



AIC
Kijabe
Hospital
Health Care to God's Glory

Surgical Management of Locally Advanced Breast Cancer in a Resource-poor Setting

Mr Peter Bird FRACS, AIC Kijabe Hospital





Locally Advanced Breast Cancer

NCCN Guidelines

- Any tumour Stage III

Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IIB	T2	N1	M0
	T3	N0	M0

Locally Advanced Breast Cancer

EUSOMA website – European Society of Breast Cancer Specialists

- Tumour >5 cm measured clinically, by ultrasound or mammography
- Proven skin involvement (not dermis alone)
- Chest wall muscle or chest wall skeletal involvement
- Fixed axillary lymph nodes
- Tumour-positive apical (infraclavicular) node



Locally Advanced Breast Cancer

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma in situ
- Tis (DCIS)** Ductal carcinoma in situ
- Tis (LCIS)** Lobular carcinoma in situ
- Tis (Paget's)** Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
- T1** Tumor ≤ 20 mm in greatest dimension
 - T1mi** Tumor ≤ 1 mm in greatest dimension
 - T1a** Tumor > 1 mm but ≤ 5 mm in greatest dimension
 - T1b** Tumor > 5 mm but ≤ 10 mm in greatest dimension
 - T1c** Tumor > 10 mm but ≤ 20 mm in greatest dimension
- T2** Tumor > 20 mm but ≤ 50 mm in greatest dimension
- T3** Tumor > 50 mm in greatest dimension
- T4** Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
 - Note: Invasion of the dermis alone does not qualify as T4
 - T4a** Extension to the chest wall, not including only pectoralis muscle adherence/invasion
 - T4b** Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
 - T4c** Both T4a and T4b
 - T4d** Inflammatory carcinoma (see "Rules for Classification")





Locally Advanced Breast Cancer

Regional Lymph Nodes (N)

CLINICAL

- NX** Regional lymph nodes cannot be assessed (for example, previously removed)
- N0** No regional lymph node metastases
- N1** Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2** Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
- N2a** Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
- N2b** Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
- N3** Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
- N3a** Metastases in ipsilateral infraclavicular lymph node(s)
- N3b** Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- N3c** Metastases in ipsilateral supraclavicular lymph node(s)

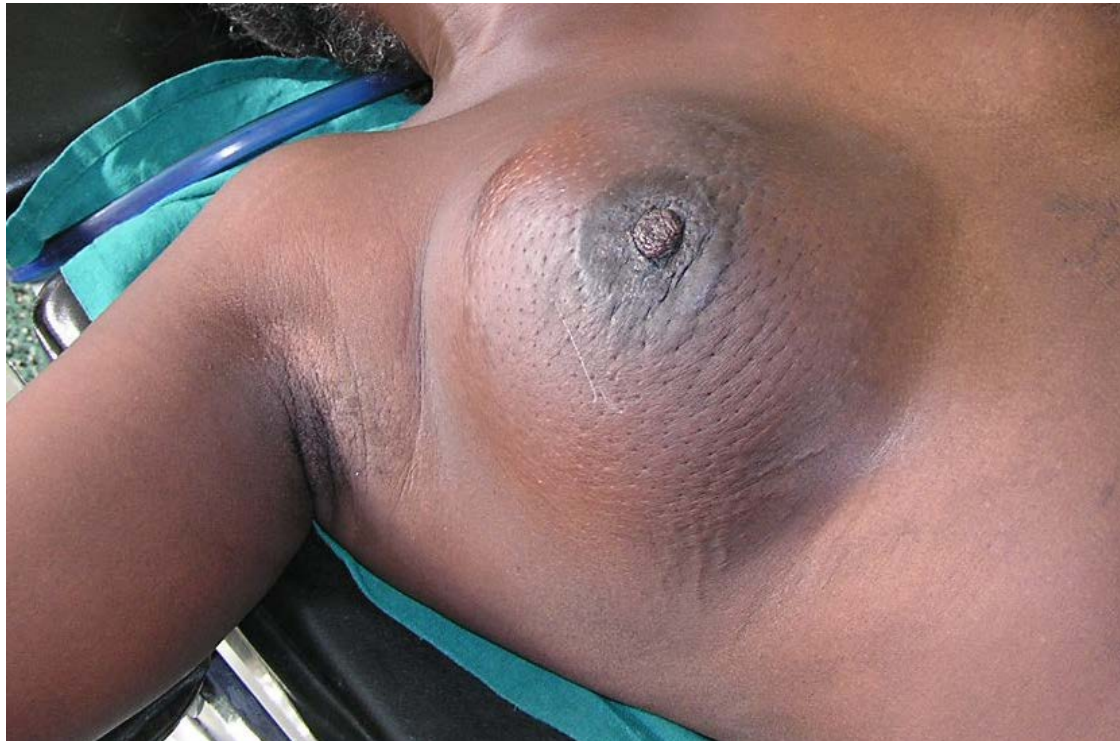




Locally Advanced Breast Cancer

- Some historical French terms...

Peau d'orange





Cancer-en-cuirasse

First described by French surgeon
Alfred Velpeau in 1838





Kijabe Breast Cancer Study

2001-2007

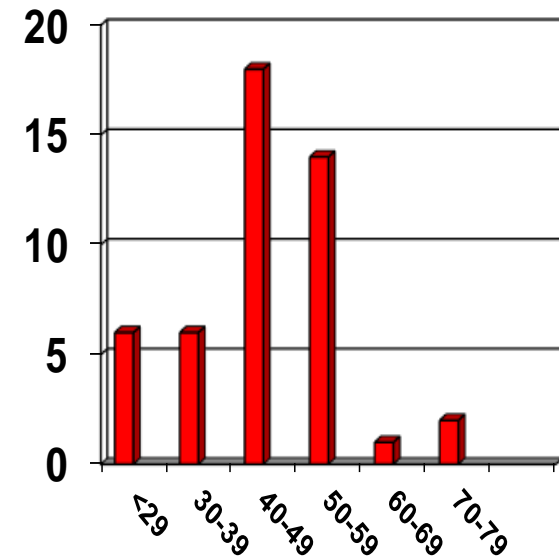
- 125 female, 4 male between 2001 and 2007
- Excluded non-Africans, non-IDC tumours
- Median age 47 (range 26-76)
- Mean parity 4.1
- Mean size of tumour (clinical) 6.8cm
- Average length of history – 12 months
- **LABC 59%**

Bird PA, Hill AG, Houssami N. Poor Hormone Receptor Expression in East African Breast Cancer: Evidence of a Biologically Different Disease? *Ann Surg Oncol.*, March 2008

Kijabe Breast Cancer Cases

2011-12

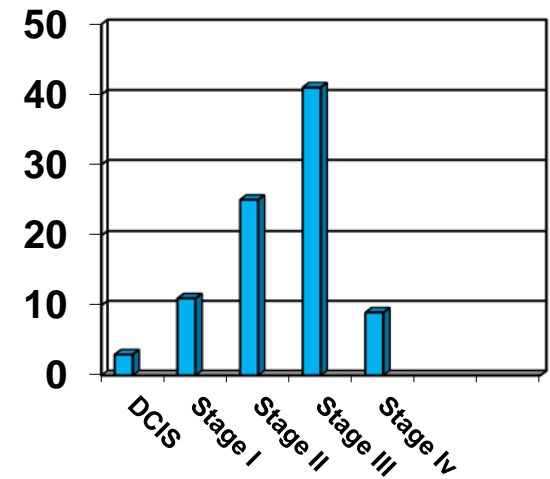
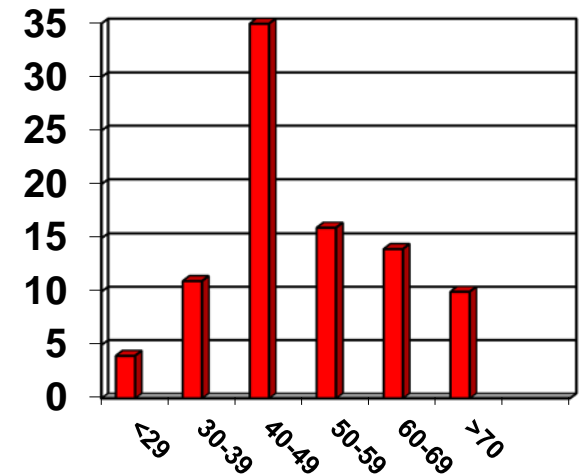
- 59 cases Jan 11 to Feb 12
- 48 IDC (NOS); 11 special types
- Median age 45
- 62.5% under 50yo
- **LABC 48%**



Kijabe Breast Cancer Cases

2015

- 92 cases Jan to Dec
- 83 IDC (NOS); 6 special types
- 3 DCIS
- Median age 50.9 (range 22-92)
- 54.9% under 50yo
- **LABC 51%**



Workup & Staging LABC

- History and examination
- CBC, LFTs
- Mammography +/- targeted US
- Liver US, CXR, CT scans (chest, abdo, pelvis, brain)
- Pathology (CBx), including ER/PR/HER2
- Breast MRI, PET scan, bone scan



Workup & Staging LABC

- History and examination
- CBC, LFTs
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Recent IHC Data from SubSaharan Africa

Country	Year Published	Pts	ER/PR % +ve	HER2 % +ve	TNBC %	Journal
Nigeria	2005	178	25/28	25	47	West Afr J Med
Kenya	2006	158	37/49	13	28	Ann Quant Cytol Histol
Nigeria	2008	192	71/64	6		Breast Cancer Res Treat
Kenya	2008	129	24/34	26	44	Ann Surg Oncol
Kenya	2010	101	46/42	23		Ann Afr Surg
Ghana	2010	75	25/33	4	75	Cancer
Ghana	2012	330	47/13	20	43	Ghana Med J
South Africa	2013	1092	64/52	26	20	Brit Cancer Res

What could account for the highly variable ER/PR/HER2 results?

- Specimen handling
 - Degradation of receptors if poorly fixed
 - incorrect concentration of formalin
 - tumour not cut before being placed in fixative
 - ratio of specimen tissue to formalin ideally 1:10
 - Long warm ischaemia time (>60 min)
- Methodology
 - Auto vs manual IHC
 - Antibody retrieval, antibody type
 - Cut off has changed over the years (Current ASCO/CAP guidelines <1%, *J Clin Oncol* 2010)
 - Double reporting in studies not uniform

Is breast cancer from Sub Saharan Africa truly receptor poor?

Prevalence of ER/PR/HER2 in breast cancer from Kenya

Sayed S, Moloo Z, Wasike R, Bird P *et al. The Breast* 2014

- 301 consecutive IDC cases
- ASCO/CAP Guidelines followed for test accuracy and reporting of results
- Rigorous specimen handling protocols
 - 10% neutral buffered formalin, rapid immersion, large specimens bivalve, times recorded etc
- Automated platforms for IHC determination
- ER/PR reporting by Allred system
 - 1% staining or more deemed positive (ASCO/CAP Guidelines 2010)
- HER2 2+ subjected to FISH analysis
- Double reporting by pathologists

Is breast cancer from Sub Saharan Africa truly receptor poor?

Prevalence of ER/PR/HER2 in breast cancer from Kenya

Sayed S, Moloo Z, Wasike R, Bird P et al. The Breast 2014

RESULTS:

- 301 cases of invasive BC (84% IDC)
- Median age 47.5
- ER positive 73%
- PR positive 65%
- HER2 18.5%
- TNBC 20.2 %

Principles in Breast Cancer Management (1)

Management of the breast cancer patient involves treating two separate entities: the locoregional disease and the systemic disease

Principles in Breast Cancer Management (2)

- In most cases with LABC, systemic treatment (PSTx) is given first:
 - able to downsize tumours for clear surgical margins (sometimes BCS), can measure treatment response and alter if necessary, better prognostication etc.
- PSTx is followed by surgery then RT then HT
- However, survival not affected by sequence of treatment

Principles in Breast Cancer Management (3)

The management of a woman with breast cancer involves a

MULTIDISCIPLINARY TEAM APPROACH

Her (his) treatment needs to be
individualized

Treatment Options for Locally Advanced Breast Cancer

- **SURGERY**
 - Breast conserving (after PSTx), mastectomy +/- chest wall reconstruction, axillary dissection
- **CHEMOTHERAPY**
 - Usually before surgery. Anthracycline-based +/- taxanes
- **HORMONAL THERAPY**
 - SERMs, AIs, LHRH analogues, oophorectomy
- **TARGETED BIOLOGICAL THERAPY**
 - Trastuzumab and other new monoclonal AB therapies
- **RADIOTHERAPY**
 - Teletherapy, brachytherapy

Treatment Options and Costs in Kijabe and Kenya

Mastectomy	USD 600
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(At Kijabe)

Radiotherapy	USD 1200
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(In private facilities. Done at KNH for USD200?)

Chemotherapy	USD 1200
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(Done in Nairobi. Done at KNH for USD200?)

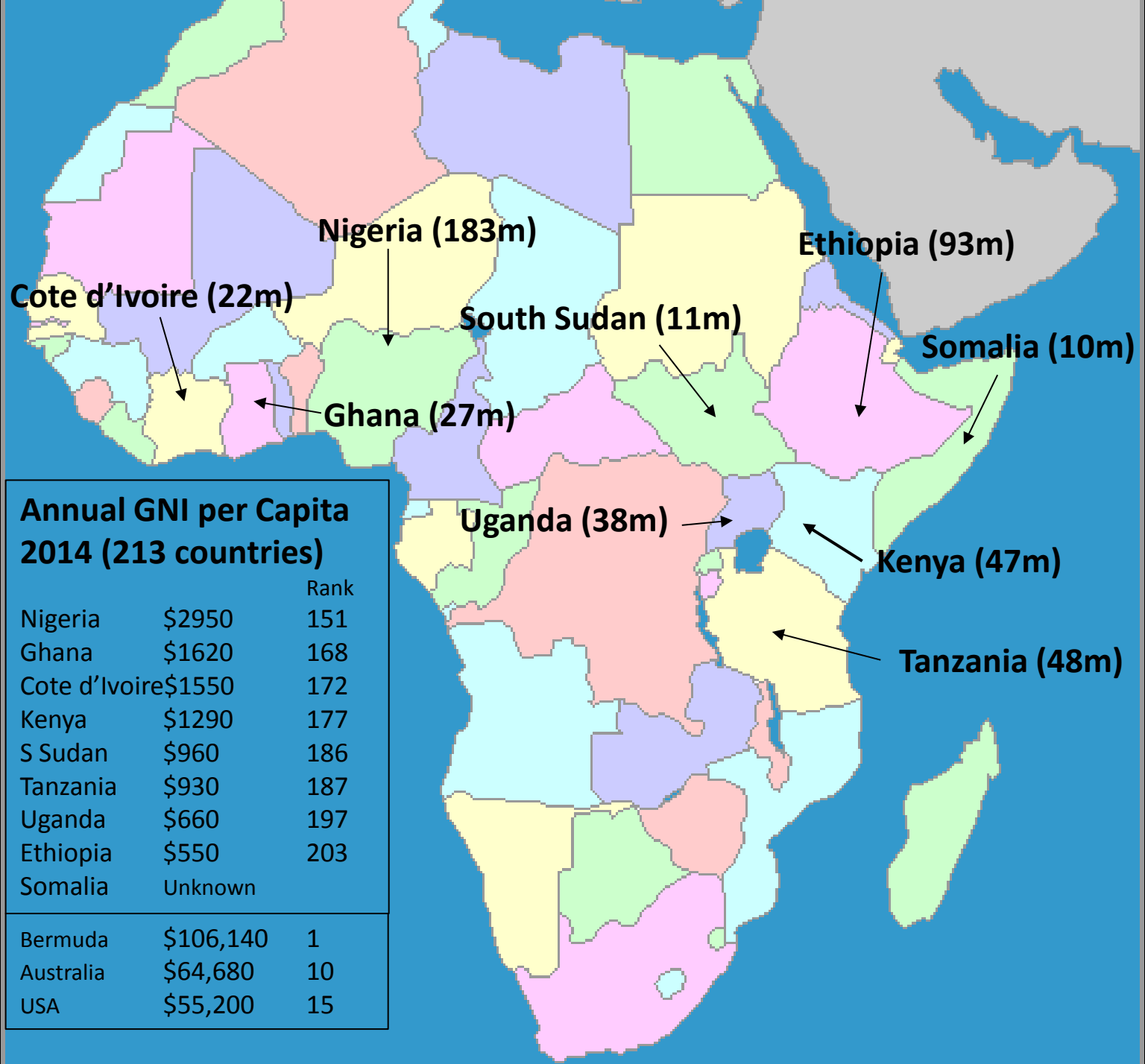
Biological Rx

(Not affordable!)

Hormonal Rx	USD 650
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(5 years of tamoxifen)

TOTAL	USD 3650
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Annual GNI per Capita 2014 (213 countries)		
		Rank
Nigeria	\$2950	151
Ghana	\$1620	168
Cote d'Ivoire	\$1550	172
Kenya	\$1290	177
S Sudan	\$960	186
Tanzania	\$930	187
Uganda	\$660	197
Ethiopia	\$550	203
Somalia	Unknown	

Bermuda	\$106,140	1
Australia	\$64,680	10
USA	\$55,200	15

Management of LABC in Kijabe, Kenya

- Patients of highly variable economic status – determines possibility of pre-op systemic Rx, extent of surgery & adjuvant Rx
- Preop systemic Rx, MRM & adjuvant therapies offered to wealthier patients
(NCCN Optimal Level available in Kenya)
- Poor patients get mastectomy & AD +/- LD flap coverage only *if* the tumour can be macroscopically excised, followed by Hormonal Rx if appropriate

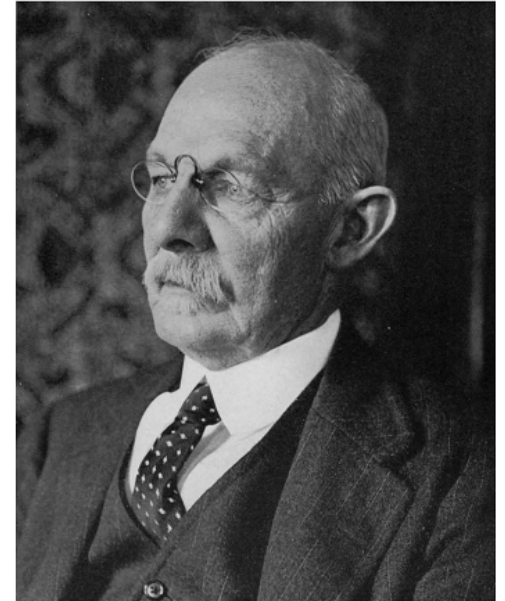
Surgical Options in LABC

- **Only attempt surgery if all macroscopic tumour can be removed!**
- Modified radical (Patey) mastectomy – breast and axillary nodes removed
- AD to Level II unless palpable disease in Level III
- “Partial radical” mastectomy if tumour invasion into muscles?
- Lat dorsi flap or STSG for large defects
- Little role for radical mastectomy, except when no adjuvant or neoadjuvant treatment is available – very deforming; but excellent local control possible (Halsted, 1894)

Halsted's Radical Mastectomy Series

Ann Surg 1894

- 50 cases of radical mastectomy (not consecutive?)
- Average age 51
- All 50 with nodal disease, so Stage II or III
- LABC 33/48 (68%)
- 27 of 50 (54%) prognosis regarded as “hopeless or unfavourable” after surgery & path assessment
- 6% local recurrence rate (“Return of the disease in the field of operation”)

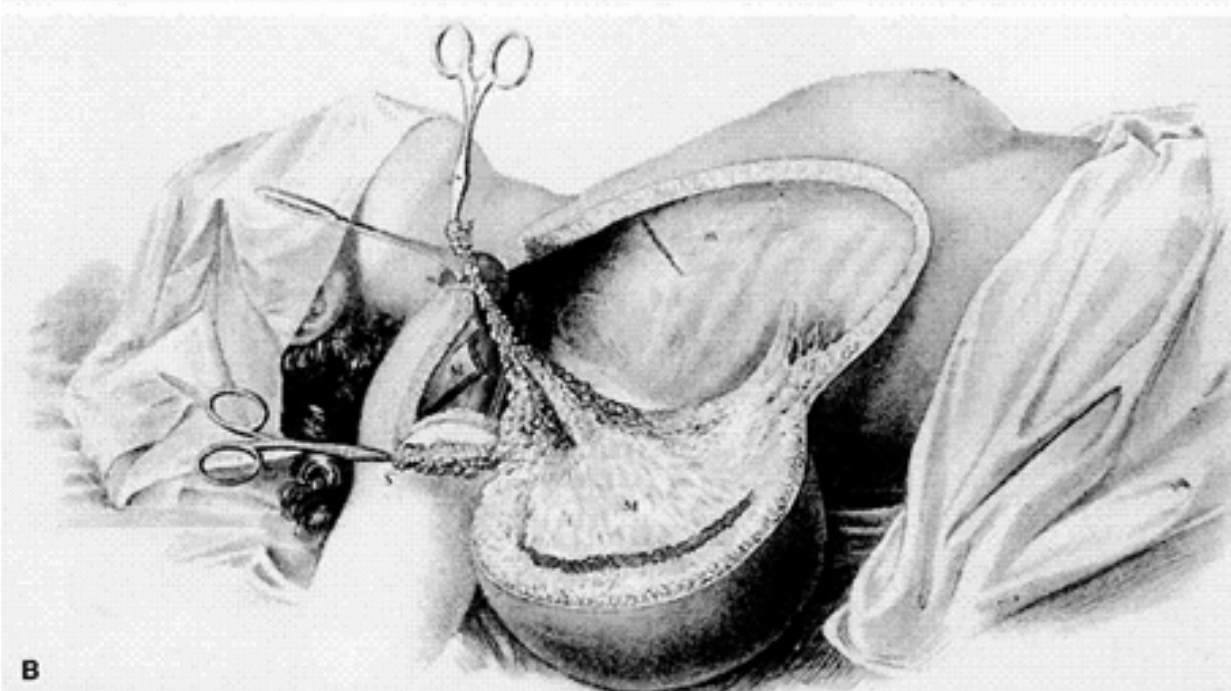
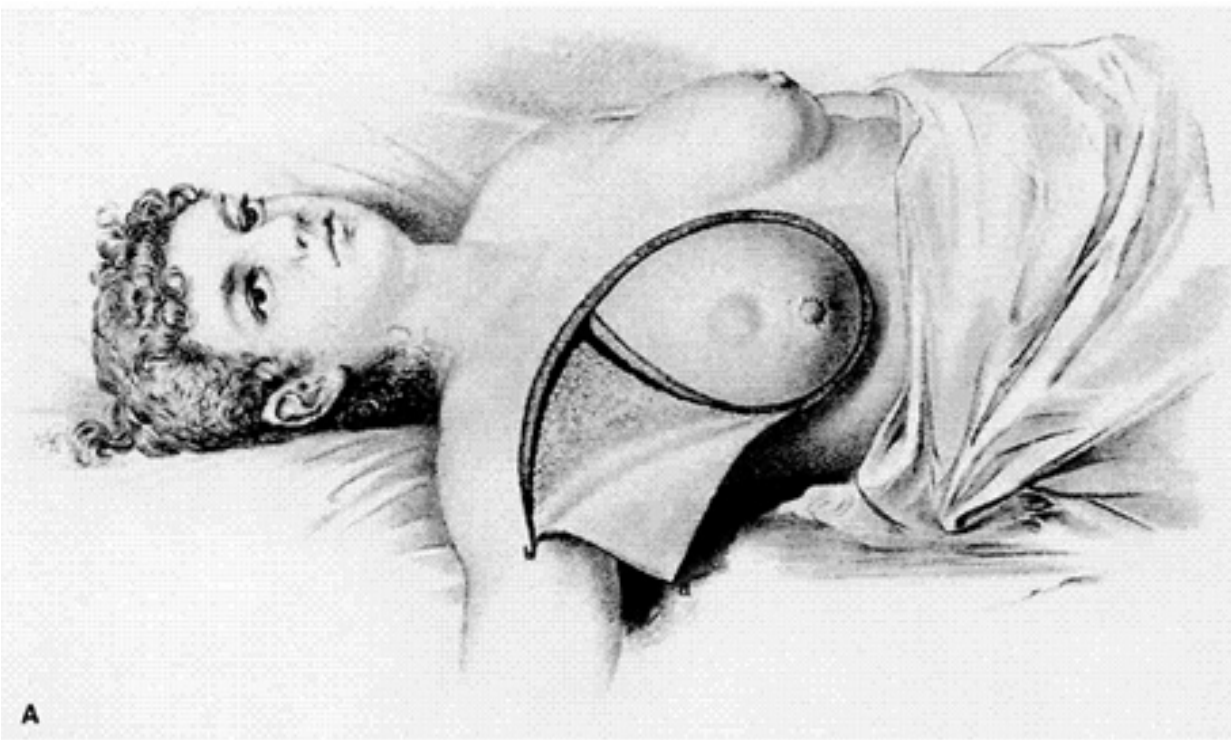


William Halsted 1852-1922

Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Ann Surg* 1894 Vol 20: 497-555

Halsted's Radical Mastectomy

- Removal of skin, breast, axillary nodes to level III, pectoralis muscles
- IM nodes not removed
- Chest wall defect skin grafted after granulating







Sixty-Three Latissimus Dorsi Myocutaneous Flaps at Kijabe Hospital

P Bird, 2000-2016

Indication	Number of cases	Pathology	Complications	Local recurrence
Coverage of anterior chest wall defect	46	Breast malignancy, soft tissue sarcoma	3 minor flap-skin dehiscences	2
Augmentation after partial mastectomy	6	Breast cancer	None	0
Delayed BR	3	Breast cancer	Implant Migration	N/A
Coverage of posterior chest wall defect	2	Recurrent soft tissue sarcoma	Partial flap necrosis x1	0
Neck contracture, Thoracoplasty	3	Burn, chronic empyema	1 minor flap-skin dehiscence	N/A
Immediate BR	3	Breast cancer	None	0

































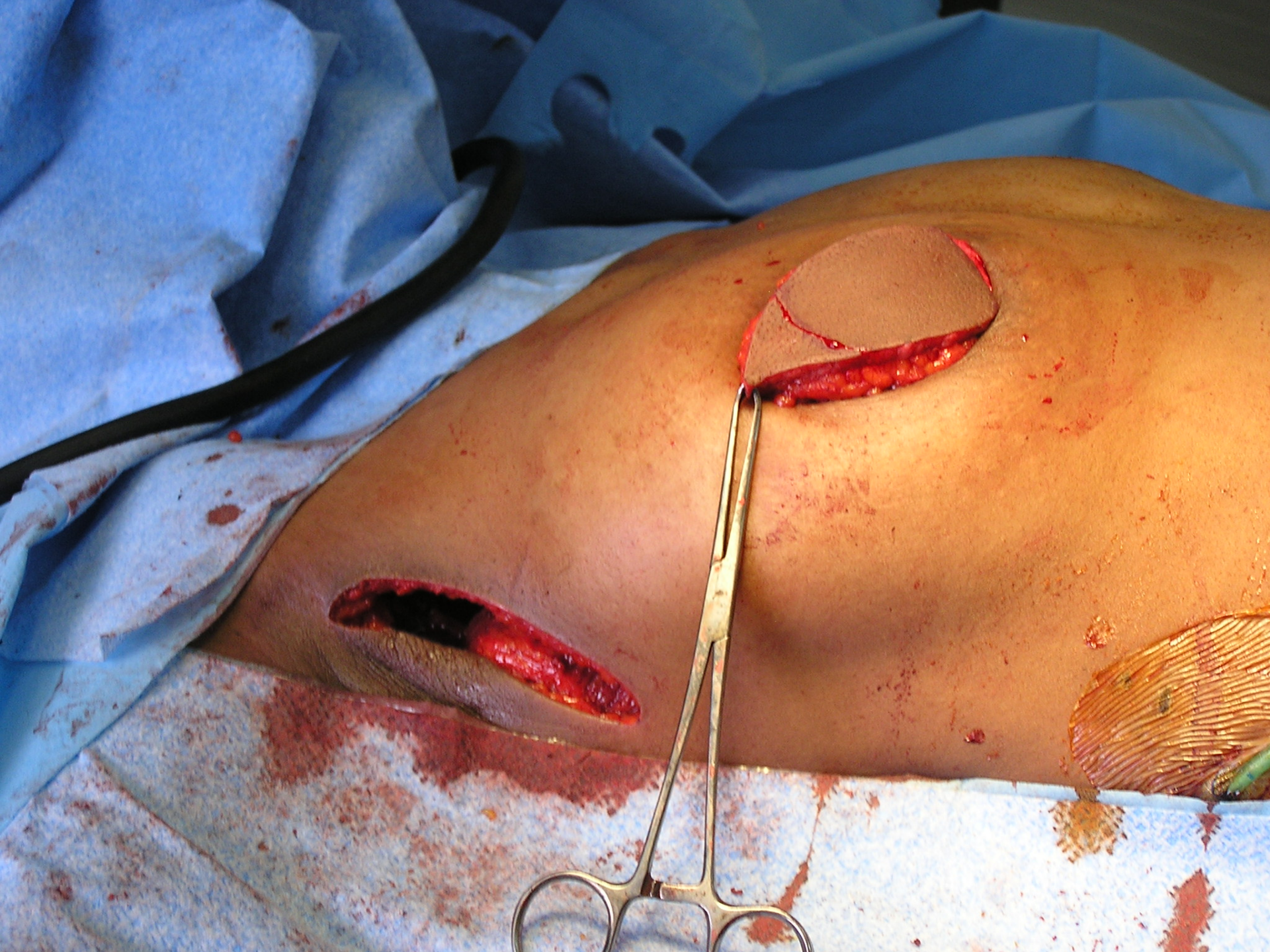


































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Biological Therapies

- Oncogene HER-2-neu receptor over-expressed in 15-20% of BCs (higher in Africans?)
- Targeted monoclonal antibody therapies work against this receptor
- Trastuzum**ab** (Herceptin) monthly for 12 months
- 2015 NCCN Guidelines recommends neoadjuvant dual MAB therapy for HER2 +ve pts with Stage II disease
 - Trastuzumab/pertuzumab/docetaxel
- Prohibitive expense (\$2500 per dose for 55kg pt)
- Trastuzumab on WHO Essential Medicines List 2015!

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Radiotherapy Resources in Africa 2010



Kenya and Neighbours 8

Kenya	2 (Private 7)
Ethiopia	2
South Sudan	0
Somalia	0
Uganda	1
Tanzania	3

Population: 243 million

Australia (public) 33

Australia (private) 26

Population: 23 million



Radiotherapy Resources in Africa 2010

	Population (thousands)	GNI per head* (US\$)	New cancer cases in 2008† (×10³)	Patients who need radiotherapy‡ (×10³)	Machine needed§	Existing machines	Teletherapy per million people	Additional machines needed
(Continued from previous page)								
East Africa								
Burundi	8074	140	5·860	3·750	8	0	0	8
Djibouti	849	1210	0·548	0·351	1	0	0	1
Eritrea	4927	300	2·489	1·593	4	0	0	4
Ethiopia	80 713	280	51·707	33·092	74	2	0·02	72
Kenya	38 765	730	27·897	17·854	40	2	0·05	38
Malawi	14 846	260	14·304	9·155	20	0	0	20
Mozambique	22 383	380	17·254	11·043	25	0	0	25
Rwanda	9721	410	6·598	4·223	9	0	0	9
Somalia	8926	..	5·809	3·718	8	0	0	8
Tanzania	42 484	460	21·180	13·555	30	3	0·07	27
Uganda	31 657	420	27·116	17·354	39	1	0·03	38

Radiotherapy Resources in Africa 2010



	Population (thousands)	GNI per head* (US\$)	New cancer cases in 2008† (×10³)	Patients who need radiotherapy‡ (×10³)	Machine needed§	Existing machines	Teletherapy per million people	Additional machines needed
West Africa								
Benin	8662	700	5.285	3.382	8	0	0	8
Burkina Faso	15 234	480	7.814	5.001	11	0	0	11
Cape Verde	499	2830	0.336	0.215	0	0	0	0
Côte D'Ivoire	20 591	980	11.485	7.350	16	0	0	16
The Gambia	1660	400	1.004	0.643	1	0	0	1
Ghana	23 351	680	16.580	10.611	24	2	0.09	22
Guinea	9833	350	6.467	4.139	9	0	0	9
Guinea-Bissau	1575	250	1.052	0.673	1	0	0	1
Liberia	3793	170	2.148	1.375	3	0	0	3
Mali	12 706	610	8.146	5.213	12	0	0	12
Mauritania	3215	980	1.978	1.266	3	1	0.31	2
Niger	14 704	330	6.571	4.205	9	0	0	9
Nigeria	151 212	1170	101.797	65.150	145	7	0.05	138
Senegal	12 211	980	6.646	4.253	9	1	0.08	8
Sierra Leone	5560	320	2.781	1.780	4	0	0	4
Togo	6459	410	3.980	2.547	6	0	0	6

Conclusions

- Most BCs in Africa present locally advanced and multidisciplinary treatment is unaffordable/unavailable
- BC management in LMICs must be tailored to best fit the economic circumstances
- Surgery is the mainstay of treatment of LABC in LMICs and surgeons need to be taught techniques to meet this challenge

Kijabe Breast Cancer Support Group



Kijabe, Kenya



Principles in Breast Cancer Management (2)

- Improvements in survival in the last 70 years have been made in treating the systemic disease
- 7-11% absolute improvement in 10-year survival for women <50

Polychemotherapy for early breast cancer: an overview of the randomised trials. EBCTCG, *Lancet* 1998



Principles in Breast Cancer Management (3)

- The ONLY reason to perform breast-conserving surgery (BCS) is cosmesis
- Oncologically, BCS is a second best option for local control
(because of increased local recurrence requiring further treatment and the need for RT, but no difference in survival)
- BCS is a compromise between cosmesis and local control

Principles in Breast Cancer Management (4)

- In most cases of BCS, adequate local control can only be achieved with clear margins (“No ink on margins”) and the addition of RT

16% absolute improvement (19% vs 35%) in BC recurrence risk

- Adjuvant RT also prolongs BC-specific survival in BCS

Reduces the overall death rate at 15 years by 3.8%: from 25.2% to 21.4%

Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011

Margins in Stage I & II Breast Conserving Surgery ("No ink on tumour")

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Int J Radiation Oncol Biol Phys, Vol. 88, No. 3, pp. 553–564, 2014

Clinical Investigation: Breast Cancer

Society of Surgical Oncology—American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD,^{*} Stuart J. Schnitt, MD,[†] Armando E. Giuliano, MD,[‡]
Jay R. Harris, MD,[§] Seema A. Khan, MD,^{||} Janet Horton, MD,[¶] Suzanne Klimberg, MD,[#]
Mariana Chavez-MacGregor, MD,^{**} Gary Freedman, MD,^{††}
Nehmat Houssami, MD, PhD,^{‡‡} Peggy L. Johnson,^{§§} and Monica Morrow, MD^{|||}

Hormonal Therapy

- Aromatase inhibitors provide superior DFS compare to tamoxifen in post-meno ER pos pts, but no survival advantage shown yet
 - ATAC Trial, Lancet Oncol 2010, 10 yr follow up
- Ovarian suppression plus SERMs in premeno ER pos pts
 - SOFT Trial: women 35 years and younger, the 5-year breast-cancer-free rate:
 - 67.7% in those on tamoxifen alone
 - 78.9% in those on tamoxifen plus ovarian suppression
 - 83.4% in those on exemestane plus ovarian suppression
 - Most marked improvement in those who received CT and remained premenopausal

SOFT & TEXT trials, NEJM 2014

Radiotherapy

- 50-60Gy given in 25 fractionated doses over 5-6 weeks
- RT is critical in achieving acceptable LR rates and improving survival in BCS
- Irradiating an axilla that has had an axillary dissection will result in a higher incidence of lymphoedema
- Tissue can only be safely irradiated once at these doses
- Survival advantage irradiating the chest wall and regional nodes after mastectomy for node positive disease, even 1-3 nodes (EBCTCG Lancet 2014)
- RT will cause skin/tissue fibrosis, telangiectasia and deformity in some cases; therefore, adjuvant RT is a relative contraindication to immediate breast reconstruction
- Rarely, can cause radiation-induced sarcoma (RIS)