The Reality in the Follow-up of Breast Cancer Survivors

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Introduction

Key Studies & Guidelines

Current State

Future Direction

Introduction

Key Studies &

Guidelines

Current State

Future Direction

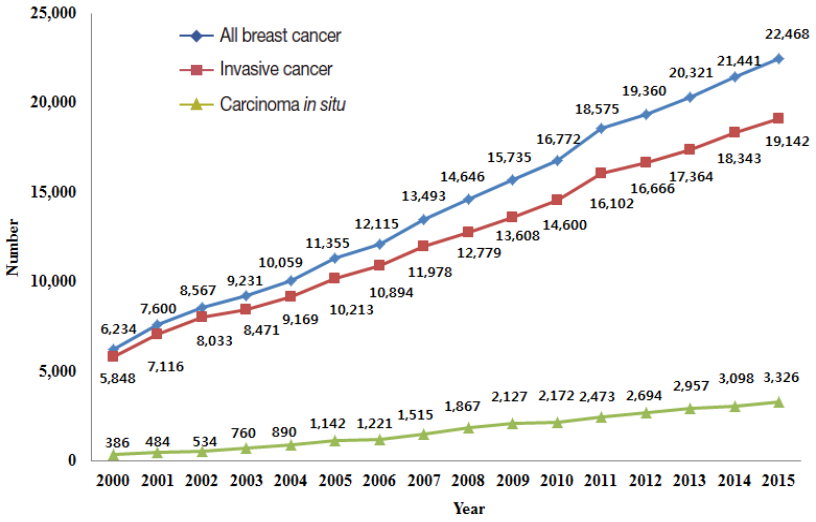
Breast Cancer Survivors

J Breast Cancer 2018 March; 21(1): 1-12 *https://doi.org/10.4048/jbc.2018.21.1.1*

Basic Findings Regarding Breast Cancer in Korea in 2015: Data from a Breast Cancer Registry

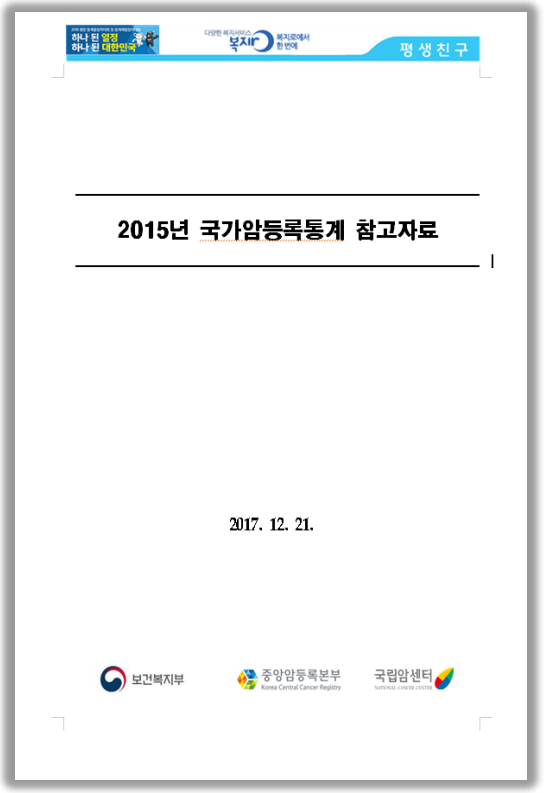
Sang Yull Kang, Yoo Seok Kim[1], Zisun Kim[2], Hyun-Yul Kim[3], Se Kyung Lee[4], Kyu-Won Jung[5], Hyun Jo Youn, Korean Breast Cancer Society

Incidence

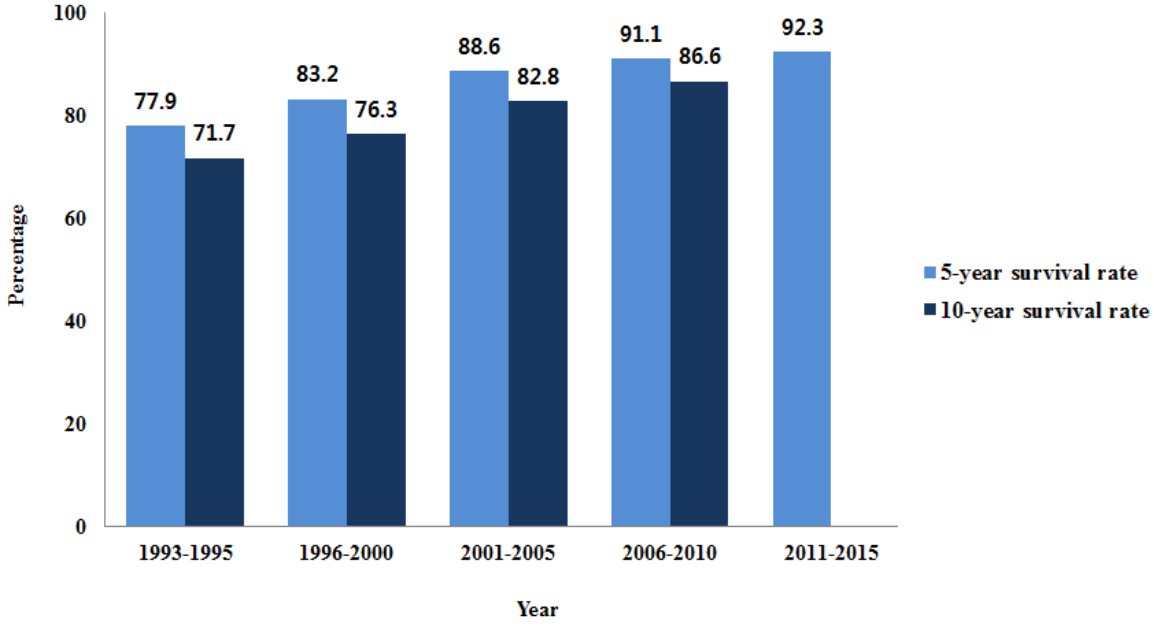


Stage

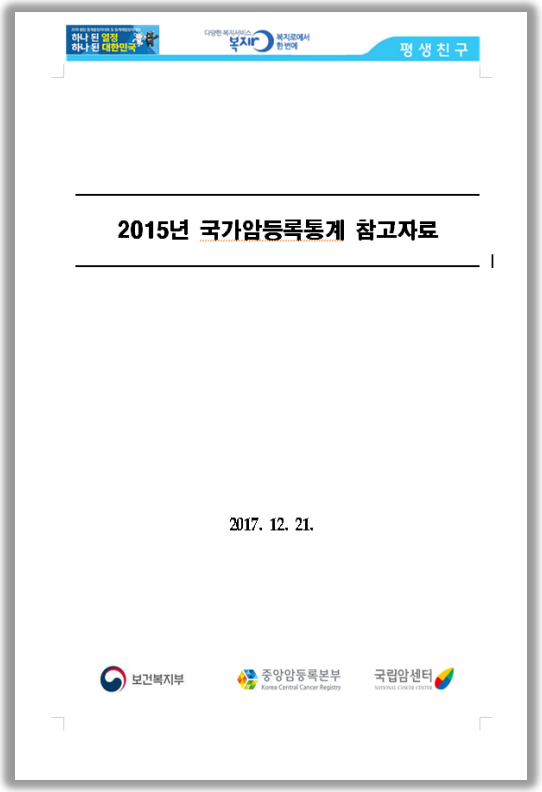
Breast Cancer Survivors



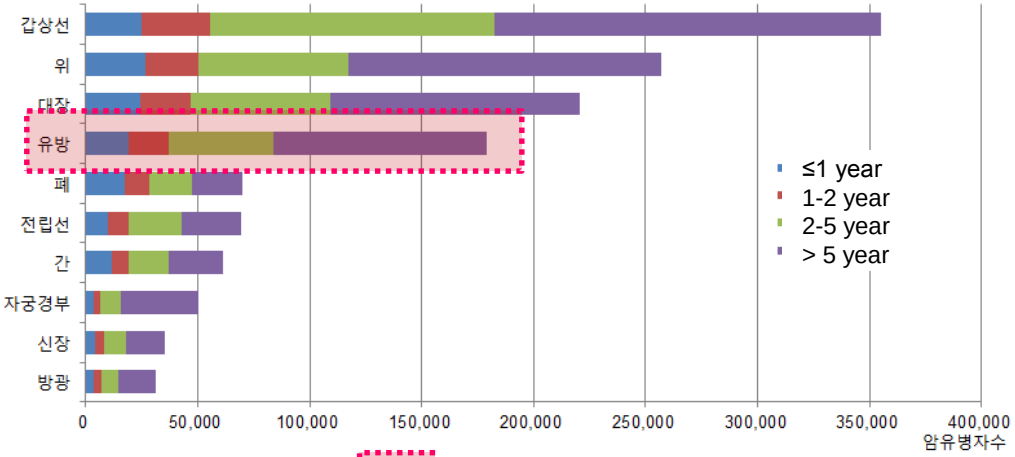
Survival rate



Breast Cancer Survivors



Number of cancer survivors in Korea



진단 후 경과 기간	갑상선	위	대장	유방	폐	전립선	간	자궁경부	신장	방광	모든 암
1년 이하	24,903	26,423	24,400	19,000	17,387	9,945	11,303	3,419	4,259	3,687	187,370
1년 초과-2년 이하	30,775	23,858	22,274	17,824	10,838	9,132	7,993	3,107	3,858	3,228	165,051
2년 초과-5년 이하	126,900	66,852	62,715	46,659	19,417	23,472	17,626	8,845	9,927	7,581	462,639
5년 초과	172,479	139,862	111,264	95,598	22,289	26,889	24,368	35,106	17,289	16,911	796,427
합계	355,057	256,995	220,653	179,081	69,931	69,438	61,290	50,477	35,333	31,407	1,611,487

OPTIMAL

Purpose of follow-up

Recognition of recurrence or new primary cancer

Assess for complications of therapy

Adherence to recommended therapy and screening

Psychosocial and decision-making support

Ruddy KJ, et al. The Breast 2009;p1405

Follow-up of Breast Cancer Survivors

Which test?

How often ?

How long ?

Recurrence

Examinations of follow-up

History & Physical examination

Mammography, Breast US

Breast MRI

Chest PA / CT, Abdominal US / CT

Bone scan

PET-CT

Laboratory test

Optimal Follow-up Modalities, Frequency and Duration for Breast Cancer Survivors

Introduction

Key Studies & Guidelines

Current State

Future Direction

Key Studies about follow-up

Impact of Follow-up Testing on Survival and Health-Related Quality of Life in Breast Cancer Patients

A Multicenter Randomized Controlled Trial **GIVIO trial**

1,320 women in 26 hospitals

Intensive F/U (n=655)

- **P/Ex, blood test**
  - 3 months for 2 yrs
  - 6 months for next 3 yrs
- **Chest PA**
  - 6 months for 2 yrs
  - then annually
- **Bone scan, LGP sono, MMG**
  - annually

Control (n=665)

- **P/Ex, blood test**
  - 3 months for 2 yrs
  - 6 months for next 3 yrs
- **MMG**
  - annually

No difference in OS, DFS, and health related QoL

The GIVIO investigators. JAMA 1994;271:1587-92

Key Studies about follow-up

Intensive Diagnostic Follow-up After Treatment of Primary Breast Cancer
A Randomized Trial

1,243 women in 12 hospitals

Intensive F/U (n=622)

- **P/Ex**
  3 months for 2 yrs
  6 months for next 3 yrs
- **Chest PA, Bone scan**
  every 6 months
- **MMG**
  annually

Control (n=621)

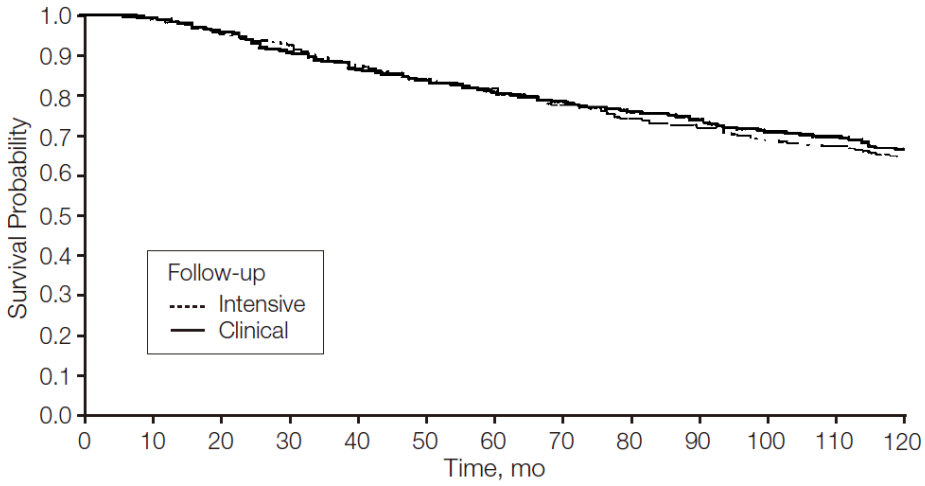
- **P/Ex**
  3 months for 2 yrs
  6 months for next 3 yrs
- **MMG**
  annually

No difference in 5 year overall mortality

Rosselli Del Turco M, et al. JAMA 1994;271:1593-7

Key Studies about follow-up

Intensive vs Clinical Follow-up After Treatment of Primary Breast Cancer: 10-Year Update of a Randomized Trial



No difference in 10 year overall survival

→ Clinical F/U could safely be recommended

Palli D, et al. JAMA 1999;281:1586

Key Studies about follow-up

Cochrane Library

Follow-up strategies for women treated for early breast cancer (Review)

5 RCTs involving 4,023 women

Regular P/Ex and yearly MMG are

as effective as more intensive approaches in terms of

timelines of recurrence detection, OS and QoL

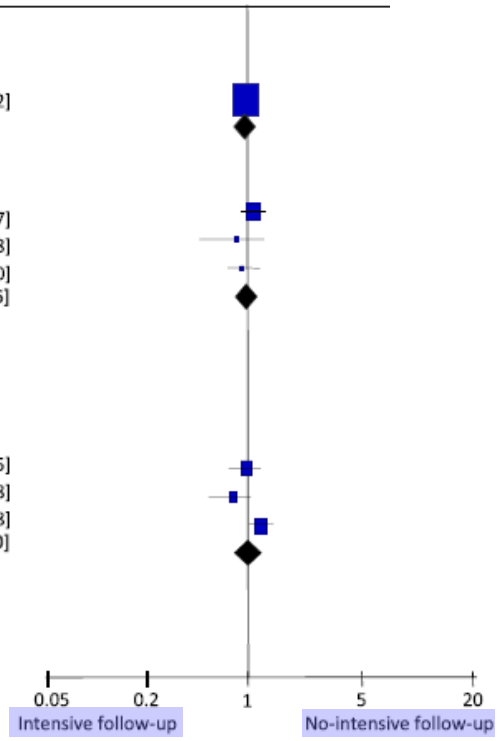
Cochrane Database of Systemic Review 2016

Key Studies about follow-up

Intensive follow-up for women with breast cancer: review of clinical, economic and patient's preference domains through evidence to decision framework

6 RCTs involving 3,534 women

Study	Intensive follow-up Events	Total	No intensive follow-up Events	Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
10-year mortality due to breast cancer						
Rosselli del Turco 1994	222	622	212	621	100.0	1.05 [0.90, 1.22]
Test for overall effect: Z = 0.57 (P = 0.57)						
5-year mortality due to breast cancer						
GIVIO 1994	132	655	122	665	46.2	1.10 [0.88, 1.37]
Kokko 2003	29	243	34	229	10.6	0.80 [0.51, 1.28]
Rosselli del Turco 1994	116	622	121	621	43.1	0.96 [0.76, 1.20]
Subtotal (95% CI)		**1520**		**1515**	**100.0**	**1.00 [0.86, 1.16]**
Total events	277		277			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.69$, df = 2 (P = 0.43); $I^2 = 0\%$						
Test for overall effect: Z = 0.02 (P = 0.99)						
5-year recurrence of breast cancer						
GIVIO 1994	182	655	176	665	37.7	1.05 [0.88, 1.25]
Kokko 2003	59	243	64	229	22.9	0.87 [0.64, 1.18]
Rosselli del Turco 1994	219	622	174	621	39.4	1.26 [1.07, 1.48]
Subtotal (95% CI)		**1520**		**1515**	**100.0**	**1.08 [0.89, 1.30]**
Total events	460		414			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.04$, df = 2 (P = 0.08); $I^2 = 60\%$						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: $Chi^2 = 13.55$, df = 5 (P = 0.02), $I^2 = 63.1\%$						



Lafranconi A, et al. Health and Quality of Life Outcomes 2017;15:206

Key Studies about follow-up

Ann Oncol. 1995 Oct;6(8):769-76.

Routine tests during follow-up of patients after primary treatment for operable breast cancer. International (Ludwig) Breast Cancer Study Group (IBCSG)

J Clin Oncol. 2013 Mar 1;31(7):961-5. doi: 10.1200/JCO.2012.45.9859. Epub 2012 Nov 5.

Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update.

Breast Cancer Res Treat. 1984;4(4):303-7.

The efficacy of bone scanning in the follow-up of patients with operable breast cancer.

Breast Cancer Res Treat. 2003 Sep;81(1):33-9.

Role of chest X-ray in diagnosis of the first breast cancer relapse: a randomized trial.

Br J Cancer. 2007 Dec 17;97(12):1632-41. Epub 2007 Nov 13.

Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature.

No evidence supporting the routine follow-up for detecting of

relapse in asymptomatic breast

Potential Adverse Effects of intensive follow-up

Radiation risks

False-positive results

Cost

Quality of life : distress, anxiety

etc...

Key Studies about follow-up

Follow-up cost of breast cancer patients with localized disease after primary treatment: a randomized trial

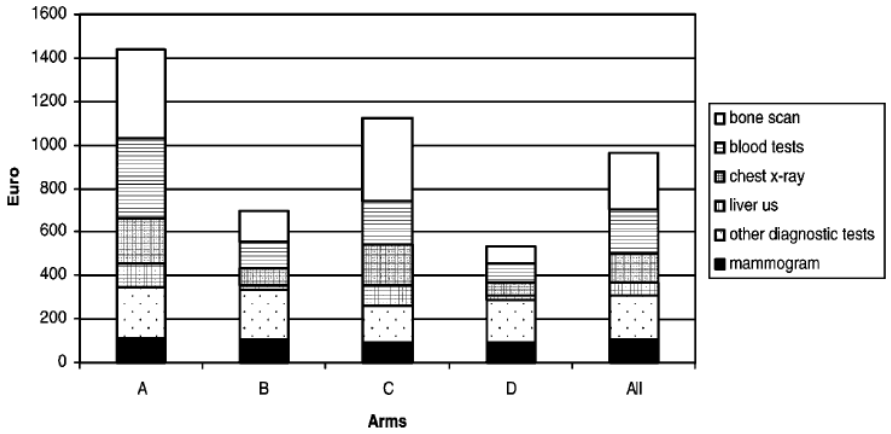
472 breast cancer patients

3 months

Arm A (frequent routine) | Arm B (frequent no routine)

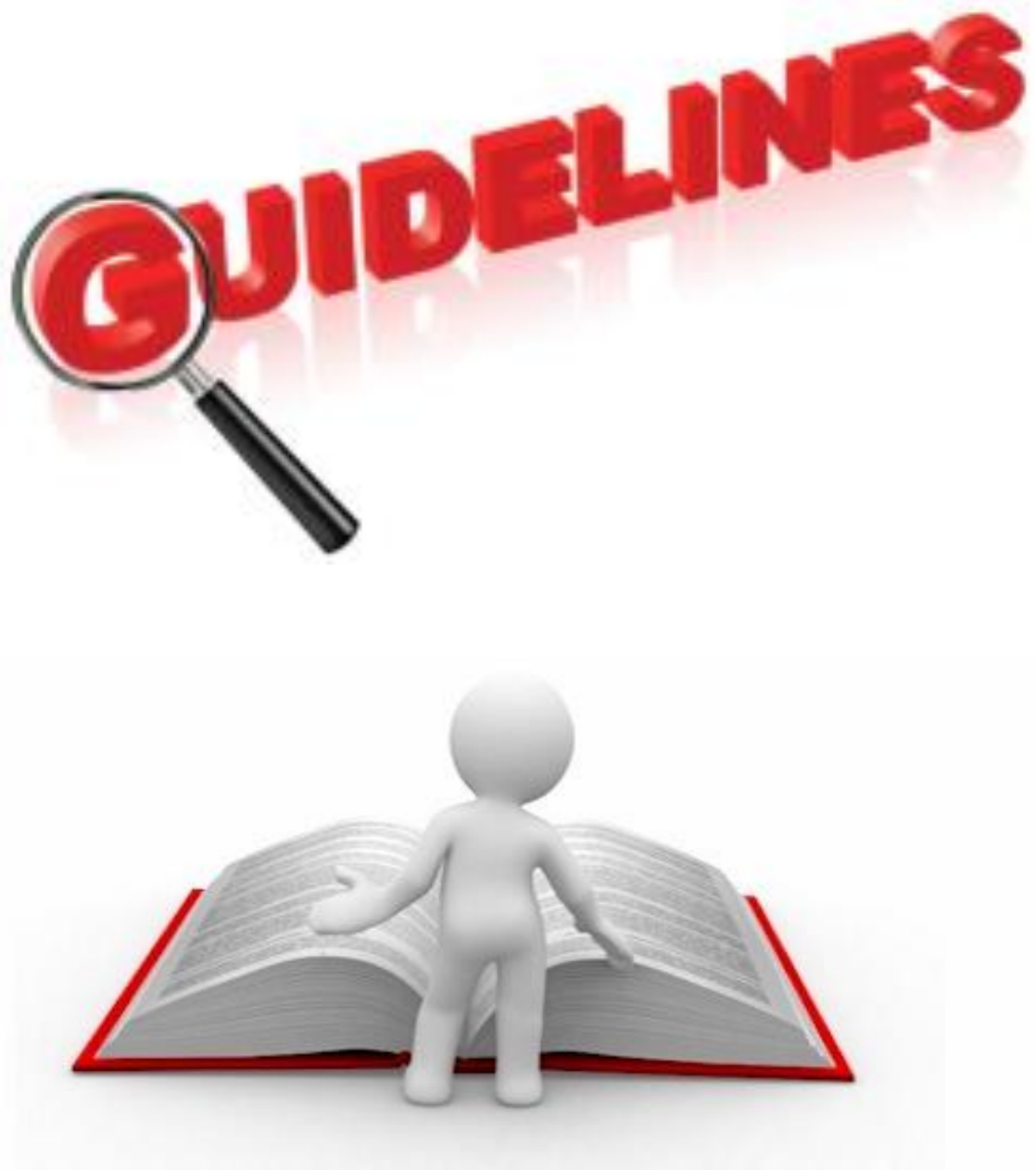
6 months

Arm C (infreq. routine) | Arm D (infreq. no routine)



No difference in DFS, OS but increase the cost

Kokko R, et al. BCRT 2005;93:255-60


GUIDELINES

Guideline of follow-up

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

Recommended	Not Recommended
History and physical examination every 3–6 months for 3 years, every 6–12 months for years 4–5, then annually	Routine blood tests such as complete blood counts and liver function tests
Mammograms every 6–12 months starting 1 year after initial image that diagnosed cancer but not earlier than 6 months after radiation	Other imaging studies including FDG-positron emission tomography and breast magnetic resonance imaging, except in rare cases
Monthly self-breast examination	Tumor markers
Annual gynecologic follow-up	
Patient education regarding symptoms of recurrence	
Referral to genetic counselor if at high risk for familial breast cancer	

Runowicz CD, et al. Cancer J Clin 2016;66:43-73

Guideline of follow-up

Non-invasive

- Interval history and physical exam every 6–12 mo for 5 y, then annually
- Mammogram every 12 mo (and 6–12 mo postradiation therapy if breast conserved [category 2B])
- If treated with endocrine therapy, monitor per NCCN Guidelines for Breast Cancer Risk Reduction

Invasive

- History and physical exam 1–4 times per year as clinically appropriate for 5 y, then annually
- Periodic screening for changes in family history and referral to genetic counseling as indicated, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
- Educate, monitor, and refer for lymphedema management
- Mammography every 12 mo[oo]
- Routine imaging of reconstructed breast is not indicated
- In the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening
- Women on tamoxifen: annual gynecologic assessment every 12 mo if uterus present
- Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter[pp]
- Assess and encourage adherence to adjuvant endocrine therapy
- Evidence suggests that active lifestyle, healthy diet, limited alcohol intake, and achieving and maintaining an ideal body weight (20–25 BMI) may lead to optimal breast cancer outcomes

Korean Breast Cancer Society "함께하는 도전, 세계를 움직이는 한국유방암학회 With you, the World Leading KBCS"

Guideline of follow-up

제7차 유방암 진료권고안

Non-invasive

- 6개월 또는 1년 간격으로 양측 유방 진찰과 유방 촬영술을 시행
- 필요에 따라서 유방 초음파와 유방확대 촬영술 시행

Invasive

문진,진찰(3년동안 3~6개월, 이후 2년동안 6~12개월, 이후 1년마다 시행)
유방촬영술(6개월~1년간격)
유방초음파
부인과검진(1년간격)
Tamoxifen을 복용시
골밀도검사(1년간격)
AI투여환자 bisphosphonate 또는 denosumab 고려
그 외 필요시
- 유방확대촬영술
- 간기능검사
- 흉부단순촬영/CT
- 복부초음파/CT
- 뼈스캔
- FDG PET
- 종양표지자 검사 등

Guidelines of follow-up

	ASCO (2016)	NCCN (2018)	KBCS (2017)
History and Physical examination	Every 3-6 mon for 3 y, then every 6-12 mon 2 y, then annually	Every 3-12 mon for 5 y, then annually	Every 3-6 mon for 3 y, then every 6-12 mon 2 y, then annually
Mammography	Every 12 months	Every 12 months	Every 6-12 months
Breast US	No comment	No comment	If necessary
Gynecologic examination	Annual	Annually for on tamoxifen	Annually for women on tamoxifen
Bone health assessment	Postmenopausal, taking an AI	On an AI, ovarian failure secondary treatment	Annually for women on AI

Guidelines of follow-up

Chest PA / CT

Abdominal US / CT

Bone scan

PET-CT

Laboratory test

Not Recommend !

Introduction

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Guidelines

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Current State of follow-up

Adherence to Surveillance Care Guidelines after Breast and Colorectal Cancer Treatment with Curative Intent

Cohorts of 6,205 breast cancer patients

64.7% : received non-recommended metastatic testing

associated factors

- white race, comorbidities, younger age

Salloum RG, et al. Cancer 2012;118:5644-51

Current State of follow-up

Use of imaging and biomarker tests for post-treatment care of early stage breast cancer survivors

258 breast cancer patients

55% : received at least 1 non-recommended imaging test

77% : received at least 1 non-recommended biomarker test

Hahn EE, et al. Cancer 2013;119:4316-24

Current State of follow-up

Breast Cancer Surveillance Guidelines

By Thomas J. Smith, MD, FACP, FASCO
Johns Hopkins Medical Institutions, Baltimore, MD

	Recommendation	Actual Practice[1]
Do	History and physical examination every 3 to 6 months for 3 years, then every 6 to 12 months for the next 2 years, then annually	3.4 in year 1, falling to two in year 5
	Yearly mammogram	1.6 in year 1, falling to 1.3 in year 2
Don't do	Routine blood tests such as CBC, LFT	Two
	Serum tumor markers	0.4, CEA; 0.7, CA 15.3
	Chest x-rays, CTs, bone scans, PET scans in patients without symptoms	0.1 for all with SD of 0.4 to 0.6

30-40% of practices
: routinely measure tumor markers and perform CT or PET

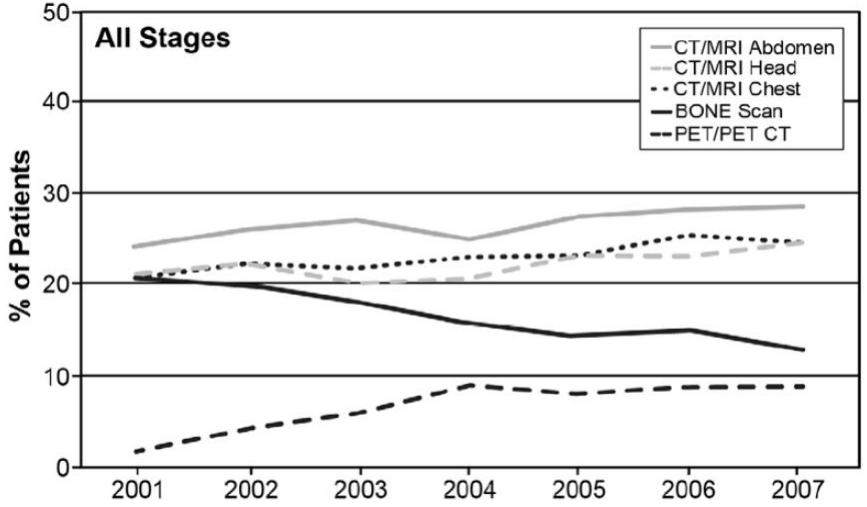
Smith TJ, et al. J Oncol Pract 2013;9:65-7

Current State of follow-up

Quality of Post-Treatment Surveillance of Early Stage Breast Cancer in Texas

8,598 breast cancer patients

Only 55.3% : adherent to current follow-up guidelines



Parmar AD, et al. Surgery 2013;154:214-25

Current State of follow-up

The reality in the follow-up of breast cancer survivors: survey of Korean Breast Cancer Society

Ku Sang Kim*, Zisun Kim[1,*], Eun-Jung Shim[2], Nam Hyoung Kim[3], So-Youn Jung[4], Jisun Kim[5], Guiyun Sohn[5], Jong Won Lee[5], Jihyoung Cho[6], Jung Eun Lee[7], Juhyung Lee[8], Hyun Jo Youn[9], Jihyoun Lee[10], Min Hyuk Lee[10]; Korean Breast Cancer Society

Questionnaire survey by e-mail

129 respondents in KBCS members

Experience of breast cancer tx

Kim KS, et al. ASTR 2015;88:133-9

Current State of follow-up

History & P/Ex

postop 1 year

2-3 years

4-5 years

after 5 years

DCIS: 6-12 months

IDC: 3-12 months

annually

DCIS: 6-12 months

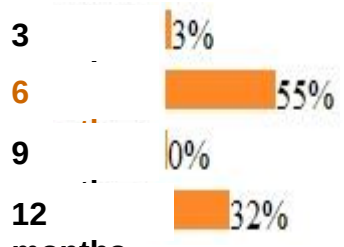
IDC: 3-6months 6-12 months

annually

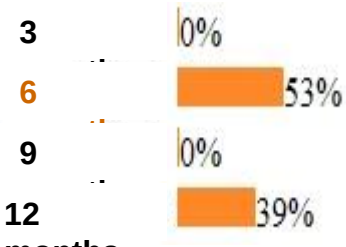
Current State of follow-up

Mammography

postop 1 year

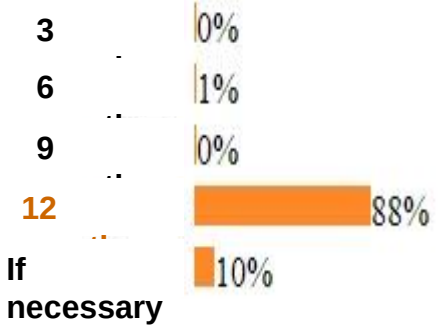


2-3 years



4-5 years

after 5 years



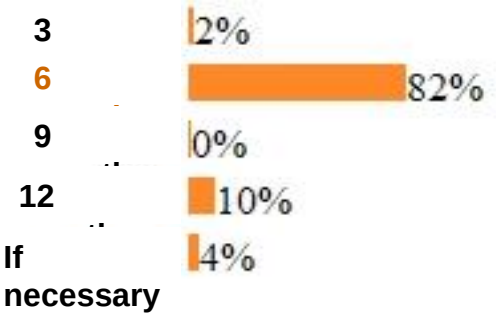
annually

6-12 months

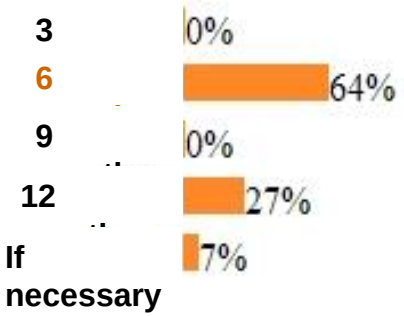
Current State of follow-up

Breast US

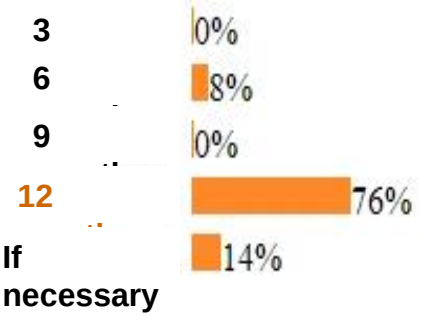
postop 1 year



2-3 years



4-5 years



after 5 years

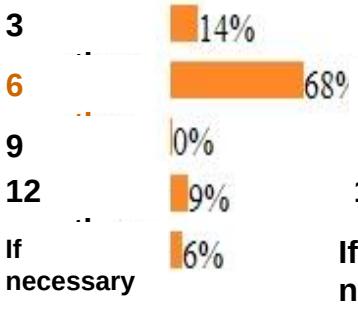
No comment

If necessary

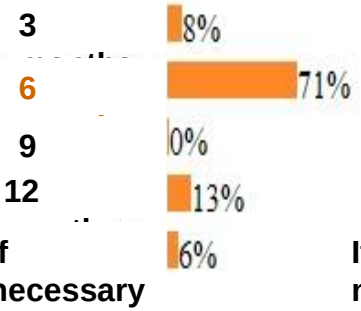
Current State of follow-up

Laboratory test

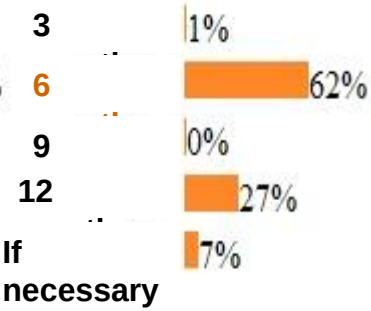
postop 1 year



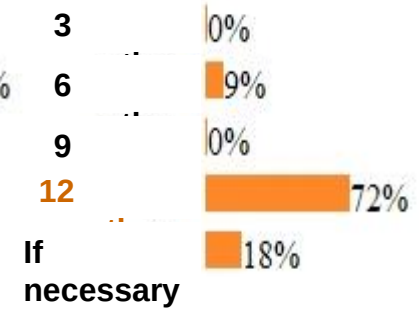
2-3 years

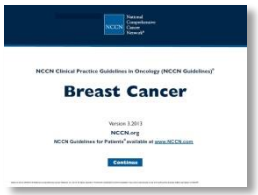


4-5 years



after 5 years



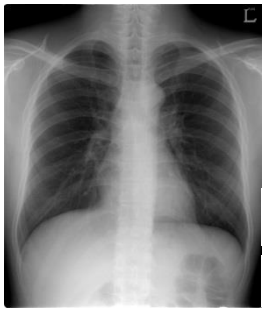


Not recommended

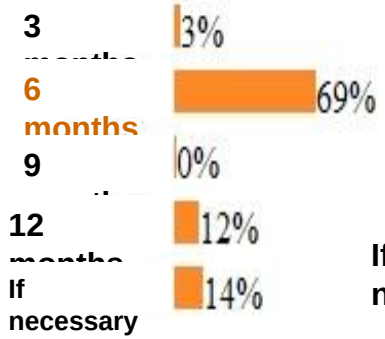
If necessary

Current State of follow-up

Chest X-ray



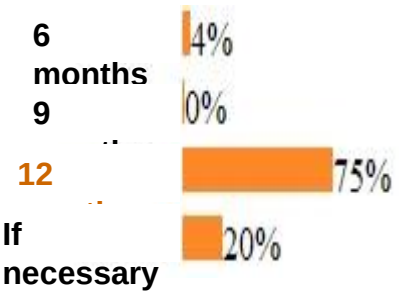
postop 1 year

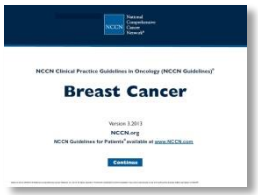


2-3 years

4-5 years

after 5 years



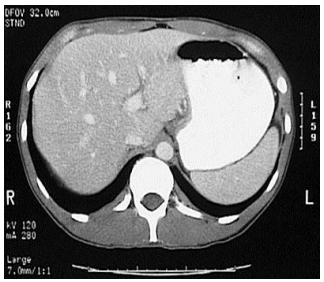


Not recommended

If necessary

Current State of follow-up

Abdominal US/CT



	postop 1 year	2-3 years	4-5 years	after 5 years
6 months	36%	30%	19%	1%
9 months	0%	0%	0%	0%
12 months	37%	44%	51%	37%
If necessary	25%	25%	28%	60%

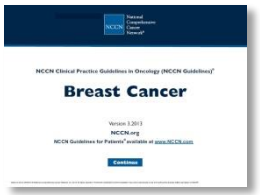
Not recommended

If necessary

Current State of follow-up

Bone scan

	postop 1 year	2-3 years	4-5 years	after 5 years
6 months	31%	27%	19%	3%
9	0%	0%	0%	0%
12	50%	54%	57%	44%
If necessary	17%	18%	23%	52%

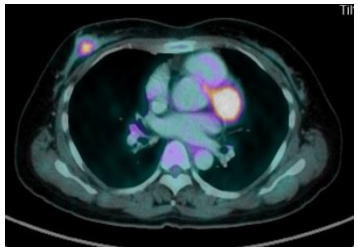


Not recommended

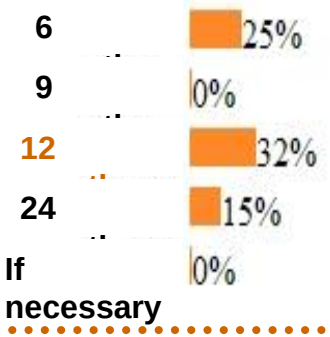
If necessary

Current State of follow-up

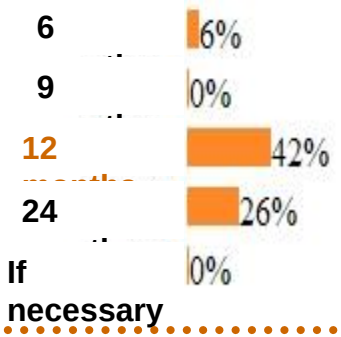
PET-CT



postop 1 year



2-3 years



4-5 years

after 5 years

Not recommended

If necessary

Current State of follow-up

Guidelines are based on the old studies which did not include

recent imaging and treatment modalities

Many breast cancer survivors want to more frequent examinations

because of anxiety for recurrence

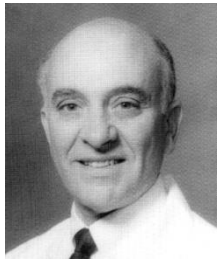
In 1994...

SCIENCE • VOL. 266 • 7 OCTOBER 1994

BRCA1 Mutations in Primary Breast and Ovarian Carcinomas

SCIENCE • VOL. 265 • 30 SEPTEMBER 1994

Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12-13



ANNALS OF SURGERY
Vol. 220, No. 3, 391–401

Lymphatic Mapping and Sentinel Lymphadenectomy for Breast Cancer

Armando E. Giuliano, M.D., Daniel M. Kirgan, M.D., J. Michael Guenther, M.D., and Donald L. Morton, M.D.

Key Studies about follow-up

Impact of Follow-up Testing on Survival and Health-Related Quality of Life in Breast Cancer Patients

A Multicenter Randomized Controlled Trial **GIVIO trial**

1,320 women in 26 hospitals

Intensive F/U (n=655)

- **P/Ex, blood test**
  - 3 months for 2 yrs
  - 6 months for next 3 yrs
- **Chest PA**
  - 6 months for 2 yrs
  - then annually
- **Bone scan, LGP sono, MMG**
  - annually

Control (n=665)

- **P/Ex, blood test**
  - 3 months for 2 yrs
  - 6 months for next 3 yrs
- **MMG**
  - annually

No difference in OS, DFS, and health related QoL

The GIVIO investigators. JAMA 1994;271:1587-92

Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 12, No 5 **May 1994**

EDITORIAL

It Is Now the Age to Define the Appropriate Follow-Up of Primary Breast Cancer Patients

A RECENT SURVEY of American Society of Clinical Oncology (ASCO) medical oncologists revealed that 55% to 65% of them use age as a factor when estimating breast cancer prognosis.[1] The data reported by Nixon et al[2] in this issue of the *Journal of Clinical Oncology* should increase this percentage. This work solidly confirms results from several previous trials that showed that primary breast cancer patients younger than 35 years have a poorer outcome than do older women. The causes for the poor prognosis in young women have not been completely elucidated to date, leaving young age as an independent prognostic factor.

(oftentimes at 3- to 4-month intervals for several years) to look for evidence of breast cancer recurrence. Possible benefits associated with close follow-up and frequent testing might be the early detection, and thus early treatment, of recurrent breast cancer. Close follow-up might also serve a psychosocial function.

Nonetheless, there are clearly limitations associated with close follow-up of such patients. An obvious limitation is the cost in terms of patient and physician time and other monetary costs. Follow-up visits can provide marked anxiety for many patients. None of the follow-up testing procedures has optimal sensitivity nor specific-

Optimal Follow-up Modalities, Frequency and Duration for Breast Cancer Survivors

There are **no randomized trials** in the literature

with sufficient power to recommend an acceptable follow-up

Introduction

Key Studies &

Guidelines

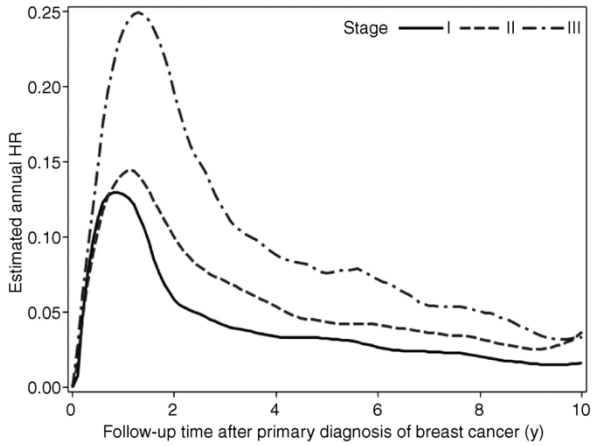
Current State

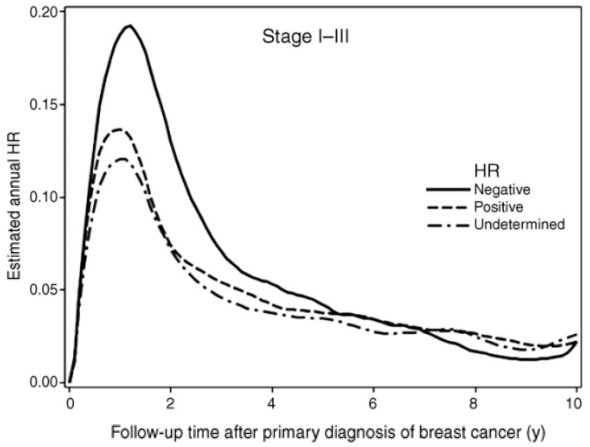
Future Direction

Recurrence of Breast Cancer

Hazard of Recurrence among Women after Primary Breast Cancer Treatment—A 10-Year Follow-up Using Data from SEER-Medicare

20,027 breast cancer patients : 36.8% recurrence





81.9% of recurrence : $\leq$ 5 years after primary treatment

Cheng L, et al. Cancer Epidemiol Biomarkers Prev 2012;21:800-9

What's the most common event in BC survivors ?

① new primary breast cancer

② loco-regional recurrence

③ distant metastasis

④ local recurrence + distant metastasis

Recurrence of Breast Cancer

Distant metastasis : multiple > bone > lung > liver

HR positive BC : **bone** metastasis

HER2 positive BC : **visceral** & **brain** metastasis

TNBC : **visceral** metastasis

Future Direction of follow-up

Imaging Surveillance After Primary Breast Cancer Treatment

Imaging characteristics according to the subtype

MMG: mass in **Luminal type**

US: mass in **HER2-negative type**
benign features in **TNBC**

MRI : non-mass enhancement in **Luminal A type**

Lam DL, et al. AJR 2017;208:676-86

Future Direction of follow-up

Breast Care

Is Symptom-Oriented Follow-Up Still Up to Date?

Innovative therapies for patients with mBC have been introduced

and novel therapies in molecular subtypes could significantly

improve the survival in early detected metastasis

In the future,

more individualized follow-up programs are conceivable

Mundhenke C, et al. Breast Care 2013;8:336-40

Future Direction of follow-up

Breast Cancer ''Tailored Follow-up'' in Italian Oncology Units: A Web-Based Survey

125 out of 233 (53.6%) referents participated

90.4% : not apply the minimal F/U guidelines

80.8% : tailored F/U performed

Urgent need of RCT able to determine the effectiveness of risk-based F/U modalities

Natoli C, et al. PLoS one 2014;9:e94063

Future Direction of follow-up

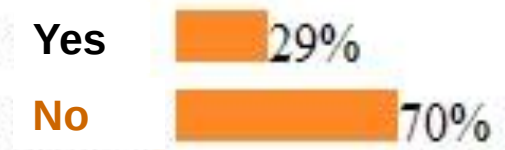
The reality in the follow-up of breast cancer survivors: survey of Korean Breast Cancer Society

Ku Sang Kim*, Zisun Kim[1,*], Eun-Jung Shim[2], Nam Hyoung Kim[3], So-Youn Jung[4], Jisun Kim[5], Guiyun Sohn[5], Jong Won Lee[5], Jihyoung Cho[6], Jung Eun Lee[7], Juhyung Lee[8], Hyun Jo Youn[9], Jihyoun Lee[10], Min Hyuk Lee[10]; Korean Breast Cancer Society

What is the most important considerable factor in follow-up?

Stage – Symptom – Subtype – Age – Operative method

Do you perform identical follow-up modalities in DCIS a



Future Direction of follow-up

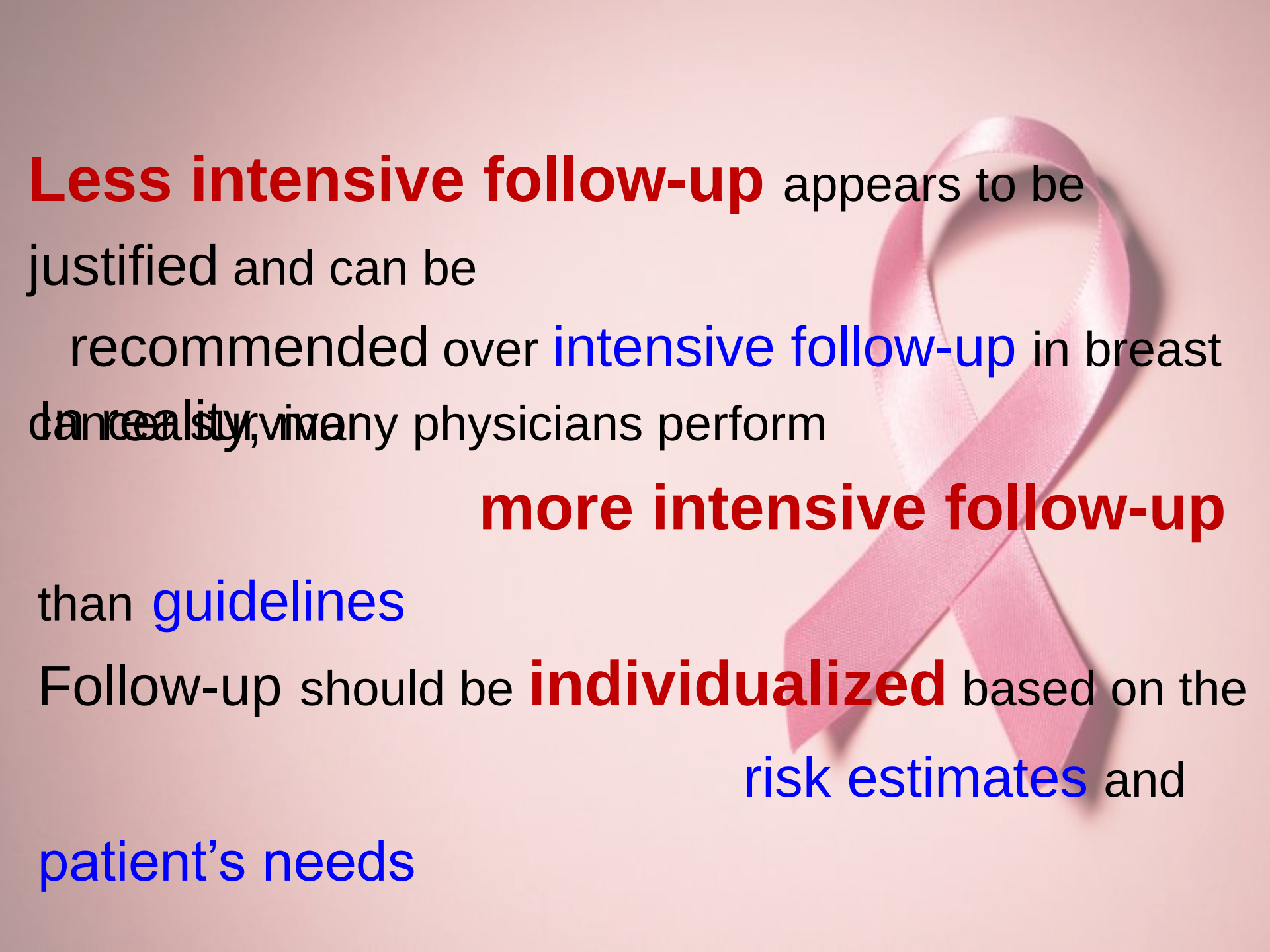
Randomized controlled trial for development of optimal follow-up modalities in Korean breast cancer survivors is urgently needed

Summary

Less intensive follow-up appears to be justified and can be recommended over intensive follow-up in breast cancer survivors

In reality, many physicians perform **more intensive follow-up** than guidelines

Follow-up should be **individualized** based on the risk estimates and patient's needs




Thank you for your attention!