Radiol Oncol 1992; 26: 320-5.

Inflammatory breast cancer
Five-year survival of patients with inflammatory breast cancer treated in the period 1986–1987 at the Institute of Oncology in Ljubljana

Jurij Lindtner

Institute of Oncology, Department of Surgery, Ljubljana, Slovenia

A review of five-year survival of 35 patients with inflammatory breast cancer treated at the Institute of Oncology in the years 1986–1987 is presented. The initial and basic systemic therapy was complemented by surgery and/or irradiation. Five year survival was 11 %, and the median duration of survival 23 months.

Key words: breast neoplasms-therapy; survival analysis

Introduction

The introductory words of different reports on inflammatory breast cancer (IBC) are incredibly alike: they invariably comprise the following two statements:

– IBC is "the most malignant malignoma" of the breast,

– IBC is a rare disease representing 1-4 % of all breast cancers.[1,2]

The fact that this is a special breast disease was noted by Bell already in 1807; he regarded the pink skin with underlying breast tumor a very bad prognostic sign.[3] By the end of the previous century, Billroth and Volkman found a name for the disease: they called it "mastitis carcinomatosa", and the term has remained in use till present days.[2] In 1889, Bryant described a carcinomatous infiltration of the subcutaneous lymph vessels – a phenomenon which has been found diagnostically relevant.[4]

The first detailed description of IBC was given in 1911 by Schumann. In 1924, Lee and Tannanbaum named the disease inflammatory breast cancer.[1] The obsolete names such as mastitis carcinomatosa, carcinoma mammae acutum, carcinoma mastoides have gradually been abandoned. The authors completed the description by yet another observation: "The inflamed skin areas are sharply delineated as in erysipelas.[1] In 1971 Haagensen noted that" in advanced form of IBC the whole breast is enlarged and hardened, whereas the overlying skin is erythematous and swollen.[2]

In 1974, Salzstein declared IBC to be a pathomorphological diagnosis, and introduced the phenomenon of "hidden (i.e. clinically occult) IBC".[1] In 1978, Lucas and Perez-Mesa,

Correspondence to: Assoc. Prof. Jurij Lindtner, MD, PhD, Institute of Oncology, Department of Surgery, 61105 Ljubljana, Slovenia.

UDC: 618.19-006.6-037

using the data on median survival of patients with IBC, tried to clarify whether IBC was a clinical or a pathomorphological diagnosis:

Diagnosis	Median survival
Clinical only	14 mos
Pathomorphological only	40 mos
Clinical and pathomorphological	16 mos

These data are in agreement with the presently prevailing belief that the diagnosis of IBC is clinical.[4]

According to the presently valid definition of the International Union Against Cancer (UICC/AJC-1986), IBC is "diffusely thickened and hardened breast skin with erysipeloid margins, and generally without a palpable tumor".[5]

A distinction should be drawn between two different forms of IBC: 1) the true IBC is characterized by an acute onset and simultaneous involvement of most part of the breast, frequently without a palpable tumor – called also classical or diffuse IBC (DIBC), and 2) the "neglected" breast cancer with a protracted anamnesis, an apparent tumor and visible signs of inflammation in the affected quadrant of the breast – also called localized IBC (LIBC). The differing data on the survival of patients with IBC could be explained by this double nature of the disease. Therefore in 1956 Haagensen warned that "the diagnostic criteria are interpreted too liberally, and as a result we may jump to a conclusion on diagnosis too quickly".[6]

With respect to TNM classification, the greatest prognostic relevance should be attributed to the factors N and M. The fatality of IBC correlates with the growth of N from N0 to N3, and from M0 to M1. A good response to an initial systemic therapy can be regarded as a favourable prognostic sign. However, the "neglected IBC, i.e. LIBC, with its protracted anamnesis and signs of inflammation limited to a part of the breast, is associated with quite a different prognosis then DIBC. "*Peau d'orange*" and mammographic evidence of thickened skin are certainly among unfavourable prognostic signs.[7] Thus, the following three prognostic categories can be distinguished:

Favourable – LIBC N0-1
Moderate LIBC N2-3; DIBC N0-1
Unfavourable – DIBC N2-3.[8]

Self-evidently, the above distribution is applicable only in patients with IBC and no clinical evidence of metastatic spread at the time of diagnosis (M0).

The presented analysis is the most recent report on the survival of patients with IBC treated at the Institute of Oncology in Ljubljana, during the first five years after the beginning of therapy.

Materials and methods

Our review of the course of IBC comprises the data on patients who commenced treatment at the Institute of Oncology in Ljubljana, during the years 1986–1987. Such a selection of patients enabled us to assess their 5-year survival results.

In the appointed 2-year period, 1227 new breast cancer patients were registered by the Cancer Registry of Slovenia.[9,10] In the same period, Hospital Registry of the Institute of Oncology in Ljubljana registered 1278 new breast cancer cases. The difference in the total numbers of new cases can be attributed to the fact that there were also some patients from other former Yugoslav republics treated at the Institute in Ljubljana.

According to the data of the Hospital Registry for the years 1986–87, 149 of newly registered breast cancer patients were permanent inhabitants of Slovenia, who were admitted to the Institute of Oncology in Ljubljana for the treatment of breast cancer classified as T4. Here, the beginning of treatment is explicitly stated because of the already mentioned Haagensen's warning on a vague diagnosis of IBC as a rare disease, whereas the emphasis on permanent inhabitants of Slovenia results from the fact that in the last few years, the data on the course of disease have been available only for patients permanently living in Slovenia.

A riview of medical records on these 149 patients with "T4" breast cancer revealed that there were only 35 among them with classical (difuse) T4d IBC (23%), and their course of disease is the subject of this report.

Results

The age distribution of the studied patients is evident from the following table:

Table 1. Age distribution.

Range	30–65 years
Mean age	51 years
Median	49 years

Table 2 shows the frequency of left or right breast involvement in our group of patients:

Table 2. Affected breast.

	No. of pts
Left	25
Right	9
Both	1
Total	35

The distribution of patients according to TNM classification was as follows:

Table 3. Distribution by TNM.

N	M	No. of T4d pts
NO	MO	3
N1	MO	16
N2	MO	5
N3	MO	6
NO-3	M1	5
Total		35

The treatment of the patients included in our study is presented in Table 4:

Table 4. Distribution by the type of initial therapy.

Treatment modality	No. of pts
Systemic	1
Systemic + irradiation	13
Systemic + surgery	2
Systemic + irradiation + surgery	6
Systemic + surgery + irradiation	13
Total	35

Discussion

IBC is not just a severe, so far insoluble therapeutic problem. The difficulties start already at the time of diagnosis. The opinions of different authors cited in the Introduction are in agreement with this statement. Here again the attention should be called to the Haagensen's description where the author states that "when sufficiently advanced", the disease is not difficult to identify. Also the hardening and enlargement of the affected breast can be regarded as diagnostically relevant clinical signs, whereas the skin edema is already questionable; TNM classification (1987) provides the following definition:

T4a – spread to the chest wall

T4b – edema (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.[5]

A demanding reader would find this definition rather vague.

It is quite easy to interpret a skin edema as an early sign of IBC, particularly when it is associated with mammographically evident thickening of the skin. On the other hand, a total breast involvement can hardly be regarded as conclusive for IBC. The fact that some patients are first seen with already advanced disease suggests that these patients themselves "took care" of the disease in its early stage, though this phase might not have lasted well over a few weeks, considering the rapid course of the disease. It is also possible that some patients do see doctor sooner than others. In such cases the symptoms of the disease are less expressed, and limited to a single quadrant of the breast. Therefore, IBC should be searched also among breast carcinomas classified as T4b. The same ambiquity is associated also with the next important sign, i.e. erythema: this can be attributed either to carcinomatous dermatolymphangiosis or to aspetic inflammation due to central necrosis of a slowly growing breast cancer. The frequent tendency to interpret these two "red"

breast cancers as one and the same entity just proves how difficult it is to draw a distinction between the two different types of erythema. This statement can be substantially confirmed by numerous reports in foreign literature, as well as by our own studies. Last but not least, the unreliability of clinical detection of the disease is best confirmed by the opinion the IBC is a pathomorphologic and not a clinical diagnosis. However, since clinical identification of the disease cannot not be avoided, we should strive to improve it through upgrading of experience. Such an approach might prevent us from misinterpreting some quackery-related inflammation for IBC.

Though *our group of presented patients* may seem small, when compared with groups of IBC patients reported by other authors, it can be assessed as medium-sized. Besides, it should be taken into account that only the patients with classical diffuse IBC were included, which is also reflected in their age distribution. Namely, there are no older patients in our group. The patients age reported in the literature ranges from 25 to 84 years, though the youngest known patient was only 12 years old.[4] Localized IBC is generally seen in older patients which, however, have been omitted from our analysis.

According to the data of the Cancer Registry of Slovenia, the incidence of IBC in our country is within the range of medium values reported in the Introduction: 35 observed patients among 1.227 evidenced by the Registry represent 2.8 % of all breast cancers. This rate is fairly reliable, considering that most patients with advanced and disseminated breast cancer start their treatment at the Institute of Oncology (a review of medical records suggests that perhaps one or two patients with IBC have started their treatment elsewhere). Taking into account all probable IBC patients, the number amounts to 3 % of all breast cancers.

We have no evidence of male patients with IBC, though according to the data from literature such cases do exist.[11]

The results of foreign and own investigations show that breast cancer equally frequently affects each breast (a slightly more frequent involvement of the left breast is negligible). In our group of patients with IBC this rate was 26 vs. 10 in favour of the left breast (taking into account that a patient with bilateral involvement was considered in both groups). According to the foreign experience, IBC is almost twice more frequent in the left than in the right breast.[12]

Our data on the *treatment* of the observed patients are scanty, and so are also the reports on these patients and their disease; namely, in one fifth of the cases the primary patient record could not be found. Therefore, the data that could be collected on the treatment of our group of all 35 patients have been presented in Table 4.

The information reveals, however, that all the patients under study received systemic therapy. This is in agreement with presently respected principles on the treatment of IBC. For the sake of comparison, I am giving below some data in on the survival of patients before the use of systemic therapy that have been reported in the same publication.[4]

a) *Surgery alone:*
- mean survival 21 months
- 19-month average survival reported by Haagensen
- 3.5 % five-year survival reported by Treves

b) *Radiotherapy alone:*
- mean survival 14 months

c) *Surgery and radiotherapy:*
- mean survival ranges between 7–29 months;
- only Perez and Fields (1987)[4] reported a 42-month average survival of patients treated by the combined approach.

The use of systemic therapy considerably prolongs the average survival, regardless the type of local therapy (if any was used at all): mean survival reported in the literature ranges between 23.6 and 46 months.[4] Mean survival results of our patients (23 months) are therefore slightly below the above cited values. Perhaps this fact could be attributed to our already mentioned strict criteria for patient selection. Figure 2 presents two data on mean survival: thus prognostically favourable group survived 31 months and prognostically unfavourable

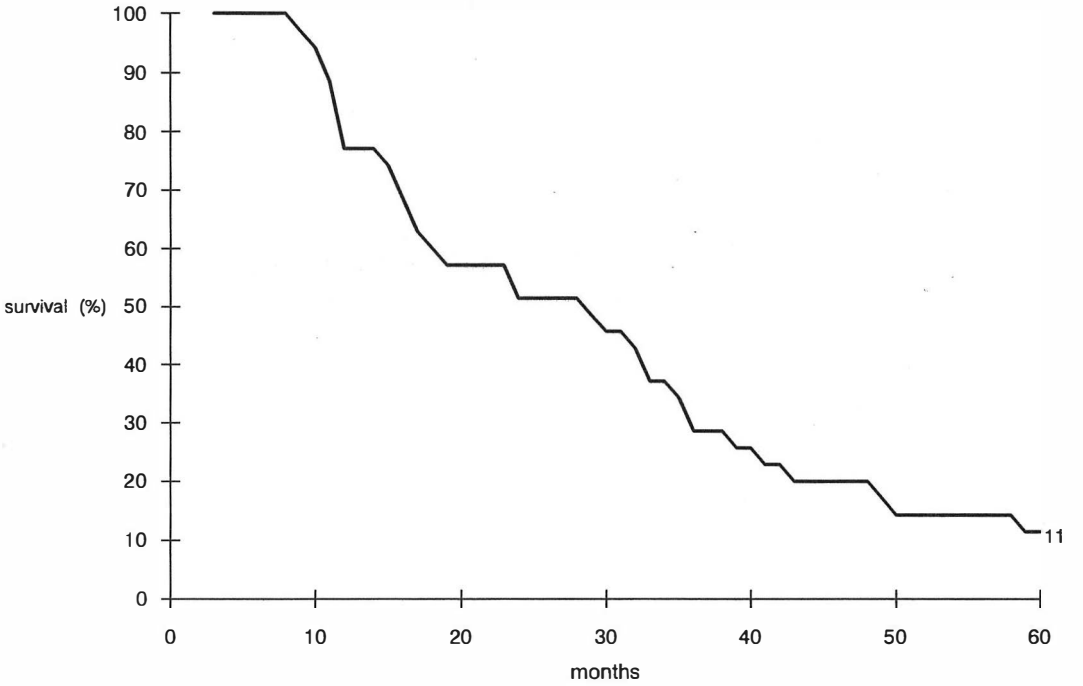

Figure 1. Curve of actual survival results in 35 patients with IBC.

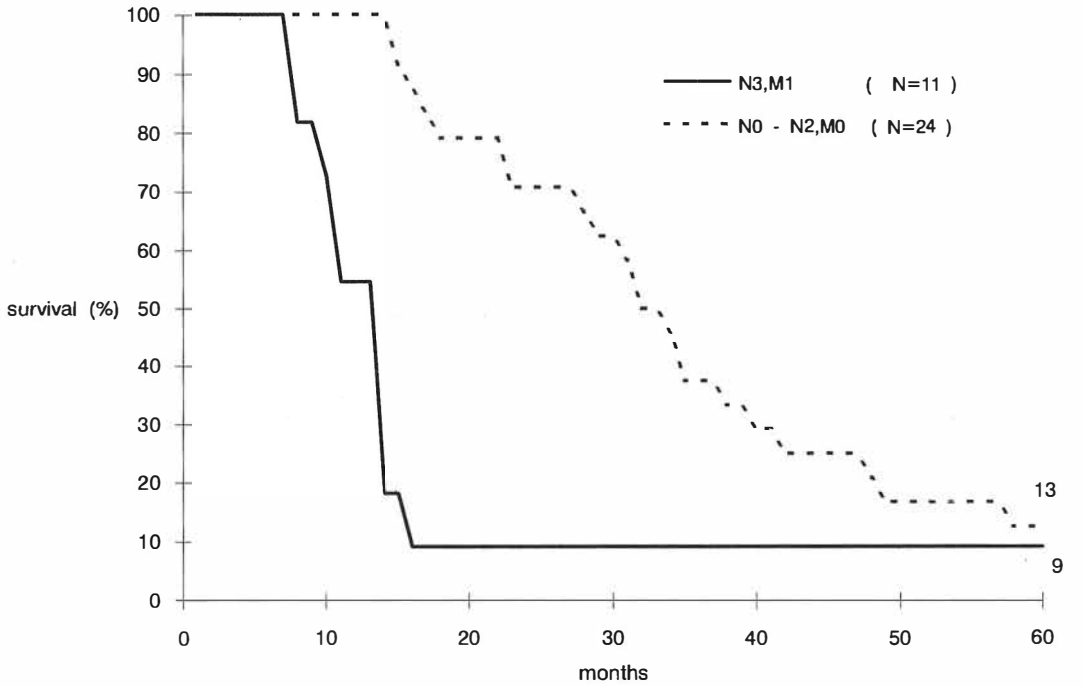

Figure 2. Curve of actual survival results in 35 patients with IBC, distributed into 2 prognostic groups.

group 14 months on average. Graph 2 also shows 5-year survival of a patient form prognostically unfavourable group (N3, M1) which could be attributed to vague clinical classification.

The data on 270 patients with IBC M0 reported by Institute Gustave Roussy[13] are as follows:

– 28% *five-year survival* of patients treated by *irradiation* (and castration when fertile);

– 40% *five-year survival* of patients treated by systemic therapy according to AVM schedule (adriamycin, vincristine, methotrexate) and maintenance chemotherapy with VCF (vincristine, 5-fluorouracil, methotrexate and endoxan).

In comparison with the patients mentioned above, only 11% five-year survival has been observed in our patients with IBC M0. Owing to the incomplete information on forms of systemic therapy no other conclusion can be drawn apart from that general observation. We should be aware, however, that any detailed analyses of this topic based on uncontrolled, non-randomized retrospective studies such as ours can be done only exceptionally and are, as a rule, not feasible.

Conclusion

Here I would repeat the initial statement: IBC is a tough diagnostic as well as therapeutic problem which is somewhat underestimated because of its rare occurrence. This cognition could represent a stimulus for further studies.

References

1. Parker LM, Sheldon TA, Cady B. Inflammatory Breast Cancer. In: Harrris JR, Hellman S, Henderson IC, Kinne DW eds. *Breast Diseases.* Philadelphia: JB Lippincott Company, 1987.
2. Haagensen CD. *Diseases of the breast.* Philadelphia-London-Toronto: WB Saundres Company, 1971.
3. Rosen PP. The Pathology of Breast Carcinoma. In: Harris JR, Hellman S, Henderson IC, Kinne DW eds. *Breast Diseases.* Philadelphia: JB Lippincott Company, 1987.
4. Swain SM, Lippman ME: Locally Advanced Breast Cancer. In: Bland KI, Copeland EM eds. *The Breast.* WB Saunders Company, 1991.
5. Yeatman TJ, Bland KI: Staging of the Breast Cancer. In: Bland KI, Copeland EM eds. *The breast.* WB Saunders Company, 1991.
6. Haagensen CD: *Diseases of the Breast.* Philadelphia-London-Toronto: WB Saunders Company, 1956.
7. Sobol-Attia J, Cure H, Ferriere JP, Bignon ZJ, Achard JL, Varnis M, Dauplat J, Lafaye C, Da Latour M, Chollet P, Plagne R. Effectiveness of an Induction Adriamycin-based Chemotherapy (AVCF) on Inflammatory Breast Cancer (Meeting Abstract). *Ann-Oncol* 1990; **23:** 1 (Suppl).
8. Tursz T, Spielmann M, Le Chevalier T, May-Levin F, Arriagada R, Toussaint C, Sarrazin D, Mouriesse H, Rouesse J. Prognostic Factors in 332 Inflammatory Breast Cancer Patients (BC). A 20-YR Experience at the Institut Gustav-Roussy (IGR) (Meeting Abstract). *Proc Annu Meet Am Soc Clin Oncol* 1991; **10:** A46.
9. *Incidenca raka v Sloveniji 1986.* Ljubljana: Register raka za Slovenijo 1990, Onkološki inštitut v Ljubljani.
10. *Incidenca raka v Sloveniji 1987.* Ljubljana: Register raka za Slovenijo 1991, Onkološki inštitut v Ljubljani.
11. Kinne DW. Male Breast Cancer. In: Harris JR, Hellman S, Henderson IC, Kinne DW eds. *Breast Diseases.* Philadelphia: JB Lippincott Company, 1987.
12. Greenspan EM. Inflammatory Breast Cancer. In: Ariel IM, Cleary JB eds. *Breast Cancer.* McGraw-Hill Book Company, 1987.
13. Rouesse J, Sarazin D, Spielman M, Le Chevalier T, Oudinot P, Guasch Jordan I, Mouriesse H, Levin FM. Le traitment du cancer du sein inflammatoire. Associacions chimiotherapie-radiotherapie. A propos de 270 femmes traitees a l'Institut Gustave-Roussy. *Bull Cancer Paris* 1989; **76** (1): 87–92.