
<td>12/22(54.5%)</td>
</tr>
<tr>
<td>BMM(-)</td>
</tr>
<tr>
<td>1/12(8.3%)</td>
</tr>
</tbody>
</table>

Total 13/34(38.2%)

P<0.05
Conclusion

In our study, the bone marrow was positive in 71/220(32.3%) patients of primary breast cancer. Tumor cell detection in bone marrow of patient with primary breast carcinoma was a good predictor for distant metastasis, especially bone metastases. But no association was found between bone marrow positivity and tumor size, nodal status, stage, histologic parameter and hormonal receptor status. In conclusion, the presence of epithelial cells in bone marrow could be validated as a poor prognostic factor in breast cancer but the role as an independent factor remains to be determined by further studies using standardized methodic protocol.

References
I. Historical aspect
*1866 - Broca reported first the breast cancer family of his wife
*1990 - Mary-Claire King research team of UCLA analyzed the relationship of HBC with chromosome 17q21
*1994 - Skolnick isolated BRCA1 gene

II. Definition of HBC
1. Hereditary breast cancer
   - More than 3 breast cancer patients in the family pedigree have relation in two generation (in maternal origin) and three generation (in paternal origin)
   - At least two patients are first degree relative
   - Include the GI cancer, ovarian cancer, testicular cancer in the family
2. Familial Breast Cancer
   - More than 2 breast cancer patients in same family pedigree
     If it represent bilaterality or early onset, HBC will be suspected.
3. Male breast cancer inside HBC
   - HBC is an autosomal dominant trait, so male and female in the direct genetic lineage have an equal chance of inheritance, but male rarely develop breast cancer
   - Early onset, bilateral tendency
   - Related with testicular cancer
   - Male breast cancer was found in HBC family

II. Characteristics of HBC
* Autosomal dominant
* 4-9% of all breast cancer
* Early onset
* Bilaterality
* Genetic heterogeneity, vertical transmission
III. Relative risk in family History
1) 1 first degree with breast cancer: 2-3 times
2) 1 first degree with early onset breast cancer: 5 times
3) 1 first degree early onset and bilateral breast cancer: 10 times
4) mother and 1 sister with breast cancer: 10-14 times

IV. Types of HBC
1. Site-specific hereditary breast cancer
   * usually early onset, bilateral
   * more than 3 breast cancer at the first degree relative of family pedigree
   * autosomal dominant
2. Hereditary breast-ovary cancer
   * breast and ovary cancer may occur simultaneously on the one family member or ovary
cancer patient and breast cancer patient are existent in the family
   * In paternal inheritance, testicular cancer can appear
3. Early onset breast cancer associated with Lynch syndrome II
   * Lynch syndrome II(colon cancer, endometrial cancer, ovarian cancer) is combined with
   early onset breast cancer
   * Non hereditary breast cancer is not common in Lynch syndrome
4. Li-Fraumeni syndrome
   * SBLA(Sarcoma, Breast cancer, Leukemia, Adrenal tumor)
   * brain tumor, lung cancer, osteosarcoma may also occur
   * related to p53 gene mutation
5. Cowden disease
   * Multiple hamartomatous syndrome
   * characteristically combined mucocutaneous skin disease
   * thyroid cancer, adenoma, GI polyp, uterine leiomyosarcoma, lipoma
   can be combined
6. Muir syndrome
   * multiple skin cancer, GI and urological malignant-benign tumor, basal cell
carcinoma, colon diverticulum
   * postmenopausal breast cancer is common
About half of the HBC(45%)-associated with BRCA1
35%-associated with BRCA2
others-related with other gene

V. Gene
1.p53 gene
2.BRCA1
3.BRCA2
4.Ataxia-telangiectasia mutant (ATM) gene
5.Loss of heterogeneity

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery date</td>
<td>1994</td>
<td>1995</td>
</tr>
<tr>
<td>Chromosome</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Length of protein</td>
<td>1863</td>
<td>3418</td>
</tr>
<tr>
<td>No.of exon</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>No.of mutation</td>
<td>&gt;125</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Identified</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Breast cancer Ovarian cancer Male Breast cancer

Lifetime Cancer Risk (%)

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery date</td>
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<tr>
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<td>&gt;50</td>
</tr>
<tr>
<td>Identified</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VI. Who develop breast cancer?

1. Major markers of increased breast cancer risk
   * Relative risk increased more than 4 times
     - Evidence of susceptibility gene BRCA1
     - Premenopausal breast cancer in mother and sister
     - Atypical hyperplasia in breast biopsy or aspirate
     - In situ cancer; ductal or lobular
   * Relative risk increased 2 to 4 times
     - Premenopausal breast cancer in mother or sister
     - Hyperplasia without atypia in breast biopsy or aspirate
     - History of breast cancer in one breast
     - Aging Caucasian woman

2. Minor markers of increased breast cancer risk
   1) General markers
      - Postmenopausal breast cancer in first degree relative
      - Previous cancer of the ovary or uterine endometrium
      - Nodular densities in mammogram are predominant
      - Obesity (in women over 50)
      - Tallness in adult life
      - Excess ionizing radiation to chest wall or breasts
      - Higher alcohol consumption
      - Higher socio-economic state

   2) Hormone-related markers
      - Non childbearing (in women under 40)
      - Delayed first childbirth
      - Short duration of breast feeding of children
      - Onset of menstruation before age 12
      - Onset of menopause after age 49
      - Prolonged use of contraceptives (in woman under 45)
      - Prolonged estrogen replacement therapy
3. Evaluating families for inherited breast cancer risk
*population average-1/9 before 85
*risk factors-family history,
   exposure to carcinogen, hormone
   reproductive history ect.
*risk estimation principle based on family history
   include as many maternal and paternal relatives as possible
   unaffected relatives included also
   at least include 3 generation
   history confirmed by pathology report
   details:age at diagnosis, tumor histology, site of primary tumor,
   metastatic disease, presence of any genetic syndromes
*Categories of risk family
   ° moderate risk family
     less striking FH
     absence of ovarian cancer
     older average age
   ° high risk family
     multiple cases of breast cancer(at least 3 cases)
     autosomal dominant pattern of inheritance
     diagnosed earlier age(< 45 yr)
     may be cases of ovarian cancer in the family
     mutation of breast cancer susceptibility gene,
     such as BRCA1, BRCA2

4. Properties of moderate risk family
   -risk families one or two relatives with breast cancer
     often postmenopausal
   -four subgroup
     ° combined effects of multiple genetic components and environment agents
     ° presence of a mutaion in a single dominant susceptibility gene with low penetrance
     ° may have an inherited breast cancer predisposition syndrome, but FH does not
       appear striking(small kindred or incomplete information)
Breast cancer is common and may occur more than once in a large family unrelated to inherited factors.

5. Risk assessment for moderate-risk families

- Relative risk: the rate of a disease in a group exposed to a risk factor as compared with a second group not exposed to that risk factor.
- Cumulative risk: prediction of risk over a defined time (e.g., the next 20 years) or a predetermined maximum life span (often to age 80 years).
- Claus model: CASH (Cancer and Steroid Hormone study) data set.

**What is High risk?**

- Or more first degree relatives with breast cancer before age 60.
- First degree relative with bilateral premenopausal breast cancer.
- Mother and maternal grandmother with breast cancer before age 60.
- First degree relative with unilateral breast cancer before age 40.

Table 1. Breast cancer risk estimates for members of moderate-risk families

<table>
<thead>
<tr>
<th>Affected relative</th>
<th>Age of Affected relative</th>
<th>Cumulative breast cancer risk by age 80,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>one first degree</td>
<td>&lt; 50</td>
<td>13-21</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>9-11</td>
</tr>
<tr>
<td>one second degree</td>
<td>&lt; 50</td>
<td>10-14</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>8-9</td>
</tr>
<tr>
<td>two first degree</td>
<td>both &lt; 50</td>
<td>35-48</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>11-24</td>
</tr>
<tr>
<td>two second degree</td>
<td>both &lt; 50</td>
<td>21-25</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>9-16</td>
</tr>
</tbody>
</table>

6. Properties of High-risk Families

- High probability of harboring a mutation in a dominant breast cancer susceptibility gene.
  1) History of breast or ovarian cancer in as many as half of all female relatives.
  - Susceptibility can be transmitted by either parent.
  - 0.33% of general populations, 5% of breast cancer.
  2) Early age of onset.
3) bilateral or multifocal breast cancer
4) two or more affected first degree relatives with breast or ovarian cancer
5) BRCA1, BRCA2 mutation
   - BRCA1 mutation carriers
     87% life time risk of breast cancer
     20% develop by age of 40 years
     51% 50
     87% 70
     65% who live to age 70 develop second primary tumor
   - Large, site specific breast cancer family (without ovarian ca) with many cases (more than five) are less likely related to BRCA1 mutations
   - Risk of other cancers
     relative risk of 3.33 for prostate cancer, 4.11 for colon cancer
   - Tumors with BRCA1 mutations have an increased growth rate, paradoxically better survival
   - Families as dominantly inherited trait that do not appear to be linked to BRCA1 or BRCA2: additional breast cancer susceptibility gene exist

7. Risk assessment for high-risk families
1) Breast cancer susceptibility related to inherited mutations in BRCA1
   - Characteristics of the family
     the number of affected relatives
     presence of ovarian cancer in the family
     age at diagnosis of breast cancer
     relationship of affected relatives
   - 6% of up to three affected members
   - 9% of with four or more affected showed linkage to BRCA1
   - Median age of onset for BRCA1 mutation
   - Carriers is less than 45 years
2) Breast cancer susceptibility related to inherited mutations in BRCA2
   70% of breast cancer families that do not carry BRCA1 mutation harbor mutations in BRCA2
<table>
<thead>
<tr>
<th>Genetic alteration</th>
<th>Sex</th>
<th>Breast cancer risk</th>
<th>Other consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>F</td>
<td>87%</td>
<td>increased risk of bilateral breast cancer and ovarian cancer, slight increased risk for colon cancer</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>Negligible</td>
<td>slight increased risk for colon and prostate cancer</td>
</tr>
<tr>
<td>BRCA2</td>
<td>F</td>
<td>87%</td>
<td>moderate increased risk for ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>6% by age 70</td>
<td>risk for other cancers has yet to be evaluated</td>
</tr>
<tr>
<td>Unknown</td>
<td>F or M</td>
<td>unknown</td>
<td>risk of breast cancer will vary significantly between mutation carriers and noncarriers: at present, this determination is not possible</td>
</tr>
</tbody>
</table>

VII. Management of women at increased risk for breast cancer

1. prophylactic surgical intervention
   - prophylactic mastectomy
   - prophylactic oophorectomy

2. clinical breast exam and mammography every 6 to 12 months from age 25 to 35

3. with BRCA1 mutation pelvic exam every 6 to 12 months

VIII. Counseling women about inherited breast cancer risk

1) assess a woman's preconceived ideas about cancer etiology
2) discuss her risk perception
3) construct detailed pedigree
4) assess life time risk of developing breast cancer
5) help guide families toward appropriate surveillance
6) identify families eligible for genetic testing
7) Institute referrals for individuals who could benefit from psychological counseling

![Breast Cancer Incidence](image)

**Breast Cancer Incidence according to Age**

- BRCA1 mutation carrier have very high possibility to develop breast cancer

*Surveillance recommendation for high risk woman*

- by age 20: under the care of a physician
- by age 25: baseline mammography
  - annual mammography till age 35 biannually thereafter
- HBOC syndrome: transvaginal ovarian US, Doppler color bloodflow imagery, CA-125 assay from age 30 and annually

*Screening program for family history woman*

- mammogram and clinical breast exam at age 35
- mammogram every year after age 40 and CBE every 4-6 months

**IX. Present condition in Korea**

1) 1993 - Korean hereditary tumor registry lead the study of BRCA1, BRCA2 mutation and national HBC family registration
2) 1994 - GS dept. of SNUH reported 3 families
  - 1 family among them - convinced of Li-Fraumeni syndrome later
3) 1995 - BRCA1 nonsense mutation was first reported in the suspected hereditary breast-ovarian cancer family
4) 1997 - frameshift mutation was reported in the suspected hereditary breast cancer patient
5) 1998 - BRCA2 frameshift mutation found at the exon 2 of SNU-B4 patient
6) FBC - 18 patients (2.0%)
   HBC - 5 patients (0.5%)
   of 885 patients who were operated due to breast cancer in SNUH.

Pedigree of Bilateral breast cancer family (KGH-CB1)

: First reported BRCA 1 mutation in Korea
  Nonsense mutation of exon 11, codon 1815
  (Korean Hereditary Tumor Registry)

X. Conclusion

1. Significance of HBC
   HBC occupies small portion less than 5% of whole breast cancer even in western contries and the significance is not yet established.
   But, the significance of HBC in breast cancer management has been increased because it is possible to prevent breast cancer development by gene control if the genetic tendency of breast cancer will be confirmed.

2. Family monitoring
   It is very important to monitor the pedigree of hereditary breast cancer prone family thoroughly and to research the breast cancer related gene for future developed management and treatment of breast cancer.
3. Ethical aspect

It must be considered of the speciality and ethical field of HBC when one study genetic factor and pedigree investigation of HBC prone family, and be careful to protect that family and patient from general society.

4. Psychological aspect

Psychological intervention may be helpful for high risk woman and encourage them to adhere to scheduled surveillance.

XI. References