

Changing Paradigms of Primary Breast Cancer Treatment

Thirty years ago, the standard treatment for anyone with breast cancer was a radical mastectomy. This required removing the breast, underlying tissue, and the axillary lymph nodes in one large operation. It was felt that the risk of breast cancer could be alleviated by removing all of the disease that was seen within the local and regional area of the breast, where the cancer had originated. Radical mastectomy, however, did not address the real risk to survival of breast cancer, namely the spread of cancer to distant organs. It was not understood that cancer cells frequently had already left the original site of the primary cancer and lymph nodes, to circulate through the lymphatic and blood systems to the rest of the body. These would eventually cause recurrence in vital organs.

The concept of simply removing the breast lump as adequate treatment for breast cancer was felt to be a dangerous “heresy” that would endanger the lives of breast cancer patients. A series of clinical trials by the NSABP (National Surgical Adjuvant Breast and Bowel Project), sponsored by the National Cancer Institute, showed that the risk of breast cancer recurrence anywhere in the body, was proportional both to the size of the tumor and some of its characteristics, such as differentiation of the cancer cells and the level of estrogen and progesterone receptors. It was demonstrated that after removal of the cancer itself, an operation that came to be termed “lumpectomy”, the 30% risk of recurrence within the breast could be reduced to 5% or less by applying radiation therapy to the remaining breast. Moreover, the actual importance of removal of axillary lymph nodes was shown to be in their prognostic value opposed to therapeutic value. Specifically, it was found that leaving the axillary lymph nodes in place after breast surgery did not increase the chances of recurrence or the chances of death. A late recurrence of cancer in an axillary lymph node could be removed at the time of a second surgery without jeopardizing the patient’s chances of cure. This also demonstrated that the number of involved lymph nodes in the axilla was one of the primary predictors of the patient’s risk of developing recurrence and/or dying of breast cancer in later years.

Prior to these studies, it was felt that extensive resection of the lymph nodes in the axilla was required and needed to be followed by radiation therapy to the chest wall and the axilla. This led to a high rate of lymphedema or swelling of the arm on the side of the breast cancer surgery due to blockage of the lymphatic channels from surgery and radiation. These studies demonstrated that these measures were unnecessary and potentially harmful. Marquette General Hospital participated in these early

studies and was one of the largest contributors in the State of Michigan for patients who volunteered to participate in these studies of lumpectomy versus mastectomy.

Since that time, Marquette General Hospital has participated in all of the NSABP studies on breast cancer which have shown that the use of chemotherapy and anti-estrogen hormonal therapy not only lessens the chances of recurrence within the breasts, or the chest wall if mastectomy has been done, and in the axilla but can also markedly decrease the risk of recurrence elsewhere in the body preventing potentially fatal metastases. At the end of the 20th Century, the paradigm had shifted to the idea of breast preservation, in order to lessen the disfiguring damage of total mastectomy. Lumpectomy followed by radiation therapy to the breast, sampling of the axillary nodes to determine the risk of developing metastases, and applying anti-estrogen hormonal therapy and/or chemotherapy to high risk patients has not only controlled the spread of cancer cells and thus improved the cure rate but also improved the cosmetic results.

As with any paradigm, however, a reality check to compare the ideal model with empiric evidence of results is necessary. The Marquette General Hospital Cancer Registry collects data on the type of breast cancer that each patient has, the type of surgery that is done, the type of “adjuvant” therapy such as radiation therapy, chemotherapy and hormonal therapy that is done after potentially curative surgery and then follows the patients for life to record the results as to whether or not they survive cancer free or develop new metastases or eventually die of their disease. This outcome analysis presents a review of the Marquette General Hospital experience from four representative years of breast cancer surgery, showing the changing rates of mastectomy versus lumpectomy, and the rates of recurrences in those patients. The years selected were 1985, 1990, 1995 and 2000. Each group of patients allows the minimum of five years of follow-up to get an accurate picture of how these patients are doing. If the paradigm of breast conservation (where possible) and application of adjuvant radiation therapy to the breast and systemic treatment with hormonal therapy and chemotherapy is valid, then we should see a roughly equivalent result between total mastectomy and breast conserving lumpectomy with breast radiation. We should also anticipate seeing an increasing use of lumpectomy versus mastectomy as more patients insist on preserving their breasts. We would also hope to see a decreasing risk of recurrence, especially distant recurrence, in vital organs outside

Patient Outcome Analysis – 2005

of the region of the breast and axilla with successful application of adjuvant systemic therapy with hormones and chemotherapy.

It should be pointed out that there are many instances in which a lumpectomy cannot be done and mastectomy is required. Larger cancers or cancers within small breasts have a poor cosmetic result with only the lump removed since very little of the normal breast tissue would be left. There are some patients who have autoimmune or connective tissue diseases that would not be able to tolerate radiation therapy and require mastectomy. There are some women, especially those who live a great distance from a radiation therapy center such as the one at Marquette General Hospital, who feel unable to commit to six weeks of traveling from their homes to a radiation therapy facility for daily treatments and therefore choose mastectomy.

In addition, there is still a fear held by some patients and even some physicians that leaving a breast which has had cancer in it in place on the chest is always a greater risk for cancer recurrence even though the theoretical paradigm and the clinical trials indicate that this is not so. These women and physicians will often then opt for mastectomy.

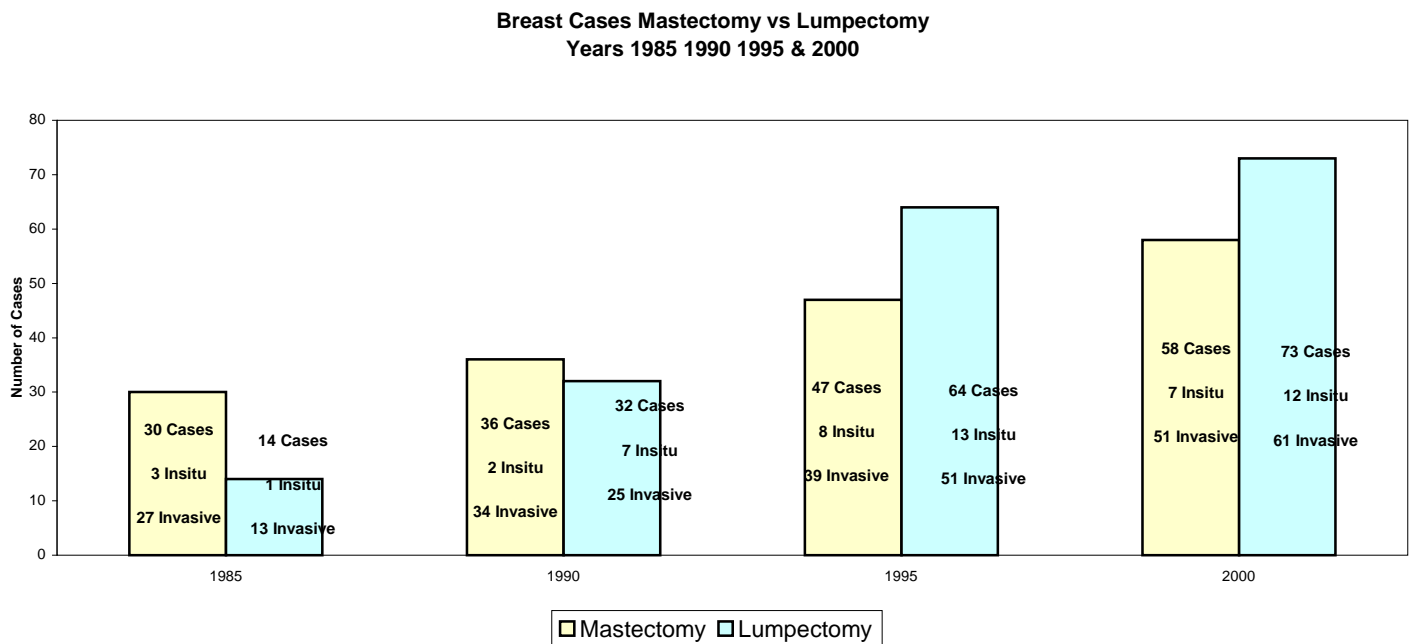


FIGURE 1

As you can see from **Figure 1**, the total number of breast cancer surgeries at Marquette General Hospital has increased markedly between 1985 and 2000. Moreover, the ratio of mastectomy to lumpectomy has essentially reversed in that period of time. As we can see, in 1985 almost three out of four breast cancer patients had a mastectomy. By 1990, the rates of mastectomy and lumpectomy were almost equal. By 1995, the rates of lumpectomy had markedly exceeded those of mastectomy and this trend continues in the year 2000. We will be examining in detail the characteristics of these 359 patients that underwent the breast cancer operations documented here and will show the results over a span of a minimum of five years of follow-up and in some cases 10 to 15 years.

In **Figure 1**, you can see that the total number of breast cases at Marquette General Hospital has steadily increased over the span from 1985 to 2000 with 47 cases treated in 1985 and 131 cases receiving definitive surgical therapy in the year 2000. Again, the relative rates of mastectomy versus lumpectomy have gradually reversed with only 29% of breast cases having lumpectomies in 1985 to 56% having lumpectomies in the year 2000. Over the same period of time, the application of post-operative anti-estrogen (hormonal) therapy and adjuvant chemotherapy had been increasingly utilized.

Recurrence After Mastectomy vs Recurrence After Lumpectomy Years 1985 1990 1995 2000

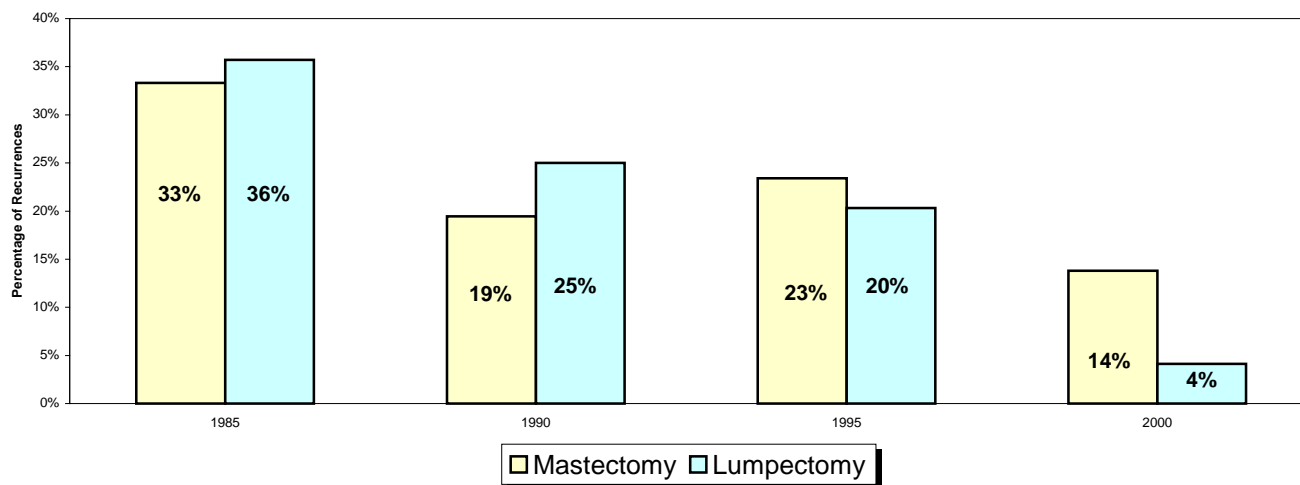


FIGURE 2

Thus, we can see that in **Figure 2** (previous page) the recurrence rates after both mastectomy and lumpectomy have gradually decreased from 1985 to 2000. Moreover, the risk of recurrence after lumpectomy versus mastectomy has reversed from 1985 to 2000. The year 2000, for which we have five year follow-up, is remarkably encouraging with only 14% of those patients having had mastectomy relapsing and only 4% of those patients having had lumpectomy relapsing. Much of this improvement in relapse and survival is due to advances not only in surgical technique but also in application of advanced techniques of radiation therapy and hormonal therapy and chemotherapy and participation of many of our patients on National Cancer Institute sponsored clinical trials.

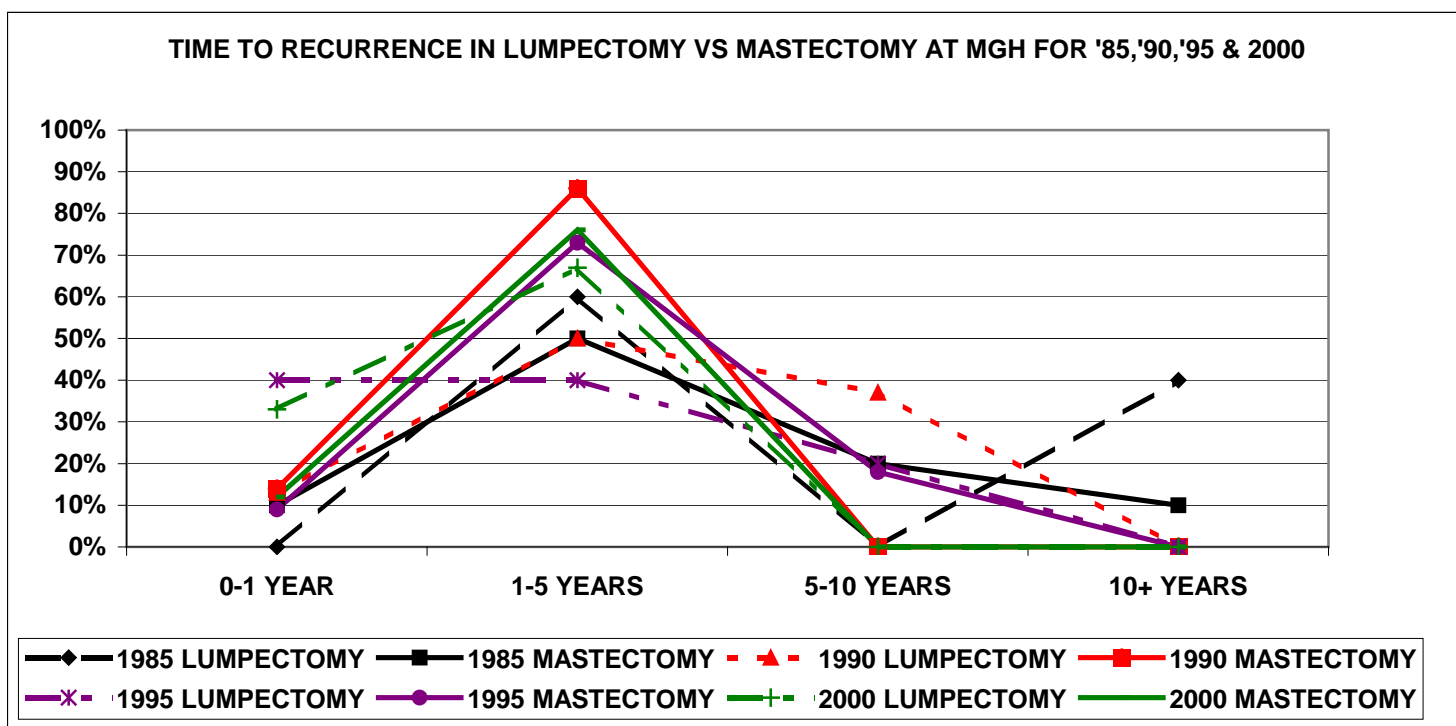


FIGURE 3

It is important to analyze the pattern of recurrences both by location of recurrence and time from diagnosis of recurrence to better understand how we can improve our treatments in the future. The time to recurrence after mastectomy has been quite consistent over the years (**Figure 3**). The majority of recurrences are seen within the first five years with a moderate number being seen between five and ten years and only a rare recurrence at 10 or more years. An almost identical pattern holds for recurrence and time to recurrence after lumpectomy. The majority of recurrences are seen within five years and almost all within ten years. After lumpectomy there are a slightly increased number of recurrences beyond ten years probably secondary to the fact that the involved

breast remains and is still at risk for the very few ipsilateral breast cancer recurrences that have been diagnosed. If the time from diagnosis to recurrence of breast cancer treated by lumpectomy and mastectomy are superimposed for all four years being studied, there appears to be very little difference in timing of recurrences according to the technique or the year in which the treatment occurred. It is also apparent that the results of five years from either technique will be an excellent predictor of results at ten years and beyond. Therefore, we can be fairly confident that the six-year follow-up on year 2000 patients will not change significantly.

Recurrence After Mastectomy vs Recurrence After Lumpectomy by Pathology at Diagnosis Years 1985 1990 1995 2000

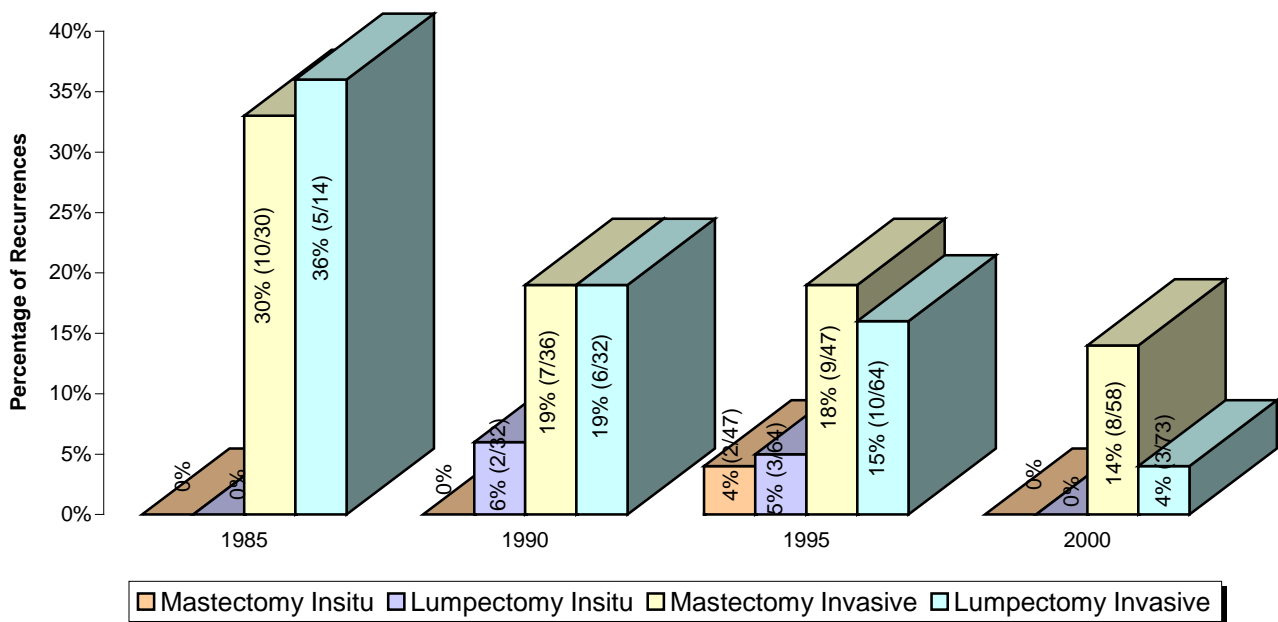


FIGURE 4

Figure 4 illustrates that there are only rare recurrences in those patients operated on for insitu disease whether they have mastectomy or lumpectomy. On the other hand, for those patients who have mastectomy or lumpectomy for invasive disease, the recurrence rates are naturally higher since these tumors have the ability to metastasize to other organs. On the other hand, the risk of recurrence with lumpectomy in a patient who has invasive breast cancer appears to have decreased to the point where it is now less than the risk for mastectomy.

Recurrence by Stage at Diagnosis After Mastectomy Years 1985 1990 1995 2000

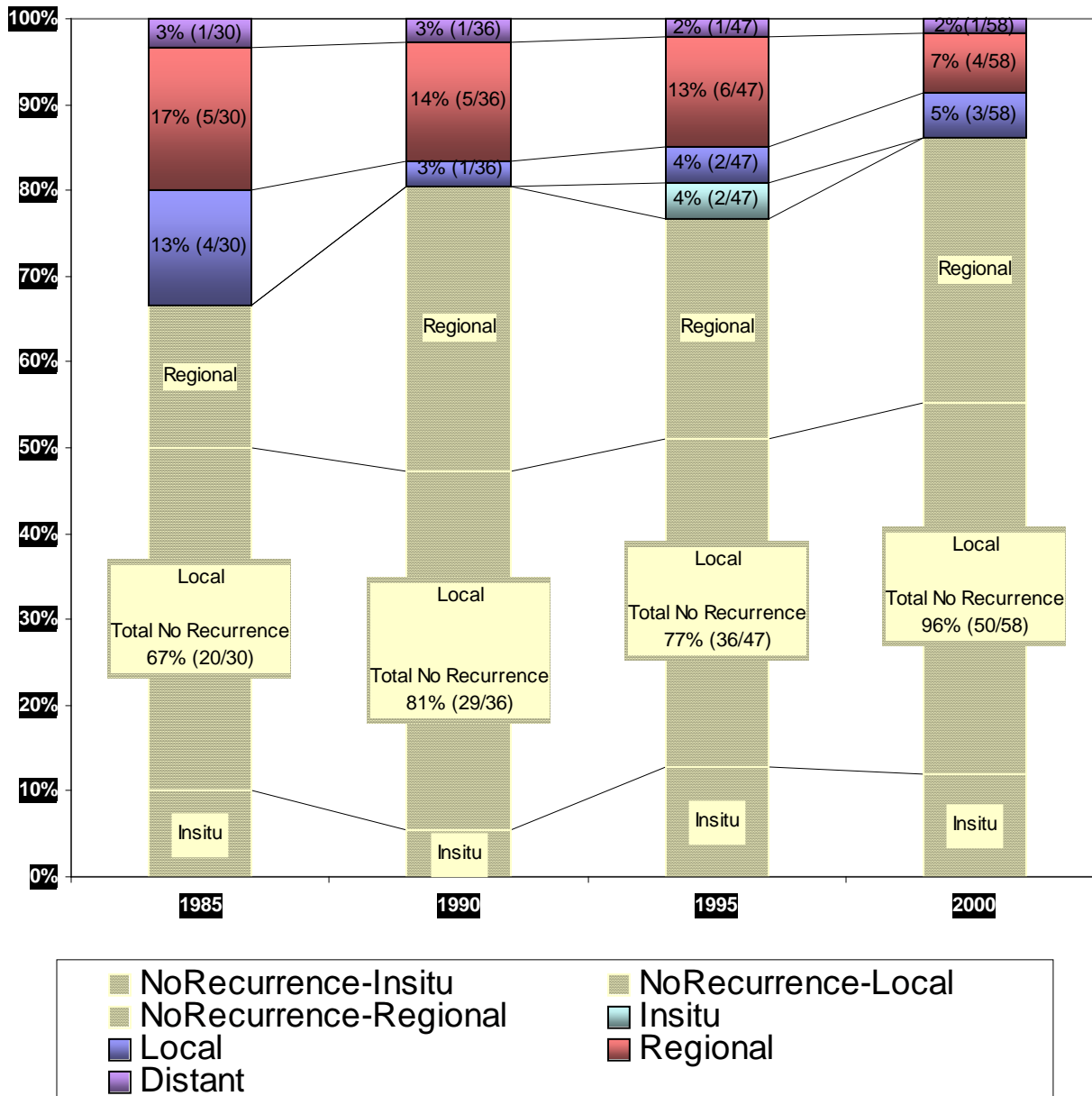


FIGURE 5

Another way to look at this phenomenon is the location or type of recurrence seen in those patients who relapse after either mastectomy or lumpectomy. In **Figure 5**, we can see the type of recurrences and the freedom from recurrence by the stage of the cancer at the diagnosis in those patients who had mastectomy.

Recurrence by Stage at Diagnosis After Lumpectomy Years 1985 1990 1995 2000

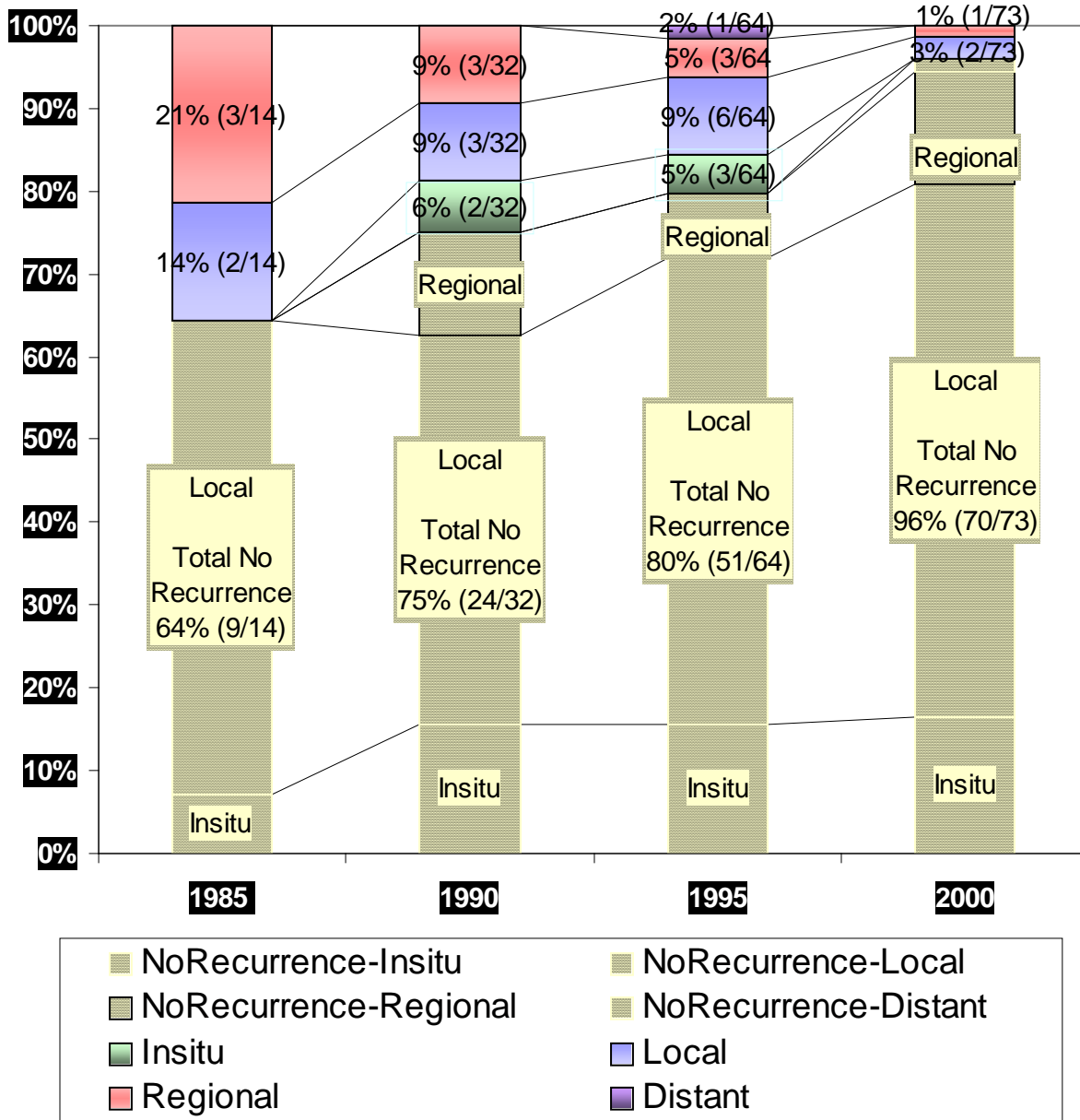


FIGURE 6

In **Figure 6**, we see the same data for those patients who have had lumpectomy. It is clear from both figures that the percent of patients with no recurrence has raised steadily from 1985 to 2000. There is essentially no difference in the pattern of relapses between mastectomies versus lumpectomies other than the minimal risk ($29/183 = 16\%$) of local recurrence within the breast. If we

look at an 86% chance of remaining disease free after mastectomy in our year 2000 patients and a 96% chance of remaining cancer free in our year 2000 lumpectomy patients it is clear we are making significant strides in our primary treatment of breast cancer.

An additional factor must be taken into account when considering the slightly higher risk of relapse or recurrence in mastectomy patients versus lumpectomy patients and this is how the decision is made. The oncologists and surgeons choose the most appropriate operation for the patient’s medical and anatomical situation while patients may choose treatment based on other non-medical factors including recommendation of friends, pre-conceived ideas of risk of lumpectomy versus mastectomy, or distance to be traveled to reach a radiation therapy facility.

Table 1.

CHARACTERISTICS OF INVASIVE CANCER THAT RECURRED

Year	Mastectomy			Lumpectomy		
	# of Cases	Mean Size (Cm)	Mean # of Nodes	# of Cases	Size (CM)	# of Nodes
1985	10	5.0	4.2	5	2.5	2.2
1990	7	3.2	4.8	8	1.8	<1.0
1995	11	2.5	1.6	12	2.3	1.6
2000	9	5.3	1.8	3	2.1	<1
Mean		3.9	3.0		2.2	1.4

Table 1 shows that indeed the patients whom had mastectomy had more advanced and therefore worse prognosis disease then those patients who had lumpectomy. Looking solely at those patients that had recurrences we see that the mean tumor size was 3.9 centimeters and the mean number of nodes was 3 in mastectomy patients while in those patients who had a lumpectomy the mean tumor size was only 2.2 centimeters and the mean number of nodes was 1.4. Since the size of the tumor and the number of nodes are two of the main prognostic factors in determining the outcome of breast cancer we should expect to see a slightly higher rate of relapse, especially regional relapse and distant relapse, in those patients who had mastectomies.

The marked progress we've seen in the treatment of breast cancer over the last two decades is a result of new scientific insights into cancer, the discovery of new drugs, and the testing of their application on patients through randomized clinical trials. For over 25 years, the Marquette General Hospital Cancer Center has been an active and contributing member of the NSABP, one of the Cooperative Clinical Trials Groups sponsored by the National Cancer Institute. Through our participation in this group, we have been able to offer our patients participation in "cutting edge" studies and technology.

In 1976, the NSABP instituted the B-06 trial a comparison of total mastectomy versus lumpectomy versus lumpectomy plus radiation therapy for the treatment of invasive breast cancer. This trial showed that lumpectomy followed by breast radiation is an appropriate therapy for women with breast cancer provided that the margins of resected specimens are free of tumor and acceptable cosmetic results can be obtained. Marquette General Hospital Cancer Center and its surgeons was the second largest contributor of patients in the State of Michigan to this study.

Several years prior to the conclusion of the B-06 trial the NSABP had demonstrated in its B-04 study that there was no advantage to the "traditional" radical mastectomy, which would remove not only the breast but also the underlying muscle down to the ribs and extensively resect the structures in the axilla. This study demonstrated that the simple complete removal of the breast had the same results. The study moreover demonstrated that the accepted practice at the time of giving radiation therapy to the chest wall and axilla of all patients who had had breast cancer and especially all those who had one or two positive lymph nodes did not improve the cure rate and did not even improve the recurrence rate, but rather increased the risk of side affects.

In the 1970's, the NSABP also demonstrated in several of its trials that relatively mild chemotherapy could increase the cure rate and decrease the risk of relapse or recurrence. At about the same time, NSABP trials showed that the administration of the oral anti-estrogen medication Tamoxifen could increase the cure rate in those women who had appropriate surgery and radiation.

Since the conclusion of these early trials in the late 1970's and early 1980's, additional refinements in surgical techniques, radiation therapy techniques and chemotherapy and hormonal therapy

medications have further improved the cure rate and decreased the relapse rate for patients with breast cancer.

Most recently, Marquette General Hospital Cancer Center patients have had the opportunity to participate in two landmark trials of the NSABP, which have shown that breast cancer can be prevented in about 50% of higher risk women by the use of Tamoxifen or Raloxifene. These trials, the P-1 Breast Cancer Prevention Trial and STAR (Study of Tamoxifen and Raloxifene) Trial, involved a total of over 40,000 women throughout North America.

Not only has this availability of clinical trials allowed women in the Upper Peninsula to participate in breast cancer treatment and prevention methods before they were available to the general public, but it has also allowed the women of the Upper Peninsula to greatly contribute to the increasing health of patients throughout North America and the world.

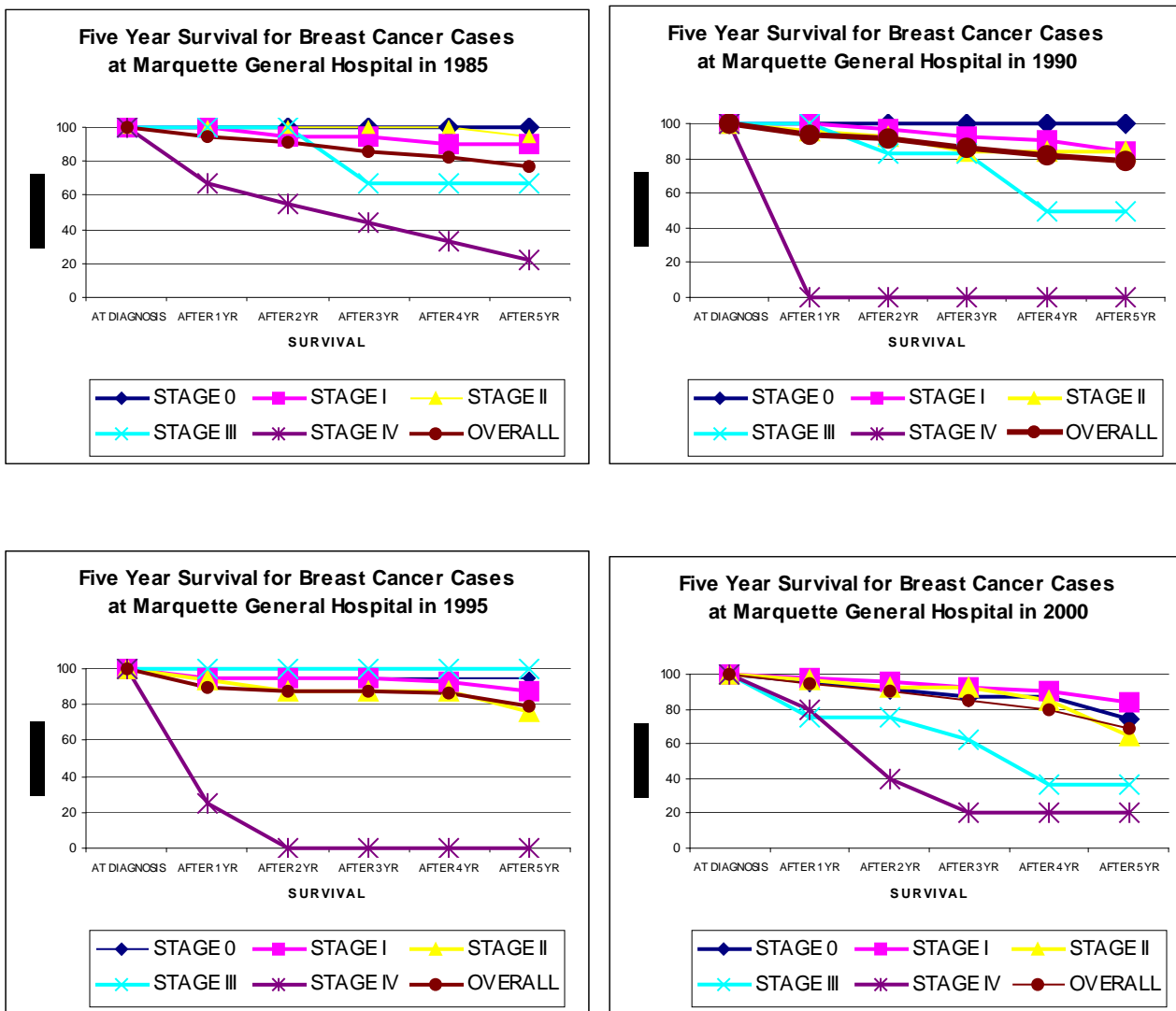
Very recently, we have participated in clinical trials, which demonstrated that antibodies against some breast cancer cells, such as Herceptin, could, in appropriate patients, decrease the risk of those cancers recurring by up to 50%. Results of tissue and blood samples donated at the time of surgery and routine blood draws are sent to the tissue bank of the NSABP in Pittsburgh. This has allowed development of genetic testing of some early breast cancers to determine whether or not they will require chemotherapy or only hormonal therapy in addition to their surgery. The genetic micro-array of 21 breast cancer genes developed from the NSABP B-14 and B-24 for breast cancer patient outcomes and tissue tests is now commercially available under the name of *Oncotype-DX* and can help physicians recommend more finely tailored treatment to some of their patients where this testing is appropriate.

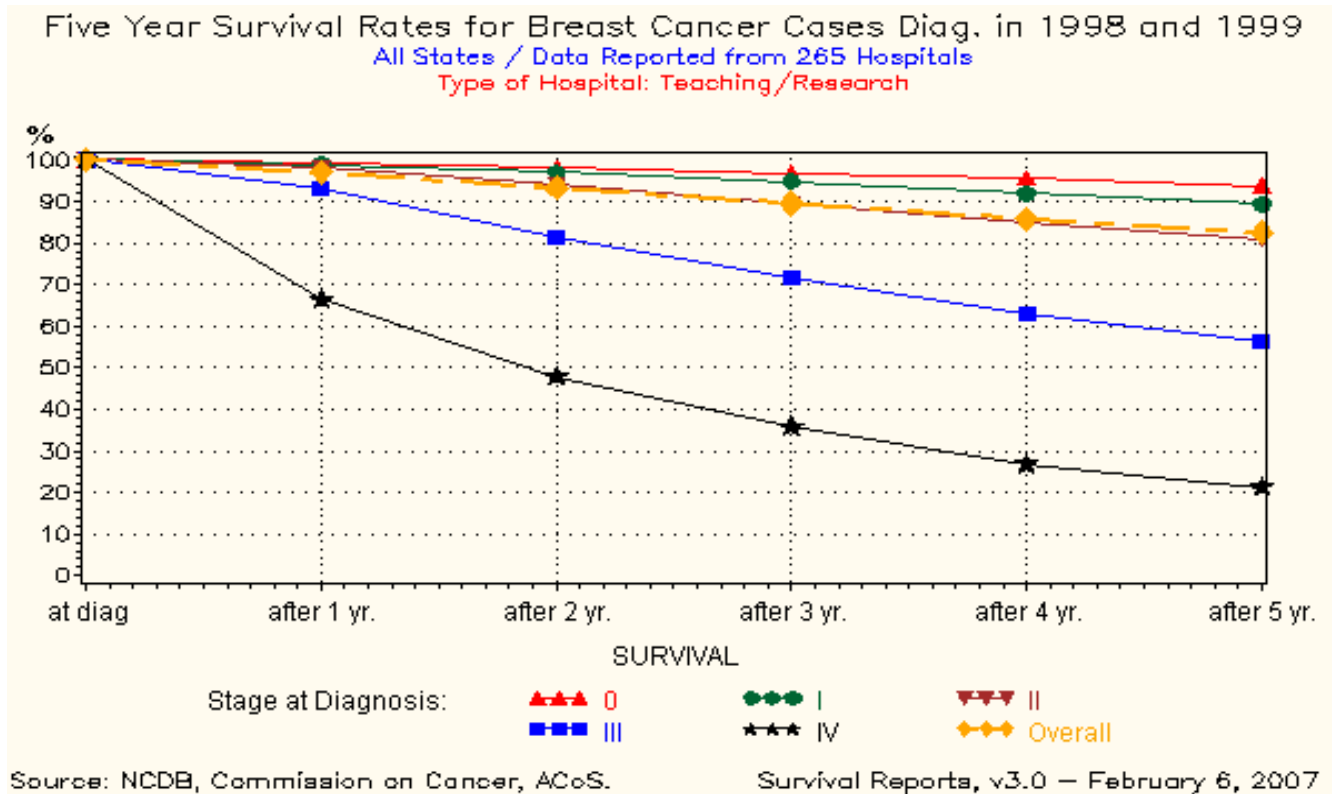
Through our collaboration with the NSABP, we have learned that breast cancers which are too large to be easily removed without leaving a cosmetically undesirable defect, can be shrunk with preoperative chemotherapy 80% of the time. This can make them small enough to allow lumpectomy and radiation and thus preserve the breast. A newly opened clinical trial is testing new and potentially more effective chemotherapy regimens to shrink breast cancers prior to lumpectomy. The tissue removed during biopsy will be studied to eventually construct another type of genetic micro-array that

may help predict the most effective type of chemotherapy medicines for a particular cancer based on a needle biopsy.

An additional clinical trial has recently been approved by the MGH Institutional Review Board comparing radiation therapy to only the part of the breast where the tumor was versus the traditional radiation of the entire breast. National studies of these methods of decreasing the amount of the breast that is radiated have been effective in small “pilot trials” and are now being compared head-to-head not only for cancer effectiveness but also for patient satisfaction and well-being.

FIGURE 7





The breast cancer 5-year survival outcomes for our patients at the Marquette General Hospital Cancer Center compared favorably with those throughout the nation according to these graphs from the National Cancer Database and the MGH Cancer Registry. Nonetheless, we continue to strive to improve our treatment to increase effectiveness and decrease side effects as much as possible. Please visit the Marquette General Hospital Cancer Center website, www.mgh.org for more information or call the Cancer Center office, 906-225-3500 for any inquiries.