February 2005

PROGNOSTIC FACTORS OF FEMALE BREAST CANCER IN MALTA

Introduction

"Diagnosis means generalizing, transcending the particular; prognosis, however, means individualizing, allowing for the particular".

■ Weissman, Theoretical Medicine and Bioethics

The practice of dividing cancer cases into groups according to the so-called stages arose from the fact that survival rates (hence prognosis) were higher for cases in which the disease was localised than for those in which the disease had extended beyond the organ of origin.

The stage of disease at the time of diagnosis and other prognostic factors may be a reflection not only of the rate of growth and extension of the neoplasm but also of the type of tumour and of the tumour-host relationship. Knowledge of these prognostic factors may serve a number of related objectives, namely

a. To aid the clinician in the planning of treatment
b. To give some indication of prognosis to the individual patient
c. To assist in the evaluation of the results of treatment
d. To contribute towards the continuing investigation of human cancer

The prognostic factors associated with breast cancer

Breast cancer is a heterogeneous disease that exhibits a wide variety of clinical presentations, histological types and growth rates. Because of these variations, determining prognosis for an individual patient at the time of initial diagnosis requires careful assessment of multiple clinical and pathological parameters. This evaluation includes consideration of an expanding list of tumour- and patient- related prognostic factors, which are especially important for decisions related to systemic treatment and predictions of overall survival.

The essential factors include[1]:

A. Tumour-related prognostic factors
* Tumour size: microscopical measurement
* Nodal status:
-the status of the ipsilateral axillary lymph nodes/ degree of involvement
-the absolute number of lymph nodes involved/ number of lymph nodes examined
* Histological grade or differentiation
* Histological type
* Mitotic figure count
* Hormone receptor status: oestrogen and progesterone receptors

B. Patient-related prognostic factors (essential factors)
* Age

C. Environmental-related prognostic factors
* Effect of local and systemic treatment

The TNM classification of Malignant Tumours published by the International Union against cancer (UICC) seeks to classify the anatomical extent of disease as determined by clinical and (where possible) histopathological findings for each case. For breast cancer it can be used to classify the topmost two essential tumour-related prognostic factors, namely tumour size and nodal status. Annex 1 contains the TNM classification for breast carcinomas[2].

Method

This study aimed to examine all the available information available and accessible to the cancer registry with regards to prognostic factors for the cases of invasive breast cancer in women registered between 1998 and 2002 (5 years). The main sources of information used were the histopathological reports. This source was supplemented by extensive information searches conducted from the hospital files of these cases.

For each registered case the following data items were sought and documented if available:
1. Age
2. Laterality (left, right or bilateral)
3. Breast subsite (quadrants, central or axillary tail)
4. Histological type
5. Histological differentiation
6. Tumour size (in mm) [T-code of TNM]
7. Nodal status [N-code of TNM]
a. whether positive or negative for metastasis
b. if positive, the degree of involvement
c. the number of lymph nodes extracted for pathological examination
d. the ratio of positive to negative nodes
8. Distant metastasis [M-code of TNM]
9. Hormone receptor status

This information was compiled into an Excel worksheet and subsequent analysis was performed to extract the proportions of each prognostic factor in the whole population of breast cancer cases. The aim was to illustrate at what stage in the disease these patients presented for diagnosis, so as to obtain the current picture for the Maltese population. This information was then compared with comparable information received from the national cancer registry of Northern Ireland. This registry had performed a similar exercise on their resident population of breast cancer cases from 1998-2002.

Results
(see results of the analysis in Annex 2)

Discussion

Age
Almost half of all cases (48.6%) were diagnosed between the ages of 50-69 years. This is the age group that is most often offered screening for breast cancer in the countries where these programmes are established. The rest of the cases include 21.8% who were less than 50 years at diagnosis; most of these being pre-menopausal, and 30% were older than 70 years.

Tumour size
Almost two thirds of cases (63.9%) for whom tumour size was documented had their tumour diagnosed at the T2 stage or earlier. However, 11.8% presented in the advanced stages of the disease with tumours greater than 5 cm or with signs of advanced local extension within the breast. Almost a quarter (23.5%) of the cases presenting at T3 stage were younger than 50 years at diagnosis, and 78.2% were younger than 70 years. In the T4 stage sector 14.3% were younger than 50 years and 48.3% were younger than 70 years old at diagnosis.

From the 258 cases with documented T1 stage at diagnosis, the biggest majority (76.4%) was diagnosed at the upper end of this stage, i.e. at T1c. At this stage tumours are between 1-2 cm large. More than half of all cases (53.6%) diagnosed at the T4 stage had their disease extending to and involving the skin of the breast.

However, it is important to note that for almost a quarter (24.1%) of all cases diagnosed with invasive breast cancer between 1998-2002, the tumour size at diagnosis could not be ascertained from the available documentation (pathologically from the histology reports or clinically from the clinical reports).

The information obtained from the Northern Ireland cancer registry shows that they have the same proportion of cases (63.8%) diagnosed in the T1 and T2 stages but they have a smaller percentage (4.4%) of cases diagnosed at T3 and T4. The proportion of cases for which the T stage could not be documented was however higher at 31.6%.

Nodal status
The cases for which the status of involvement of the regional lymph nodes could be ascertained amounted to 63.9%. Of these roughly 50% did not have metastasis to their regional lymph nodes at the time of diagnosis. The majority (87.9%) of the cases that had positive lymph nodes had metastasis measuring less than 2cm at diagnosis

The information obtained from the Northern Ireland cancer registry shows that they proportions of the cases classified to the N stage categories (including the Nx or unknown category) are similar to those found in the Maltese group.

Distant metastasis
At the time diagnosis only 1.2% of cases were found to have distant metastasis. In the rest of the cases the information necessary to exclude that there were distant metastasis at diagnosis was not attainable. Hence 98.8% remained with the M criterion of the TNM classification as unknown.

Laterality

There was a small preponderance of cancers arising in the left breast (42.2%) over those arising in the right breast (39.7%). Ten cases had cancers diagnosed in both breasts at the time of diagnosis. However, it is worth noting that even for this most commonly documented information, for 17.1% of cases the side of the affected breast was neither documented in the histology reports nor found in the clinical notes.

Hormone receptor status

Hormone receptor status was ascertained for roughly half of the cases. About 80% of cases for which hormone receptor status was documented were positive for the oestrogen receptors, while about 70% were positive for progesterone receptors.

Localisation: breast sub-site

The most commonly affected breast sub-site was the upper-outer quadrant. However, for 68.1% of the cases the exact location of the tumour at diagnosis could not be ascertained from the information sources reviewed.

Morphology

Ductal adenocarcinoma amounted to 73% of the tumour morphologies documented. The second most common morphological type were the lobular carcinomas with 8.1% followed by the mixed ductal and lobular tumours at 3.3%.

Conclusions and Recommendations

Breast cancer remains a major cause of mortality and morbidity and of significant concern to many women. Breast cancer is the most common cancer and leading cause of cancer deaths among women above the age of 30 years in Malta.

The two most important factors in reducing the mortality from breast cancer are:

a. early detection
b. effective treatment.

The results of this audit show that two-thirds (66.4%) of the female breast cancers diagnosed between 1998-2002 in Malta and for whom the tumour size at diagnosis was measured and documented were T2 and above. Tumours diagnosed at T2 and above are considered as 'advanced cases'[3]. Compared to the data received from national cancer registry of Northern Ireland, where an organised screening programme is functioning, the proportion of tumours diagnosed at T2 and above (proportion with cases with documented tumour size) for the same time period was 46.5%. In Malta, many breast cancer cases of all ages are presenting at stages that are not amenable for long-term cure from the disease. Investing in the education of women about breast cancer will encourage them to seek medical care earlier in the disease process, with the aim of decreasing their morbidity experience and their risks of mortality from the cancer.

A prerequisite for a reduction in breast cancer mortality is a more favourable stage distribution of the diagnosed cancers. In the absence of a local national screening programme it is important to know the stage distribution of the breast cancers that are currently being diagnosed so that a

sound evaluation of the burden can be obtained. This evidence will be necessary when assessing the need for preventive, diagnostic, therapeutic and rehabilitative care options for this disease.

The analysis of the information collected from this audit could have been more effective if more prognostic factors were documented for more cases. This could be aided by:

a. introducing and enforcing more standardised histopathological reporting
b. further education of the clinicians writing the clinical notes.

An example of a standardised histopathology reporting form recommended by the *European Guidelines for quality assurance in mammography screening (3rd edition)* is shown in Annex 3.

References:

1. Gospodarowicz M.K., Hensen D.E., Hutter R.V.P., O'Sullivan B., Sobin L.H., Wittekind Ch. Prognostic factors in Cancer, Second edition, International Union against Cancer, 2001 Wiley-Liss Publications

2. Sobin L.H., Wittekind Ch. TNM Classification of malignant tumours, Fifth edition, International Union against Cancer, 1997 Wiley-Liss Publications

3. European Commission, European guidelines for quality assurance in mammography screening, Third edition, Europe against cancer, 2001

ANNEX 1

TNM Classification of Breast Tumours

T- Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in-situ: intraductal carcinoma, or lobular carcinoma-in-situ, or Paget's disease of the nipple without a tumour

T1 Tumour 2 cm or less in greatest dimension
- T1mic Microinvasion 0.1 cm or less in greatest dimension
- T1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
- T1b More than 0.5 cm but not more than 1.0 cm in greatest dimension
- T1c More than 1.0 cm but not more than 2.0 cm in greatest dimension

T2 Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension

T3 Tumour more than 5.0 cm in greatest dimension

T4 Tumour of any size with direct extension to chest wall or skin only as described in T4a to T4d
- T4a Extension to chest wall
- T4b Oedema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
- T4c Both 4a and 4b, above
- T4d Inflammatory carcinoma

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis to movable ipsilateral axillary node(s)
- N1a Only micrometastasis (none larger than 0.2 cm)
- N1b Metastasis to lymph node(s), any larger than 0.2 cm
- N1bi Metastasis to 1-3 lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension
- N1bii Metastasis to 4 or more lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension
- N1biii Extension of tumour beyond the capsule of the lymph node metastasis less than 2.0 cm in greatest dimension
- N1biv Metastasis to a lymph node 2.0 cm or more in greatest dimension

N2 Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures

N3 Metastasis to ipsilateral internal mammary lymph node(s)

M – Distant metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

ANNEX 2

Cases of female breast cancer registered for 1998-2002

AGE

All cases by age groups

Age groups	**Total**	%
0-4	**0**	0.0
5-9	**0**	0.0
10-14	**0**	0.0
15-19	**1**	0.1
20-24	**1**	0.1
25-29	**2**	0.2
30-34	**15**	1.5
35-39	**28**	2.7
40-44	**74**	7.2
45-49	**102**	10.0
50-54	**153**	15.0
55-59	**119**	11.7
60-64	**106**	10.4
65-69	**117**	11.5
70-74	**108**	10.6
75-79	**91**	8.9
80-84	**65**	6.4
85+	**42**	4.1
Total	**1024**	100.3

TUMOUR SIZE T (mm)

A. All cases by T stage

			N. Ireland
T group	**No.**	%	%
1 T<20 mm	**258**	25.2	36.5
2 T>=20, <50 mm	**396**	38.7	27.3
3 T>=50 mm	**64**	6.3	2.8
4 T any size with extension to chest wall/skin	**56**	5.5	1.6
is ca-in-situ	**3**	0.3	0.2
x Unknown	**247**	24.1	31.6
Total	**1024**	100.0	100.0

B. By T group and age groups

	T1		T2		T3		T4		Tx	
Age groups	Female	%	Female	%	Female	%	Female	%	Female	%
0-19	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4
20-29	2	0.8	1	0.3	0	0.0	0	0.0	0	0.0
30-39	9	3.5	14	3.5	3	4.7	3	5.4	14	5.7
40-49	53	20.5	78	19.7	12	18.8	5	8.9	28	11.3
50-59	76	29.5	102	25.8	20	31.3	10	17.9	62	25.1
60-69	58	22.5	98	24.7	15	23.4	9	16.1	43	17.4
70-79	46	17.8	74	18.7	11	17.2	18	32.1	49	19.8
80-89	14	5.4	27	6.8	3	4.7	10	17.9	42	17.0
90+	0	0.0	2	0.5	0	0.0	1	1.8	8	3.2
Total	**258**	**100.0**	**396**	**100.0**	**64**	**100.0**	**56**	**100.0**	**247**	**100.0**

Tumour size (cont.)

C. Cases staged at T1 by sub-groups

T1 sub-groups	**No.**	%
T1a <5mm	**5**	1.9
T1b >=5, <10mm	**54**	20.9
T1c >=10, <20mm	**197**	76.4
T1x Unknown	**2**	0.8
Total	**258**	100.0

D. Cases staged at T4 by sub-groups

T4 sub-groups	**No.**	%
T4a extension to chest wall	**4**	7.1
T4b peau d'orange, extension to skin or satellite skin nodules in same breast	**30**	53.6
T4c both 4a and 4b	**1**	1.8
T4d inflammatory carcinoma	**1**	1.8
T1x Unknown	**20**	35.7
Total	**56**	100.0

NODAL STATUS (regional lymph nodes: ipsilateral axillary & ipsilateral internal mammary LNs)

A. All cases by N stage

N group	**No.**	%	*N. Ireland* %
0 no metastasis	**323**	31.5	35.1
1 metastasis to movable ipsilateral axillary LNs	**291**	28.4	23.8
2 metastasis to ipsilateral axillary LNs fixed to one another or to other structures	**39**	3.8	3.6
3 metastasis to ipsilateral internal mammary LNs	**1**	0.1	1.0
x Unknown	**370**	36.1	36.5
Total	**1024**	100.0	100.0

B. Cases staged at N1 by sub-groups

N1 sub-groups	**No.**	%
N1a only micrometastasis <0.2cm	**0**	0.0
N1b metastasis >=0.2cm	**3**	1.0
N1bi 1-3 Lns with metastasis, <2cm	**127**	43.6
N1bii metastasis to >=4 LNs, <2cm	**72**	24.7
N1biii extension of tumour beyond LN capsule, <2cm	**60**	20.6
N1biv metastasis >=2cm	**29**	10.0
Total	**291**	100.0

Number of lymph nodes extracted for histological examination (maximum no. was 34)

	No.
1-9	299
10-19	231
20-29	10
30-39	3
LN extracted but no. not specified	38

DISTANT METASTASIS

All cases by M stage

M group	**No.**	%
0 no distant metastasis	**0**	0.0
1 distant metastasis	**12**	1.2
X distant cannot be assessed	**1012**	98.8
Total	**1024**	100.0

LATERALITY

All cases by side of tumour

Side	**No.**	%
1 right	**407**	39.7
2 left	**432**	42.2
3 bilateral	**10**	1.0
9 unknown	**175**	17.1
Total	**1024**	100.0

HORMONE RECEPTOR STATUS

A. By oestrogen receptor status

Oestrogen receptors	**No.**	%
n negative	**114**	11.1
y positive	**422**	41.2
x unknown	**488**	47.7
Total	**1024**	100.0

B. By progetsteron receptor status

Progesteron receptors	**No.**	%
n negative	**159**	15.5
y positive	**363**	35.4
x unknown	**502**	49.0
Total	**1024**	100.0

LOCALISATION: BREAST SUB-SITE

All cases by breast subsite

Breast sub-site	No.	%
0 nipple	**6**	0.6
1 central	**42**	4.1
2 upper-inner quadrant	**32**	3.1
3 lower-inner quadrant	**21**	2.1
4 upper-outer quadrant	**178**	17.4
5 lower-outer quadrant	**26**	2.5
6 axillary tail	**10**	1.0
7 bilateral	**10**	1.0
8 overlapping (ill-defined)	**2**	0.2
9 not otherwise specified	**697**	68.1
Total	**1024**	100.0

MOST VALID BASIS OF DIAGNOSIS (Vbx)

All cases by most valid basis of diagnosis

Vbx	No.	%
0 death certificate only	**12**	1.2
1 clinical only	**30**	2.9
2 diagnostic imaging	**5**	0.5
5 cytology	**41**	4.0
6 histology of seconadries	**9**	0.9
7 histology of primary	**927**	90.5
8 autopsy	**0**	0.0
9 unknown	**0**	0.0
Total	**1024**	100.0

Microscopically verified = 95.4%

MORPHOLOGY

A. All cases by histological type

Hitological type	No.	%
800-801 carcinoma, nos*	**85**	8.3
814 adenocarcinoma, nos*	**22**	2.1
821 tubular adenocarcinoma	**7**	0.7
848 mucinous adenocarcinoma	**23**	2.2
850 ductal adenocarcinoma	**748**	73.0
851 medullary adenocarcinoma	**6**	0.6
852 lobular adenocarcinoma	**83**	8.1
8522 mixed ductal & lobular ca	**34**	3.3
854 mammary Paget's disease	**13**	1.3
902 Phyllodes	**1**	0.1
959 lymphoma	**2**	0.2
Total	**1024**	100.0

** nos = not otherwise specified*

B. Ductal adenocarcinoma, by differentiation

Differentiation	**No.**	%
1 well differentiation	**65**	8.7
2 moderate differentiation	**302**	40.4
3 poor differentiation	**284**	38.0
9 unspecified differentiation	**97**	13.0
Total	**748**	100.0

February 2005

ANNEX 3

Histopathology reporting form

Surname _____ Forenames_____ Date of birth _____

Screening no. _____ Hospital no. _____ Side □ Right □ Left

Patholologist _____ Date of reporting _____ Report no. _____

Histological calcification □ Absent □ Benign □ Malignant □ Benign & malignant
Specimen radiograph seen? □ Yes □ No
Mammographic abnormality present in specimen □ Yes □ No

Specimen type □ Localisation biopsy □ Open biopsy □ Segmental excision
□ Mastectomy □ Wide bore needle core

Specimen weight _____ g Size _____ mm x _____ mm x _____ mm

Benign lesion present
□ Complex sclerosing lesion/ radical scar □ Fibroadenoma □ Multiple papilloma
□ Periductal mastitis/ duct ectasia □ Fibrocystic change □ Solitary papilloma
□ Sclerosing adenosis □ Solitary cyst □ Other (please specify) _____

Epithelial proliferation □ Not present □ Present with atypia (ductal)
□ Present without atypia □ Present with atypia (lobular)

Malignant lesions non-invasive □ Not present
□ Ductal, high grade □ Ductal, other
Growth pattern (s) _____ Cell type/ pattern _____
□ Lobular □ Paget's Size (ductal only) _____

Microinvasion □ Not present □ Present □ Possible

Invasive □ Not present □ Mucinous carcinoma
□ Ductal/ no specific type (NST) □ Tubular carcinoma
□ Lobular carcinoma □ Mixed (please tick component types present)
□ Medullary carcinoma □ Not assessable
□ Other primary carcinoma (please specify) _____
□ Other malignant tumour (please specify) _____

Maximum diameter of invasive tumour _____ mm

Whole size of tumour (to include DCIS extending >1 mm beyond invasive area) _____ mm

Axillary nodes present □ Yes □ No Number positive _____ Total number _____

Other nodes present □ Yes □ No Number positive _____ Total number _____
Site of other nodes _____

Excision margins □ Reaches margin □ Uncertain □ Does not reach margin (nearest ____ mm)

Grade □ I □ II □ III □ Not assessable

Disease extent □ Localised □ Multiple □ Not assessable

Vascular invasion (blood or lymphatic) □ Present □ Not seen

Oestrogen receptor status _____ **Progesteron receptor status** _____

Comments/ additional information _____

Histological diagnosis □ Normal □ Benign □ Malignant