Radiation and the Treatment of Breast Cancer

A Cancer Decisions® Report

© Ralph W. Moss, Ph.D.

Introduction

For most of the 19th and 20th centuries, surgery was the sole treatment for breast cancer. Sometimes, radical operations were performed with little prospect of cure. In 1937, the British surgeon Geoffrey L. Keynes (1887-1983) wrote:

> "Widespread operations...have no real justification and the idea of conservative treatment of cancer of the breast may become less repugnant to us" (Keynes 1937).

Keynes, brother of the famous economist John Maynard Keynes, therefore treated 325 women by removing only the breast tumor rather than the entire breast. He reported a 5-year survival rate of 71 percent for patients with stage I disease, which was comparable to what was being achieved at the time with radical mastectomy (Perez and Brady 2003: 1358). Keynes also implanted radium seeds at the site of the excision as well as in the armpit (axilla) to prevent recurrences. This was an early use of radiation therapy to treat breast cancer.

In addition, there were a few non-conformist doctors who believed that radiation by itself, or possibly along with limited surgery, was a safe option for most women with early-stage breast disease. The best-known advocate of this position was Vera Peters, MD (1911-1993), of the Princess Margaret Hospital, Toronto.

We look back today on Keynes and Peters as innovators. But at the time only a few other doctors followed them in their breast-sparing approaches. Most prominent of these was George Crile, Jr., MD (1907-1982), of the Cleveland Clinic, Ohio, the son of one of the founders of that Clinic. George Crile, Jr., the head of general surgery at the Cleveland Clinic, became the first US surgeon to advocate limited surgery for cancer of the breast. His words from half a century ago seem prescient today: "In our haste to stamp out cancer by [the] indiscriminate use of surgery we are forgetting the patient and even disseminating disease," he told a conference in Alabama in 1955. Instead, he said, the medical profession should put more emphasis on "changing the environment in which cancer lives and thrives rather than to develop the perfect operation to alter the course of the disease." He added that radical or extensive surgery "appeared to do more harm than good" (*New York Times*, April 5, 1955).

In fact, for over 15 years, Crile was the *only* American surgeon to offer the option of limited surgery. After he retired he wrote a book, *What Women Should Know About the Breast Cancer Controversy*, which caused a furor when it was published in 1973. Many surgeons of the day assailed it as a threat to women (Crile 1973). (I well remember how some surgeons at my own institution tried to enlist my aid in branding this an "unproven method of cancer management," which was tantamount to calling it "quackery.")

But Crile's book became a bestseller and inspired many women back in those salad days of feminism. Change was in the air. Bernard Fisher, MD (b. 1918), of Pittsburgh, finally organized a randomized controlled trial (RCT) to compare radical vs. conservative treatments (Fisher 1977). His work proved that for most patients lumpectomy plus radiation yielded the same survival rates as radical mastectomy.

It is hard for us now to imagine how daring it was for Fisher to perform this trial. As surgeon Richard Evans, MD has explained:

> "For the first time in history, surgeons did a study in which cancer cells were knowingly left behind, untreated within the lymph nodes of some patients. In some patients (about 20 percent of them) these cancer cells did grow and the cancer-containing lymph nodes had to be removed, several months after the original surgery. Surprisingly, patients treated in this way lived just as long as patients who had their lymph nodes removed at the time of mastectomy."

But that was not all:

> "The study concluded that surgeons could prudently leave a small number of cancer cells within a patient's lymph nodes without threatening her survival. The study further concluded that these cancer cells could grow into a sizable tumor mass…large enough to be felt by the doctor. Allowing tumor cells to grow untreated within a patient seemed contrary to all known principles of sound cancer treatment. It may have been risky, but it proved an important point. This study was greeted with dismay and hostility by many surgeons" (Evans 1980 and Evans 2000).

Eventually, the National Cancer Institute (NCI) and the medical profession as a whole were compelled by the data to accept a combination of lumpectomy plus radiation as a reasonable choice for most cases of early-stage breast cancer. Radiation was usually given in doses of 45 to 50 Grays (Gy), with a further 10 Gy radiation "boost" to the tumor bed (the area from which the tumor was removed). Most textbooks on cancer treatment now recommend this basic form of treatment, which has become known as breast conserving therapy (BCT).

After this combination was accepted, however, a few people began to wonder about the relative contribution of the two modalities to the results. Was it possible that radiation, for all its apparent benefit, did not appreciably increase the overall survival of the women who received it? If so, **was it worth taking it at all?**

Radiation has now become so much a part of breast cancer treatment that it is extremely unusual to see its usefulness or its contribution questioned. Yet it may surprise you to know that there are still many unanswered questions concerning what (if any) long term benefit patients can reasonably expect to gain from radiation therapy following surgery for breast cancer.

Why is this? How much is really known about the use of radiation in the treatment of breast cancer? Is there really a survival advantage to be gained from receiving radiation following breast cancer surgery? What are the risks of radiation therapy, and are patients typically given information concerning those risks at the time treatment decisions are being made? How can there still be uncertainties surrounding a treatment that – after a quarter of a century – has become such a universal part of breast cancer therapy?

In this report we shall take a close look at the scientific evidence that underpins the use of radiation in the treatment of local and regional (stages 0, I, II and operable stage IIIC) breast cancer, and shall discuss both the good and the harm that radiation can do.

Understanding the risk of recurrence

It is an unfortunate fact that breast cancer has a tendency to recur. The goal of radiation is to reduce the risk of recurrence.

Radiation is used in various ways in the treatment of breast cancer, primarily:

- As part of breast conserving therapy (BCT) as a means of preventing recurrence and enabling women to avoid mastectomy;
- After mastectomy in cases that are considered at high risk of recurrence, particularly where the chest wall and axilla (armpit) may be involved;
- As a means of reducing pain and disability (i.e., as a palliative treatment) in advanced breast cancer that is not amenable to surgery.

There is little doubt that radiation following lumpectomy can significantly reduce the chance of a recurrence. For example, a 1995 study by the aforementioned Bernard Fisher and colleagues compared the outcome of mastectomy, lumpectomy plus radiation (a treatment combination that is known as breast conserving therapy, or BCT) and lumpectomy alone without radiation in women who had tumors 4 centimeters (cm) or less in diameter, and who had either negative or positive axillary lymph nodes. After 12 years of follow-up, the cumulative incidence of a recurrence of tumor in the same breast was 35 percent in the group treated with lumpectomy alone vs. 10 percent in the group treated with lumpectomy and breast irradiation (Fisher 1995). Based on this and other studies, **there is no doubt that radiation can indeed reduce the risk of a recurrence in the same breast.**

However, the situation is rather more complicated than this.

Although we are apt to speak about breast cancer generically, as though it were a single disease, breast cancer is in fact an assortment of quite different clinical conditions. Whether a patient will benefit from radiation treatment (and if so, by how much) depends in large measure on individual factors such as the age of the patient, the type, pathology, stage, grade and extent of breast cancer they have.

For example, a 2001 study published in the *Journal of Clinical Oncology* illustrates the different outcomes that can be expected with different breast cancer subgroups. In this study 1,772 patients with early (stage I or II) breast cancer were enrolled, of whom 879 were treated with breast conservation, and 893 with modified radical mastectomy. After 10 years, 10 percent of the patients who had been treated with BCT and 9 percent of the patients who had been treated with mastectomy had experienced a recurrence. The researchers found that factors such as a relatively young age (35-40 years), the size of the original tumor, whether or not the surgical margins were clear at the time of excision, the presence of microvascular invasion (i.e., whether or not the tumor had begun invading the tiny blood and lymphatic vessels in the tissues surrounding the tumor), lobular versus ductal tumor origin (and in the former case the presence of what is called "extensive intraductal component" (or EIC – discussed below) all contributed to the likelihood of recurrence following initial treatment (Voogd 2001).

It is also important to note at the outset that **radiation is not a sure-fire means of preventing the return of breast cancer.** Even among patients who have undergone BCT, somewhere between 10 and 30 percent will suffer a recurrence of their cancer within 10 years. Recurrences of this sort may be local (i.e., in the previously affected breast); regional (i.e., in the lymph nodes that are anatomically close to the breast); or distant (i.e., in a part of the body far removed from the original tumor).

As you can see, there are many factors to consider in evaluating the potential usefulness of radiation in any particular case. **Any sweeping generalizations about the benefit of radiation therapy should be carefully examined.** The tendency of radiation oncologists to speak about treatment benefit in terms of relative versus absolute risk reduction is a prime example.

Relative vs. Absolute Risk

It is extremely important for breast cancer patients to understand exactly what radiation oncologists mean when they talk about reducing the risk of recurrence. Risk of any kind, including risk of disease recurrence, can be expressed in one of two ways: either as *absolute risk*, or as *relative risk* – and the two are very different.

A reduction in absolute risk refers to the actual difference in risk between those who receive a treatment and those who do not. By contrast, relative risk reduction is expressed as *the percentage decrease in risk* between those who receive a treatment compared to those who do not. When risk is expressed as a percentage in this way, the benefit always appears significantly larger and more impressive than it actually is. More often than not, especially when they are trying to persuade patients to take a treatment, physicians use relative risk as their preferred measure.

To illustrate the way in which false impressions of benefit can be created by using relative instead of absolute risk, let us consider a disease that occurs in 2 percent of the population. If by taking a drug only 1.5 percent of the population succumbs to the disease

in question, then it would be quite accurate to say that the drug reduces the risk of the disease by 25 percent. This figure expresses the benefit of the drug as a relative risk reduction.

But absolute risk is a calculation that is based on what your risk is to begin with. Since the risk of developing the disease is only 2 percent to start with, the benefit of our hypothetical drug does not seem quite so unequivocal: by taking the drug, 1.5 per hundred people will develop the disease instead of 2 per hundred. Which sounds more impressive to you – a risk reduction of 25 percent (relative risk) or a risk reduction of 0.5 percent (absolute risk)?

To further illustrate the way in which gains expressed as relative risk distort perspective in medical reporting, consider the example of a 2004 meta-analysis published in the *Journal of the National Cancer Institute*. In this study, researchers pooled the results of published randomized, controlled trials comparing outcomes in women who received radiation following lumpectomy to those who did not receive radiation. In this way, the researchers hoped to determine whether radiation following breast conserving surgery had measurable consequences for patient survival. They found that there was an *increase in the relative risk of mortality of 8.6 percent for those women who did not undergo radiation.* However, looked at another way, since the study population had a 90 percent 5-year survival rate to begin with, the addition of radiation raised that expectation to 90.86 percent – hardly an overwhelming gain (Vin-Hung 2004).

The authors of this study explicitly pointed out the need to consider the characteristics of the individual patient in any assessment of likely gains from radiation therapy. In their discussion, they wrote:

"On an individual level, it is less obvious whether all patients should receive radiotherapy. Decision making requires an assessment of absolute risks, and the decision may depend on the histopathologic characteristics of the tumor and on a woman's comorbidities and life expectancy. For example, even if we accept that the mortality increase of 8.6 percent applies to all women, a 65-year-old woman with a 1-cm estrogen receptor–positive tumor and negative lymph nodes would have a minuscule improvement in survival due to radiotherapy. According to the SEER data, her chances of survival at 5 years and 10 years are 95 percent and 85 percent, respectively. With an estimated 8.6 percent relative excess mortality without radiotherapy…the absolute survival benefit with radiotherapy is 0.5 percent and 1.5 percent, respectively" (Vin-Hung 2004).

So when your radiation oncologist speaks to you about the benefit of radiation in reducing the risk of breast cancer recurrence, make sure you ask him or her to express the benefit in terms of **absolute, rather than relative, risk**. This way, you will get a far more accurate sense of the treatment's worth.

In summary it can be said that global generalizations about the effectiveness of radiation therapy in the treatment of breast cancer are difficult to arrive at. A great deal depends on the individual patient characteristics (age and menopausal status, for example) as well as the type, grade and stage of breast cancer that is being treated. Assessments of the likely benefit of radiation treatment can only be reliably made when these individual characteristics are taken into consideration. While certain general principles are valid for a wide spectrum of patients, specific treatment recommendations must ultimately be tailored to fit the individual. It is also extremely important to establish whether the purported benefit in any particular case is being expressed in terms of absolute or relative risk reduction.

The use of radiation in different stages of breast cancer

For the sake of this discussion we will follow the example of the National Cancer Institute's Professional PDQ® Web site (www.cancer.gov), and separate the disease into general categories by stage, thus:

- Stage 0: ductal carcinoma in situ (DCIS)
- Stages I, II, IIIA and operable stage IIIC invasive breast cancer
- Stages IIIB, inoperable stage IIIC, stage IV and recurrent breast cancer

In DCIS, and stages I, II, IIIA and operable IIIC breast cancer**, the role of radiation is to prevent recurrence following surgery.** The incidence of local-regional recurrence after BCT for stage 0, I and II patients ranges between 5 percent and 22 percent (Huston 2005). However, even here there are disagreements: some estimates put the risk range of recurrence following BCT for DCIS at between 15 percent and 30 percent (Gauthier 2007).

In stages IIIB, inoperable IIIC, stage IV and recurrent breast cancer, the purpose of radiation therapy is different. Here its role is no longer preventive, but palliative. This report focuses on the use of radiation in a preventive capacity. (Its palliative role is an extensive and entirely separate topic, which we do not address here.)

DCIS

Ductal carcinoma in situ (DCIS) is a premalignant, noninvasive tissue change that may develop within the ducts of the breast. Although DCIS carries the name "carcinoma," it is not yet strictly speaking a full-blown malignancy, but is regarded as one of several risk factors for the eventual development of invasive cancer.

Because of the increased use of screening mammography, DCIS, once a rare diagnosis of uncertain significance, has become a very frequently encountered disease. DCIS now constitutes up to 30 percent of breast cancer diagnoses - even though it is not strictly speaking cancer at all. (This mischaracterization of DCIS as frank cancer has

implications for cancer statistics, since it artificially inflates the figures for incidence of cancer, thereby making cancer "cure" statistics look considerably more robust than they actually are.)

Wherever possible, lumpectomy (also known as breast conserving surgery, or BCS) is the surgical approach of choice for DCIS. However, DCIS is not always a well-circumscribed lesion (area of abnormality). It can be diffuse, extending outwards into normal tissue in such a way as to make "clean" surgical removal very difficult. There are also various different cellular types involved in DCIS that are associated with a greater likelihood of later malignancy, as well as a greater likelihood of recurrence following surgical resection – for example, the presence of what is known as "extensive intraductal component" (EIC), or lesions of the "comedo" type, which exhibit areas of dead (necrotic) tissue. It is perhaps not surprising that for many years the customary treatment for DCIS was mastectomy - and in some circumstances still is. DCIS is regarded with particular seriousness when it is extensive or multifocal – that is, when the abnormality is not confined to one particular area but is found in multiple or diffuse areas within the breast. Under these circumstances mastectomy makes sense.

Therefore it is important to understand at the outset that DCIS can take many forms, some of which are significantly more likely than others to become invasive, and some of which are harder to remove successfully. When we speak about DCIS here, we are using a blanket term to describe a condition that in fact has many faces. Please bear this in mind as we progress through the discussion.

There are no randomized clinical studies specifically comparing the outcome of treating DCIS with mastectomy alone (i.e., without radiation afterwards) versus lumpectomy (breast-conserving surgery) followed by radiation. So, how do we know that radiation treatment really adds anything to simple lumpectomy (when possible) in the treatment of DCIS? There is some indirect evidence.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-17, organized by the aforementioned Dr. Bernard Fisher, randomly assigned 818 women with localized DCIS following surgery (excisional biopsy) to receive either breast irradiation (50 Gy) or no further therapy (Fisher 1998). The incidence of either a recurrence of DCIS or a new invasive breast cancer occurring in that same breast **was reduced from 26 to 12 percent by the addition of radiation to surgery.**

As Dr. Fisher wrote: "Incidence of local-regional and distant events remained similar in both treatment groups…" (Fisher 1998). Notice that while radiation therapy reduced the rate of local recurrence it did not change either the regional or distant recurrence rate.

This is unquestionably a positive effect. Yet as we shall see again and again during this discussion, while adding radiation after lumpectomy does significantly reduce the likelihood of recurrence in the same breast - i.e., it improves local control – the question

of whether radiation actually improves survival (which is mostly tied to the widespread dissemination of disease) is far from certain.

DCIS patients, when weighing the risks and benefits of post-surgical (adjuvant) radiation treatment, should therefore understand that while radiation definitely does reduce the risk of recurrence in the same breast, it does not diminish the risk of further DCIS or invasive breast cancer occurring in the opposite breast, and neither does it improve overall survival. However, since overall survival following uncomplicated DCIS is already extremely high, the fact that radiation treatment does not improve survival is probably not going to weigh as heavily in decision-making as the fact that the risk of local recurrence is significantly reduced by radiation.

Similarly, for women whose DCIS displays unfavorable characteristics such as extensive intraductal component (EIC) or 'comedo' histology (see above), the risks associated with the condition (including the risk of recurrence) are proportionately higher. Under these circumstances, the benefit of undergoing radiation may seem more clear-cut.

Stages I, II, IIIA and operable stage IIIC

These stages of breast cancer, although they differ widely in terms of prognosis, are commonly treated in similar ways, and thus are grouped together here (again, following the classification of the National Cancer Institute). The patient typically undergoes breast conserving therapy – i.e., surgery followed by adjuvant treatment – usually both radiation and chemotherapy – and long-term hormonal therapy.

Traditionally, surgery meant the Halsted radical mastectomy, but, largely as a result of Bernard Fisher's work, radical mastectomy has increasingly been replaced by lumpectomy (also called breast-conserving surgery or BCS). External-beam radiation therapy is usually given after surgery (and, where applicable, chemotherapy) with doses to the entire breast of 45 Grays (Gy) to 50 Gy, in 1.8 Gy to 2.0 Gy daily fractions over a five-week period.

An additional localized dose, or 'boost,' is commonly delivered to the tumor bed. The boost can be delivered either by external-beam radiation or by using some form of radioactive implants (a technique called brachytherapy). One randomized European trial is often cited in support of boosting: it showed that the addition of a 10 Gy boost of radiation reduced the risk of local recurrence. This is true, but in absolute terms the improvement was *less than one percent,* from 4.5 percent to 3.6 percent. The follow-up time for this observation was also short, averaging just 3.3 years (Romestaing 1997). **This seems like a slim reed on which to hang such a widespread practice.**

In fact a Swedish retrospective study challenged the basis of this practice by analyzing which patients really did seem to benefit from a boost, and which did not. The study found that the following categories of patients stood to gain significantly from boosting:

- Patients who did not receive adjuvant chemotherapy;
- Patients with high-risk tumor characteristics; and
- Patients younger than 40 years of age, regardless of the type of tumor involved.

In other categories of patients the benefits of boosting are far less apparent (Kurtz 2001).

The question of whether direct radiation to the armpit (axilla) is beneficial in cases where positive lymph nodes have been discovered also remains unsettled. A large-scale phase III clinical study is currently in progress to attempt to address this question, but results are not expected until 2009.

Evaluating radiation's contribution to survival

The role of radiation therapy in breast cancer was the first issue in all of oncology to be addressed by a randomized, controlled clinical trial (RCT). Although that first clinical trial took place in 1948, there is still considerable uncertainty over the actual contribution of such treatment (Cuzick 2000).

Recurrence of breast cancer following treatment is a psychologically traumatic event. There is no doubt that radiation is an effective way of decreasing the likelihood of a local recurrence of breast cancer within the irradiated field. In fact, the rate of local recurrence can be reduced by as much as 30 percent through the use of postoperative radiation. The prevention of local recurrence is thus clearly radiation's strong suit and for that reason is widely used in this context. Reducing the possibility of recurrence undoubtedly contributes to patients' peace of mind.

Yet, at the same time, **the question of whether or not radiation actually increases overall survival remains controversial**. This is admittedly a paradox. How can one prevent recurrences yet not increase actual survival? Richard Evans, MD, has argued that *local* recurrences after breast conserving treatment are not intrinsically ominous and do not necessarily imply a new, and more sinister, phase of the disease, especially if the recurrence is of a non-invasive type (e.g., DCIS). However, *regional* recurrences (i.e., in the supraclavicular (above the collar bone) or axillary lymph nodes, or in or near the chest wall are typically more serious than a strictly local recurrence, and distant recurrence is more serious still. Furthermore, a recurrent cancer, even a local one, may not always be identical to the original tumor in terms of its pathology, but may have a different and possibly less favorable profile.

So what evidence is there that radiation as part of BCT actually prolongs life? A 2005 study which looked at pooled data found that 15-year breast cancer mortality was reduced from 35.9 percent to 30.5 percent in women who received radiation therapy following lumpectomy. This suggested (although it did not prove) that there may be a 5 percent reduction in breast cancer-related deaths for women who underwent radiation treatment (Clarke 2005).

However, a very large pooled analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) and published in *The Lancet* had earlier made the disturbing point that while radiation conferred a reduction of almost two thirds in the rate of local recurrence (8.8 percent versus 27.2 percent over 10 years), and while radiation reduced annual breast cancer mortality rates by 13 percent, it *increased* annual mortality rates from other (radiation-induced) causes such as vascular and cardiac damage by 21 percent. **The analysis concluded that radiotherapy could be responsible for an increase in 20-year survival of about 2-4 percent. However, this increase would be more than offset by the radiation-induced mortality increase particularly in older patients.** (EBCTCG Lancet 2000). Here is the actual wording of the study:

> "Overall 20-year survival was 37.1 percent with radiotherapy versus 35.9 percent control… on average after year 2, radiotherapy reduced annual mortality rates from breast cancer by 13.2 percent (SE 2.5) but increased those from other causes by 21.2 percent. ...Radiotherapy regimens able to produce the two-thirds reduction in local recurrence seen in these trials, but without long-term hazard, would be expected to produce an absolute increase in 20-year survival of about 2-4 percent (except for women at particularly low risk of local recurrence). The average hazard seen in these trials would, however, reduce this 20-year survival benefit in young women and reverse it in older women."

The significance of recurrence in breast cancer

Many - probably most - women accept their oncologist's recommendation to follow conservative surgery with adjuvant radiation. Doctors often tacitly impart the impression that a recurrence of breast cancer is a dire event, likely to lead to death, and must therefore be prevented at any cost. Yet we see that there is disagreement whether, statistically, women who have just had conservative surgery, without radiation therapy, actually do have an increased risk of death.

Richard Evans, MD, has an explanation for this paradox. Evans was a student of the celebrated John S. Stehlin, Jr., MD, of Houston, Texas, who (like George Crile, Jr.) taught that radical surgery was not always necessary in treating breast cancer. Evans followed Stehlin in becoming an early and outspoken advocate of conservative, organ-sparing surgery. In 1980, when lumpectomy was first coming into vogue, Evans postulated that there were fundamentally different kinds of recurrences in breast cancer.

The first type of recurrence, said Evans, is within the field of the initial surgical operation, including the surgical scar. (In patients who are treated with radical mastectomy, this may include the chest wall and the axilla, or armpit). A recurrence of this kind in a woman who has already had the most radical breast cancer surgery may indeed be a marker of the systemic spread of the cancer. There is no disputing, said Evans, that, given only the treatment options available at the time, there was a grave prognosis associated with this sort of recurrence.

Why? When a woman has had a mastectomy the breast tissue on the affected side has (by definition) been almost all removed. The recurrence therefore is unlikely to have originated from the affected breast. It is more likely to have originated in some site distant from the breast scar, and to have traveled via the bloodstream (or possibly the lymphatic system) back to the site of the original surgery, rather like a pigeon coming home to roost.

This first type of recurrence is therefore an indication that there were circulating cancer cells left in the woman's body. This type of recurrence is an "early and obvious manifestation of advanced disease…usually appearing before the distant metastasis is discovered," said Evans in a cogent presentation of this argument written for the layperson (Evans 2000).

But there is a second type of recurrence, which was not a "recurrence" at all (in the sense given in the example above) but should more accurately be called the *local persistence* of the original disease. Evans defines this as the "emergence of clinically perceptible disease outside the field of the initial surgical treatment." This includes any breast tissue that was left after limited surgery, the adjacent lymphatic tissue, or the contralateral (opposite) breast, as well. This second type of recurrence is not a sign of distant metastatic disease, Evans postulated. The cancer was there in microscopic form and simply grew into a palpable tumor over time.

Evans was not the first to make this observation. Sakari Mustakallio, a pioneering Finnish doctor who treated breast cancer patients with excisional biopsies, followed by low-dose radiation, is considered the first to recognize this concept (Mustakallio 1972). In a case series, he reported a ten-year survival rate, even among those who had had local or regional recurrences, of 74 percent, which was comparable to those treated more radically. A few years later a French group reported similar results (Spitalier 1978).

This second type of recurrence is what usually follows limited (conservative) surgery. To repeat: it arises from the *persistence* of malignant or pre-malignant cells in the breast or nearby lymphatic tissue (lymph nodes), and is not a sign of systemic spread.

Additional support for distinguishing *recurrence* from *persistence* comes from C.D. Haagensen's *Diseases of the Breast*, a celebrated textbook of a generation ago (Haagensen 1971). This text reported on the average length of survival after local recurrence in a group of 73 patients who were treated with radical mastectomy. All of these patients were initially evaluated as stage I. However, those who had recurrences on the chest wall lived on average only 27.5 months, while those who had recurrences in the lymph nodes under the breast bone (so-called parasternal recurrences) lived 67.5 months.

What could account for this striking 40 month difference? Haagensen offered no explanation at the time but Evans plausibly suggested that these breastbone recurrences were a classic form of locally persistent disease. These tumors didn't go away and then come raging back. They remained where they were from the time of the initial surgery only to eventually reveal themselves.

> "While their clinical emergence may alter the patient's prognosis from that associated with stage I to that associated with stage II, they do not carry the grave prognostic significance of traditional 'local recurrence'," Evans wrote in his first contribution to this debate (Evans 1980).

The key statement in Dr. Evans' first paper is this:

> **"A patient who survives a carcinoma of two to three centimeters arising in one breast without developing distant metastases may be expected to survive the recurrence of a similar volume of tumor in adjacent breast or lymph tissue"** (ibid.)

Evans' hypothesis applies only to the clinical emergence of "locally persistent disease." It emphatically does not apply to traditional "local recurrence," which is reappearance of disease within the field of initial surgical treatment.

I have spoken about Evans' ideas on surgery in detail because I believe his theory helps explain why radiation can decrease the rate of local recurrences yet still not significantly improve overall survival for breast cancer patients. The explanation is that radiation therapy is only likely to prevent locally persistent disease, which is caused by cancer cells that remain within the immediate area of the breast and its local lymph nodes. But these small, locally persistent cancers are of no more danger to the woman than the original tumor was; in a real sense, they are *part of* the original tumor.

Evans' hypothesis leads to the presumption that provided that the persistent - or what is commonly called the "recurrent" - lump is discovered and removed when it is approximately the same size as the original tumor, it may be no more dangerous than the original was. And so, Evans concluded, if a woman is willing to face the possibility that her tumor may locally persist, may become clinically evident, and may then need further treatment, she could theoretically avoid adjuvant radiation therapy after lumpectomy. However, for obvious reasons, most women are deeply troubled by the prospect of recurrence and would prefer to do what they can to reduce that risk.

Use of Biomarkers

Since Evans first wrote, understanding of the biology of breast tumors has grown by leaps and bounds. In particular, the use of biomarkers, such as Her2, not to mention estrogen and progesterone receptors, has revolutionized our thinking about the biology oc breast cancer. Thus, I think it would be important to have a recurrent tumor tested to see if it has a similar marker profile and histological type, as the initial tumor had. It is also possible that, due to exposure to prior adjuvant treatments such as radiation and chemotherapy, a recurrent tumor may display an increased degree of invasiveness. Thus, while I accept the basic premise of Evans's thesis, I think decisions concerning how best

to treat a recurrent tumor need to be made, wherever possible, on the basis of currently available testing techniques.

It is also important to distinguish between recurrent lesions of an in situ type (i.e., a further, new episode of DCIS) and those of a more invasive type. The latter are known as "ipsilateral breast tumor recurrences" or IBTR.

Unlike in situ recurrences, which, in keeping with Evans' thesis, pose no excess risk to the patient and are no more intrinsically ominous than the initial lesion, IBTR following optimal prior therapy is generally considered to be a flag for increased risk of distant recurrence and is therefore assumed to be associated with an increased risk of mortality. Furthermore, locoregional recurrences that involve the chest wall and axilla can be very difficult to control, and are often associated with considerable pain and disability.

Because there are so many potential variables to be considered in determining the optimum treatment for IBTR, an experimental clinical decision-making software tool called 'IBTR!' (the exclamation point is intentional) is currently being developed by researchers at the New England Medical Center (NEMC). Physicians can access this tool via the NEMC Web site: http://160.109.101.132/ibtr/).

What if the tumor has already spread beyond the confines of the affected breast? Leaving aside its palliative qualities, can radiation provide any benefit for the woman whose tumor has already metastasized? Breast irradiation does not deliberately target or include the places where distant cancer cells tend to lurk, such as the bone marrow. Indeed, sometimes those cells are already circulating in the bloodstream. Breast irradiation can do nothing about existing microscopic distant metastases, which are the ultimate source of recurrences to the chest wall, the bones, the brain or elsewhere in post-mastectomy patients. It should not therefore affect the rate of the really dangerous recurrences (Evans' "type-one" scenario).

Here then is the essence of the adjuvant radiation dilemma: it is incontestable that radiation reduces the rate of local recurrences (especially when those recurrences are due to persistent disease). But it has also, historically, had little impact on overall survival, and has increased deaths from causes other than breast cancer.

Several randomized, controlled clinical trials have looked directly at the question of whether adjuvant radiation extends survival. These studies vary in terms of the nature of patients selected, the methods of surgery and the type of radiation employed, as well as the inclusion of chemotherapy or hormonal therapy, and the length of follow-up time. Despite these many permutations, the results are consistent. *All show the same marked reduction in the incidence of local recurrence after radiation, and yet none reveals a significant benefit in terms of overall survival.*

National Surgical Breast Project B-06: This study had the longest median follow-up, 144 months (12 years). The local recurrence rate was reduced from 35 percent in those who had surgery alone to 10 percent in those who were also irradiated afterwards. But the median overall survival rates were almost identical: 58 for the surgery group vs. 62 percent for those who received radiation, a difference that was not statistically significant (Fisher 1995).

Swedish study: In the Swedish study there was also a significant difference in the local recurrence rate, of 24 vs. 9 percent. But the ten-year survival rates were identical at 78 percent (Liljgren 1999).

Ontario Study: There was a big difference in the local recurrence rate, of 24 vs. 9 percent. But again, there was no significant difference in the eight-year survival rates, 76 vs. 79 percent (Clark 1996).

Milan III Study: Here, once again, there was a big difference in the local recurrence rate of 18 vs. 2 percent. But again, there was no difference in overall survival. (Veronesi 2003)

Because of its dramatic impact on recurrence rates, radiation therapy is now usually considered a standard adjuvant treatment after limited surgery for breast cancer. However, readers should be aware of the important fact that it has, at best, a small impact on overall survival. That pattern seems quite clear by now, and has been confirmed by numerous studies. The 2007 JNCI article (Hooning 2007, discussed above) showed the probable reason why: even in its post-1980s version, radiation still causes adverse effects on the heart in some patients, which nullify any survival benefit.

The National Cancer Institute's PDQ also reports a few studies that show a "positive" effect of radiation on breast cancer. But these are generally too short-term to yield meaningful data. As we have shown, **the apparent benefits of radiation appear long before the harmful effects start to emerge.** Prof. Jack Cuzick of the Cancer Research UK Centre for Epidemiology, Mathematics and Statistics (formerly the Imperial Cancer Research Fund), whom I find to be one of the most useful commentators on this issue, has remarked on the point:

> "More recent trials have reported larger overall mortality benefits from radiotherapy, but the follow-up from these trials is shorter, so uncertainty remains about the long-term mortality effects, especially for non-breast-cancer deaths" (Cuzick 2000).

The 2007 JNCI article (Hooning 2007) in particular undermined any such premature claims of benefit.

Dangers of radiation

As mentioned above, radiation therapy carries dangers of its own. Radiation has been described as a "complete carcinogen" because it is independently capable of both initiating and promoting second cancers. It can also damage the heart and lungs, contribute to lymphedema, and cause brachial plexopathy (damage to the brachial plexus, the main nerve trunk to the arm). Historically, the damaging effects of radiation have led to increased deaths from various causes: a considerable number of women have inadvertently traded death from iatrogenic causes (i.e., conditions caused unintentionally by treatment itself) for death by breast cancer.

Medical Imaging

The risks of radiation exposure are cumulative. It is a tragic irony that repeated exposure of the breast tissue to ionizing radiation during medical imaging can add significantly to the risk of breast cancer Particularly in younger women, repeated exposure of the breast tissue to radiation increases the risk of subsequently developing breast cancer – a consideration that *should* be taken into account (but typically isn't) in recommendations for screening mammography. (Currently, women are encouraged to begin having annual mammograms at age 40.) One study, published in the *New England Journal of Medicine*, concluded:

> "Our additive model for lifetime risk predicts that exposure to 1 cGy at the age of 40 increases the number of deaths from breast cancer by 42 per million women" (Miller 1989).

Since that study was published, radiographic techniques have changed greatly. A heightened consciousness among mammographers and radiation oncologists of the risks inherent in radiation exposure has led to significant improvements in the dosages associated with mammography. Even so, radiation from yearly mammograms during ages 40-49 has been estimated to cause 1 additional breast cancer death per 10,000 women (NIH Consensus Statement on Breast Cancer Screening for Women Ages 40-49).

Heart Damage

The fact that breast irradiation can increase the risk of heart disease is not a new finding. Reports of heart damage from radiation began emerging as early as 1927, but even so, for the first 60 years of the 20th century, the heart was routinely described a "radioresistant" organ (i.e., resistant to the negative effects of radiation) and cardiac complications of radiation therapy were often described as rare and insignificant.

It took systematic studies, over several decades, primarily by Prof. Luis Fajardo of Stanford University and others, to dispel this dangerous misperception (Cohn 1967 and Fajardo 1968). During the 1970s a Swedish team conducted a randomized, controlled clinical trial (RCT) involving 960 breast cancer patients. These patients received either surgery alone or surgery preceded or followed by radiation. A total of 58 patients had

heart attacks during the 20-year follow-up period. **Patients who had received high doses of radiation had twice the risk of heart attacks as those who did not**. There was also a 2.5-fold increased risk of ischemic heart disease, i.e., the kind caused by a decrease in the blood supply to the heart.

The difference between the two groups only began to appear after 4 to 5 years and the heart attack incidence rates continued to increase in the irradiated group for 10 to 12 years. There was some evidence that most of the deaths were due to radiation-induced damage to the small blood vessels of the heart (Gyenes 1998).

In another study, the strength of the heart was measured 15 to 20 years after treatment for breast cancer. It was found that 25 percent of patients treated with radiation to the left breast had heart-related problems on standard stress tests, compared to none in the control group. The authors' main conclusion was that left-sided chest irradiation (which more frequently affects the heart) may represent a risk factor for ischemic heart disease (Gyenes 1994).

Because of studies such these, modifications were made in the 1980s to the way that radiation was delivered after surgery for breast cancer. Radiation oncologists have often claimed that with more precise equipment and techniques, heart damage was no longer a clinically relevant problem. This seemed plausible. However, the latest study shows that such complacency may have been ill-founded.

While admitting that radiation therapy caused some deaths by heart disease in the past, the oncology profession has claimed that radiation-induced cardiac mortality was a thing of the past. Citing improved ways of delivering radiation therapy, they asserted that the delivery of radiation had improved to the point that it no longer caused this sort of collateral damage. The dangers of radiation to the heart were almost universally dismissed as a thing of the past, and countless women were told that the procedures performed on them were safe.

In *Clinical Oncology*, a textbook published in 2001 by the American Cancer Society, the seriousness of the danger was minimized half a dozen times in the course of just two paragraphs:

> "Cardiac toxicity due to irradiation is rare…. Effects on the endocardium are rare…. Below a total dose of 4500 cGy, radiation-induced damage is uncommon…. Tamponade [an obstruction to filling of the heart by pressure from a surrounding collection of fluid, ed.] occurs infrequently. In general, pericarditis is self-limited… Chronic pericarditis is uncommon. Acute myocardial infarction [is] rare..." (Lenhard 2001: 243-244).

Many Web sites similarly continue to claim that modern radiation therapy is entirely safe. For example:

> "Radiation therapy techniques have changed dramatically since then [the 1970s, ed.]. New technology allows doctors to use the lowest dose of radiation possible. They can also more precisely target the radiation to the breast and away from the heart—so the heart receives a minimal amount or none at all" (www.breastcancer.org)

"Since modern radiotherapy techniques designed to treat the chest wall now exclude the heart from radiation...it is anticipated that cardiac problems will be reduced," according to a statement from the Royal College of Radiologists. The key word here was "anticipated."

Yet the same authors conceded: "There is a need for further randomized trials to examine whether, with modern techniques, chest wall radiotherapy can improve overall survival, particularly in node-positive patients" (Royal 2002).

According to Prof. Cuzick, writing in 2000, it was still uncertain "whether the newer kinds of radiotherapy, which allow for more accurate delivery of the dose, can achieve reduction in breast cancer mortality without increasing cardiovascular mortality."

The Hooning study published in the March 7, 2007 issue of the *Journal of the National Cancer Institute* (JNCI) has seemingly settled that issue. It has shown that **postoperative radiation does indeed increases the risk of heart disease in many women who receive it following surgery for breast cancer.** Using modern radiation delivery techniques, developed in the 1980s, the pattern of harm has been *shifted*, but it has not been removed.

In the JNCI study, researchers at the Netherlands Cancer Institute in Amsterdam evaluated a total of 4,414 breast cancer patients who survived for at least 10 years after receiving radiotherapy between the years 1970 and 1986. The patients were followed for a median of 18 years. These patients' rates of cardiovascular disease were then compared with those seen in the general population (Hooning 2007). In other words, this was a very large and prolonged study.

There were a total of 942 "cardiovascular events" during the follow-up period. The good news was that radiation therapy *limited to the breast itself* did not increase the risk of cardiovascular disease. However, inclusion of either the left or right internal mammary chain of lymph nodes *did* significantly increase that risk.

Not surprisingly, internal mammary chain irradiation performed during the "bad old days" of the 1970s increased the risk of a heart attack (myocardial infarction) by a factor of 2.55 compared to no radiation, and raised the risk of congestive heart failure 1.72-fold. However, radiotherapy given in the 1980s was *also* associated with an increased risk of heart disease: **a 2.66-fold greater risk of heart failure and a 3.17-fold greater risk of dysfunctional heart valves**. (This was one of the first studies to investigate radiation-related heart valve failure.)

In the 1980s, it also became common to add adjuvant chemotherapy to radiotherapy. The standard chemotherapy regimen used during the 1980s was CMF (which stands for the three drug combination of cyclophosphamide, methotrexate and 5-fluorouracil). However, this JNCI study found that the addition of CMF chemotherapy to radiation conferred **a 1.85-fold increased risk** of congestive heart failure. This finding has caused a great deal of surprise since neither these drugs, singly or in combination, were ever thought to be particularly cardiotoxic (Hooning 2007).

It is chilling to realize that nowadays CMF chemotherapy has largely been replaced by regimens based around so-called anthracycline drugs, the most prominent of which is Adriamycin (doxorubicin). This class of drugs is already well known to carry its own risks of cardiotoxicity, including life-threatening congestive heart failure. This risk increases exponentially the greater the lifetime dose.

A review in the journal *Seminars of Oncology* concluded: "10 percent to 26 percent of patients administered cumulative anthracycline doses above those recommended… develop congestive heart failure, and that more than 50 percent of patients administered these doses will experience measurable functional impairment months to years after the end of therapy." Also, the susceptibility of patients to anthracycline-induced cardiotoxicity varies widely, with a dramatic increase **with advancing age** (Jensen 2006).

The risk is further augmented by the addition of **Herceptin** (trastuzumab), another cardiotoxic drug that is frequently used in the treatment of breast cancer. Herceptin can itself cause heart damage ranging from mild and transient to life-threatening congestive heart failure. To quote the package insert warning, mandated by the U.S. Food and Drug Administration (FDA), Herceptin "has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke." (Mural thrombosis refers to the formation of a blood clot on the lining of the heart, or on the wall of a large blood vessel).

Unfortunately, Herceptin may also work in combination with radiation to damage the cardiovascular system (Shapiro 1998). Since Herceptin is a relatively new drug (first approved in September 1998), the long-term effects of this combined radiation and chemotherapy are unknown. In one study, however, the overall incidence of congestive heart failure was 0.8 percent for women receiving Adriamycin alone, but 2.6 percent for patients receiving both Adriamycin and radiation to the left breast. This study included several fatalities (Valagussa 1994). In another study, immediate and harmful effects on the heart were seen in up to 41 percent of patients (Lenhard 2001).

Adriamycin has a long-term effect on the heart muscle. In a clinical trial of women with metastatic breast cancer, 29 percent of the patients who received Adriamycin developed cardiotoxicity (Harris 2002). In another study Adriamycin was associated with a significant increase in the risk of death in patients who were already affected by congestive heart failure (Lenhard 2001). Unfortunately, discerning which patients are most likely to suffer heart damage from Adriamycin is still an inexact science. The total dose of the drug, the age of the patient, preexisting heart problems and concurrent therapies are all considered risk factors.

In view of these ominous warnings, studies focusing on the cumulative cardiac risk of radiation therapy in patients who have also been given Adriamycin and/or Herceptin-containing chemotherapy regimens are urgently needed.

The JNCI study also found a disturbing **three-fold increase in the risk of heart attacks among radiotherapy-treated patients who also smoked tobacco**. The authors properly cautioned: "Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease" (Hooning 2007). Easier said than done! The more logical solution would surely be to refrain from giving adjuvant radiation to patients who insist on smoking.

The 2007 JNCI paper is not the only study to demonstrate that residual damage from left breast irradiation is associated with a significantly increased mortality due to cardiac damage. A paper in the *Journal of Clinical Oncology* in late 2007 compared a group of women who received conventional tangential beam radiation for right-sided breast cancer with a similar group who received the same type of radiation but to their left breast. At the outset, both groups had the same estimated 10-year risk of coronary artery disease (7 percent). At 12 years post-treatment, a significantly higher proportion of women who received left-sided radiation exhibited cardiac abnormalities on stress testing (59 percent versus 8 percent). Even more disturbing was the fact that 70 percent of the women who exhibited stress test abnormalities had lesions in their left anterior descending coronary artery. Thirteen of these women underwent cardiac catheterization, and 12 out of 13 (92 percent) were shown to have coronary stenosis (narrowing) at that time (Correa 2007).

It is worth repeating that although it is common to hear such concerns dismissed as being a problem that accompanied older techniques of radiation delivery, the question of heart damage following breast irradiation is still an issue with modern radiation treatment. As Robert G. Prosnitz, MD, and Lawrence B. Marks, MD, of the Department of Radiation Oncology at Duke University, pointed out in an editorial in the *Journal of Clinical Oncology*, complacency on this subject is unwise.

They also point out that it is a mistake to assume that if a woman has a right-sided breast tumor then her risk of radiation damage to the heart is non-existent. Although left-sided breast irradiation is a more obvious concern, patients who receive right-sided radiation may not entirely escape damage to the heart as those with regional lymph node involvement may also require radiation to the internal mammary chain. In at least two of the largest studies on this subject to date, up to 25 percent of the women with right-sided breast tumors (who were automatically placed in control groups and assumed to be free of risk) actually did receive internal mammary radiation because of regional lymph node involvement, and thus were at risk for cardiac damage. Prosnitz and Marks state:

> "Although modern RT [radiation treatment] techniques have reduced radiation exposure to the heart, they may not have eliminated cardiotoxicity. It appears that contemporary RT methods may still cause cardiovascular disease. Changes in myocardial perfusion, wall motion, and EF [ejection fraction] have been

> demonstrated in patients undergoing treatment with modern techniques. Whether these radiographic changes will ultimately have clinical significance is unclear" (Prosnitz 2005).

The range of cardiovascular problems that can follow intense irradiation of the heart is in fact very broad. It includes six major categories and various subcategories (see Table 1):

Table 1
Major Adverse Effects to the Cardiovascular System
(Adapted from Fajardo, *et al.*, 2001 and the DeVita, et al. , 1997)

Pericardial disease
- Acute pericarditis during irradiation
- Delayed acute pericarditis
- Pericardial effusion (delayed)
- Constrictive pericarditis

Myocardial dysfunction
Diffuse myocardial fibrosis (with or without pericardial disease)
Coronary artery disease (CAD)
Electrical conduction abnormalities
Valvular heart disease

What complicates the issue is that radiation affects the heart and cardiovascular system unevenly: different parts of the system are affected in different ways, and individuals also differ in their responses. For the sake of simplicity, I will not discuss the complicated mechanisms by which radiation damages the heart and circulatory system. What is most relevant is the experimental and clinical evidence of such damage.

Laboratory Data

There is also a considerable body of laboratory data demonstrating the harmful effects of radiation on the heart. Most of these experiments have been carried out on the New Zealand white rabbit, because its reactions to heart irradiation are similar to those of humans.

In one such study, after a single 20 Gy dose of radiation, fully 94 percent of the rabbits developed some form of heart disease (Fajardo 1970). First there was an acute reaction, which disappeared within 48 hours. But starting on the 50th day, a delayed reaction set in, and this reached its full development by 90 days. By 150 days, half the experimental animals had died. What is particularly striking about these experiments is the degree to which radiation was shown to cause myocardial fibrosis (a thickening of the heart muscle).

Similarly, in the human clinical situation, the heart reacts to radiation with both an acute and a long-term response. As in the test animals, the initial response vanishes rather quickly. But then, some months or even years later, the patient may experience heart pain

(angina), difficulty breathing, or even a full-scale myocardial infarction (heart attack). The problem is that since they occur a considerable time after treatment, these radiation-induced effects are indistinguishable from 'ordinary' (i.e., randomly occurring) heart problems. There is nothing about such events that screams out "radiation-induced heart disease." The cardiologist may, or may not, make a connection to the patient's prior exposure to radiation.

The latest findings should caution us against hubris in the medical field. It took tremendous investigative work by Prof. Fajardo and others to prove that radiation damages the heart. As a result of their work, some changes were indeed made – the internal mammary chain is now usually avoided—and radiation oncologists hailed these changes as proof that radiation treatment was now safe.

Although the accuracy of radiation delivery and targeting has improved considerably, other problems remain largely unaddressed, especially now that anthracycline-based chemotherapy is the standard of care for breast cancer.

Radiation is a classic two-edged sword. It does substantially reduce the risk of recurrence of breast cancer in the irradiated field. But this may come at the price of increased risk of damage to the heart, especially when the left breast is irradiated, and when the internal mammary chains are irradiated. Patients and their physicians need to carefully weigh benefits and risks before on this or any other potentially toxic treatment.

Of course everything possible should be done to prevent a recurrence. However, the evidence that the benefits of adjuvant radiation outweigh the risks is still far from certain. Although the NCI's PDQ Web site emphasizes some positive studies, it eventually concedes that the results of these positive trials "need to be placed in the context of the totality of available evidence."

However, while PDQ goes into great depth on these positive studies, the "totality of evidence" is never in fact presented to the reader. In the negative column, they refer only to a single meta-analysis. So, in this instance, PDQ's presentation gives an unduly positive evaluation of adjuvant radiation after surgery for breast cancer.

Other Radiation Damage

It is not only the heart that can be damaged by breast irradiation. The lungs are also extremely radiosensitive, and lung damage is not at all uncommon following adjuvant radiation for breast cancer, particularly where the chest wall is involved. Radiation pneumonitis (inflammation of the lungs) can occur in as many as 5 to 15 percent of patients undergoing radiation involving the thorax (chest). Sometimes onset of this complication is delayed, and the problem appears months after treatment. In most cases, the condition resolves gradually, with the help of symptomatic treatment such as steroids, but in severe cases, this condition can progress to radiation fibrosis and interstitial lung disease (ILD), resulting in permanent damage.

Radiation-induced angiosarcoma (RIS), an aggressive form of connective tissue cancer, occurs in approximately 0.2 percent of people irradiated for breast cancer. The disease has a long latency period – i.e., many years may elapse between the use of radiation in this context and the development of angiosarcoma. But on occasion such tumors may arise within a relatively short time span (Deutsch 2003). (I personally had this happen to a friend of mine – the wife of a world-famous cancer surgeon.)

Radiation-induced sarcoma is more common in women who have treatment-associated lymphedema (the so-called Stewart-Treves syndrome). It is also more common in women in their mid- to late-sixties, and in those who have received chest wall irradiation.

My basic point is that while radiation-associated cardiac damage may be less common now than it once was, and while RIS is a rare occurrence, the fact that these serious treatment-associated complications occur at all is often under-acknowledged. Certainly adjuvant radiation can improve local control and reduce recurrence of cancer in the same breast, but there are risks associated with its use, and women have a right to ask their radiation oncologists to address these concerns directly.

On the positive side, a number of new refinements to traditional radiation delivery systems are likely to make treatment safer in the near future. Notable among these is the use of small, implantable GPS (global positioning system) devices that guide radiation delivery. Known by the trade name Calypso®, this system of delivery compensates for the minute movements that take place due to breathing, heart beat, etc., during treatment, thereby keeping the radiation field accurately targeted at all times. The Calypso® technology is currently only FDA approved for use in prostate cancer patients, but its use in breast cancer patients is being actively studied.

Another important new development is the use of scanning proton beam technology. This is an adaptation of the proton beam radiation technique that was originally pioneered by Loma Linda University in California. Scanning proton beam radiation offers a means of delivering radiation with great accuracy not only to the specific target area of the breast, but also to many of the potentially involved lymphatic nodes and vessels that drain the area.

Locally advanced breast cancer – concurrent chemotherapy and radiation

The medical literature also provides ample discussion of several clinical trials that found an overall survival advantage for chemoradiation (i.e., the concurrent use of chemotherapy and radiation, as opposed to sequential use) in treating locally advanced breast cancer. Let us look at some of these.

First Danish Trial: In the Danish Breast Cancer Cooperative Group Study (#82B), 1,708 premenopausal women with high-risk disease were randomized to receive either the three-drug chemotherapy regimen CMF (cyclophosphamide + methotrexate + 5-fluorouracil) alone, or CMF with additional radiation.

After 10 years, overall survival among the women who were given chemotherapy plus radiation was 54 percent, as opposed to 45 percent in those given chemotherapy alone. This nine percent difference was statistically significant (Overgaard 1997).

Second Danish Trial: The same group also studied postmenopausal women who had high-risk (stages II or III) breast cancer. Six hundred and eighty-six such women were randomized to receive postoperative radiation therapy to the chest wall and regional lymph nodes plus the anti-hormonal drug tamoxifen, while 689 women received tamoxifen alone. Both the local-regional recurrence rate (8 vs. 35 percent) and the overall survival rate (45 vs. 36 percent) favored the combined treatment (Overgaard 1999).

Canadian Trial: A third Canadian study found similar results, although in this case the results did not reach statistical significance (Ragaz 1997).

Italian Series: One might well conclude that chemoradiation would be a wise choice for women with high-risk breast cancer facing this situation. Yet I find it odd that PDQ fails to cite a retrospective study from Italy showing *diminished* survival in women given chemoradiation. Once again, the addition of radiation did reduce local recurrences. But the overall survival of those given chemotherapy alone was 77.6 percent compared to just 59 percent in those who received combined chemoradiation. The authors concluded: "The study confirmed that [radiation therapy] reduces the risk of local recurrence but without a statistically significant reduction in mortality" (Micheletti 1998).

In order to help with the "totality of available evidence" I would like to analyze some of the RCTs that have studied radiation for breast cancer after mastectomy. To my knowledge, there have been seven major studies, designated Manchester I and II, NSABP-B-02, Oslo I and II, and Stockholm I and II (see Table 2).

Table 2
Some RCTs of Radiation for Postmastectomy Breast Cancer
(1949-1984)

Name of Trial	Years	Follow-up yrs	Outcome
1. Manchester I	1949-1952	34 yrs	decreased survival
2. Manchester II	1953-1955	—	—
3. NSABP B-02	1961-1968	5 yrs	no sig. diff.
4. Oslo I	1964-1967	10 yrs	no sig. diff.
5. Oslo II	1968-1972	10 yrs	no sig. diff.
6. Stockholm I	1971-1976	13.5 yrs	no sig. diff.*
7. Stockholm II	1976-1984	6.5 yrs	no sig diff.**

* For node-positive (N+) patients, radiation therapy was slightly better
** Radiation therapy was slightly better for postmenopausal patients

Manchester Trial: This was the first RCT to study the question of adjuvant radiation for breast cancer. Over 1,000 women received the standard treatment of the day, radical mastectomy, at the Christie Hospital in Manchester, England. Some patients received radiation following surgery, while others didn't. Although ostensibly simple in its design, this Manchester trial contained a number of subtle complexities, since treatment techniques changed over time and there were also some possible irregularities in their data.

Nonetheless, the Manchester study remains extremely valuable, not only for its size but also for the length of the follow-up observation period. Results were first reported in 1959 and there were subsequent reports issued into the 1980s. The really surprising fact was that during the first 15 years of patient follow-up, the survival curves of the two treatment groups (radiation vs. no radiation) remained roughly the same. Then, against all expectations, **the overall survival curve began to shift *downward* in the irradiated group.**

In fact, there turned out to be a ***43 percent greater chance of dying*** after 15 years if the patient had radiation than if she didn't! This increased death rate was attributed not to breast cancer but mostly to cardiovascular disease, especially in those whose disease had been in the left breast, i.e., over the heart (Paterson 1959). This study, in the words of breast cancer surgeon Jay Harris, MD, "raises the possibility of late toxicity from treatment" (Harris 1991: 377). This is cautiously worded, but I can see no other likely explanation for the difference.

The findings of the Manchester RCT were significant in another way. The trial showed that when one was considering the after effects of radiation, **one had to look long-term**. Well-meaning studies that reported five- or ten-year survival figures after radiation treatment were, and are, not adequate. With adjuvant radiation, one needs to look at the decades-long effects in order to accurately judge the safety or effectiveness of this procedure. In this study, radiation turned out to be more dangerous, long-term, than anyone had previously suspected. In fact, this 1959 paper was among the early reports that led to an awareness of radiation's potential danger to women with breast cancer.

NSABP B-02: NSABP stands for the National Surgical Adjuvant Breast and Bowel Project. The NSABP has played a very important role in the development of RCTs in oncology in the United States. The founder and head of the NSABP is Bernard Fisher, MD, of Allegheny University, in Pennsylvania. I have already mentioned the famous B17 trial which he led.

Trial B-02 was begun in 1961, but the first five-year results were not published until 1970. In this study, patients were randomized to receive either (a) radiation therapy after surgery or (b) no further treatment after surgery. (The protocol was complicated by the further randomization of some patients to a chemotherapy arm, but this needn't concern us here.)

After five years*, there was no survival advantage in the group that received radiation therapy.* In fact, while the number of local-regional recurrences was diminished in that group, a surprising finding was that **the number of distant metastases was *higher*** in the irradiated group: 40.0 vs. 32.3 percent. But this was a small study and none of the results in the subgroups reached statistical significance (Fisher 1970).

Oslo Trials: The third and fourth trials both took place at the Norwegian Radium Hospital (Radiumhemmet) in Oslo between 1964 and 1972 and are usually grouped together for analysis. After mastectomy, a total of over 1,000 women were randomized to receive either radiation therapy or no further treatment. Ten-year survival results were then tabulated (Host 1986).

In neither trial was there a survival advantage associated with radiation. The relapse-free rates were nearly identical. However, once again, there was a *slightly worse* overall survival in the group that received cobalt-60 irradiation compared to those who received no further treatment (75 vs. 80 percent survival). Not surprisingly, the excess of deaths in the irradiated patients seemed to be due to fatal heart attacks caused by radiation's damage to the heart.

Stockholm Trial: The fifth RCT on this topic was done at the Radium Hospital (Radiumhemmet) in Stockholm between 1971 and 1976. About 650 patients were randomized to receive either modified radical mastectomy alone or the same treatment followed by radiation therapy.

In patients whose lymph nodes were negative for cancer, the administration of radiation was associated with a decrease in local recurrences but had ***no effect* on distant metastases or survival**. However, in this study the use of postoperative irradiation *was* associated with a modest increase in survival in node-positive patients (Rutqvist 1989). This was among the first studies to suggest that a subgroup of patients with aggressive disease might benefit from this treatment.

Veronesi Studies: In addition, there were two other studies that are worth mentioning. These are based on the work of Professor Umberto Veronesi, MD, a breast cancer surgeon who later became Italy's Minister for Health. One was an RCT, while the other was a meta-analysis of three European clinical trials. These Veronesi studies compare four different ways of treating early-stage breast cancer:

1. Halsted radical mastectomy alone
2. Quadrantectomy (surgical removal of one-quarter of the breast) followed by radiation therapy
3. Lumpectomy plus radiation therapy
4. Quadrantectomy alone, without radiotherapy

Although the patients' treatment paths varied, it did not seem to make much difference which treatment was chosen. In other words, the "overall survival curves were identical in the four groups of patients," as Veronesi reported, "so that the three breast conserving

radio-surgical procedures had the same survival rates as [the] Halsted mastectomy." But, as is almost always seen, "the annual rate of local recurrences was lower with the more radical treatments: ([the] Halsted mastectomy and quadrantectomy plus radiotherapy)" (Veronesi 1993; Veronesi 1995).

Stockholm-Oslo Update: In 1990, there was an updated report on the combined results of the Stockholm and Oslo studies. These were the trials in which patients received only treatment with modern "megavoltage" equipment. This was in response to many experts' belief that the failure of the other trials had been due to their use of older, less powerful and less focused "orthovoltage" equipment.

Yet, once again, the results in *both* node-negative and node-positive patients revealed **no significant differences in survival.** However, when the overall data was parsed into subgroups, some possibly significant patterns did emerge. Thus, for node-positive patients the use of irradiation was associated with a decrease in metastases and a *22* percent reduction in mortality as well. But the reader should understand that subgroup analysis of this kind is problematical from a statistical point of view. In addition, the follow-up period was not long enough to rule out the kind of late deaths that were seen in the Manchester trial (Paterson 1959).

Finally, another, more complicated Swedish trial examined the effect of four treatments, one of which was postoperative radiation therapy. (The others were various combinations of chemotherapy or the anti-estrogen drug tamoxifen.) Again, there was no significant difference among the various groups. The best results were among the patients who received a combination of radiation and tamoxifen. However, the number in each subgroup was too small to be of any predictive value (Rutqvist 1990).

Sometimes a meta-analysis can reveal meaningful trends from various studies, each of which individually fails to return a positive answer. Because the RCTs discussed above generally failed to affirm any life-prolonging effects of adjuvant radiation therapy, these various trials were combined in a 1986 meta-analyses. This analyzed the 7,941 patients who had been included in previous, inconclusive RCTs. In addition, the authors took the opportunity to update the data from these trials. They included results from the Manchester, Oslo, and Stockholm trials as well as another small unpublished trial from Heidelberg, Germany. Only the American NSABP-02 trial was excluded because the follow-up data were deemed inadequate.

*Yet, after 15 years, there was a **lower** rate of survival associated with the use of radiation therapy. Of patients followed for more than 15 years, the death rate was 31 percent in those who received adjuvant radiation therapy vs. 25 percent in those who did not.*

The reason that few doctors notice the sometimes deleterious effects of adjuvant radiation is the relatively long time-lag between cause and effect. "No differences were found in survival in the first 10 years of follow-up, in trials employing either radical mastectomy or simple mastectomy," wrote biostatistician Dr. Jack Cuzick, *et al.*, of the Imperial Cancer Research Fund, London, in a clear-eyed review of the topic (Cuzick 1987). But

after 10 years, "a significant excess of deaths was observed among patients given radiotherapy." Cuzick's meta-analysis did not provide a breakdown of the causes of these excess deaths, but a subsequent overview found that this increase was due – no surprise -- to cardiovascular mortality (Cuzick 1994). This is of course the same pattern seen in many other studies.

Two subsequent and much larger overviews confirmed and extended Dr. Cuzick's observations (EBCTCG, 1995; EBCTCG, 2000). The later of the two involved the examination of the cause of death of more than 10,000 women out of a total of about 22,000 women treated in 40 randomized trials worldwide. This is a very high number of patients to be included in such an analysis, yielding a high degree of confidence in its findings.

As Dr. Cuzick states, there was no clear benefit of adjuvant radiation therapy. After 20 years of follow-up, breast cancer deaths were reduced by 4.8 percent. But non-breast-cancer deaths were simultaneously elevated by 4.3 percent. Thus, in this study, there was only a 0.5 percent survival advantage to adding radiation therapy to mastectomy. However, the increase in non-breast-cancer deaths emerged later than the decline in breast cancer deaths. As in Dr. Cuzick's earlier analysis, most of the excess in non-breast-cancer deaths was due to cardiovascular disease, which increased by 30 percent.

Hamilton Meta-Analysis: To be fair, there is also a more positive evaluation from McMaster University in Hamilton, Ontario. Radiation oncologist Tim Whelan, MD, and his colleagues performed a meta-analysis of RCTs of women who received systemic therapy for node-positive breast cancer. While conceding that "previous trials failed to detect a difference in survival that results from its use," this Hamilton meta-analysis focused on 18 trials involving a total of 6,367 patients.

Unfortunately, the trials in question differed significantly in many respects and thus were difficult to generalize. Women were mostly treated with a modified radical but also with different kinds of surgery. In addition, "the type of systemic therapy received, sites irradiated, techniques used, and doses of radiation delivered varied between trials," according to the authors. In this analysis, "radiation was shown to reduce the risk of any recurrence, local recurrence and mortality." However, these results were seen only in women who also received "systemic" therapy, meaning either chemotherapy or hormonal therapy (Whelan 2000).

Sometimes those who have a strong commitment to a particular point of view choose to only look at those studies that support their preconceived position, even in the face of evidence to the contrary. But I believe that the totality of the data – the work of many groups over many years – leads to the conclusion that (a) **even modern methods of delivering radiation carry a risk of inducing heart damage; and (b)** while there may be a subgroup of patients with aggressive disease who could benefit from radiation after mastectomy, **adjuvant radiation still does not result in an appreciable increase in**

overall survival for most women. It may still be advisable, however, for a percentage of high-risk patients, or for those who are focused on the issue of preventing recurrences.

In 2000, the National Institutes of Health (NIH) held a Consensus Conference to try to settle this thorny question of post-surgical radiation in breast cancer. The conference emphasized Dr. Cuzick's EBCTCG overview of more than 22,000 women comparing adjuvant radiotherapy to no radiotherapy. They reported the improvement in local-regional tumor control rates from 70 percent to 90 percent. They then claimed that this resulted in a significant improvement in the overall survival rate and in the disease-specific survival rate after a follow-up time of 20 years (NIH 2000). Women were reassured that radiation would help extend their lives.

But, looked at more closely, what those figures really showed was that postoperative radiation saved 4.8 percent of treated women from death by breast cancer at a cost of simultaneously *causing* the premature deaths of 4.3 percent by cardiovascular disease. So this involved and expensive procedure actually yields a long-term net gain of about 0.5 percent. This hardly seems like a "significant improvement" in any common usage of that term. Yet this is the basis on which tens of thousands of women have been subjected to radiation.

I should also point out that in February 2006 the *Lancet* published another meta-analysis of the question of post-surgical adjuvant radiation therapy for breast cancer (EBCTCG 2006). Many hailed this study as proof that radiation was indeed effective in this context.

"These data help strengthen the argument that there is a substantial benefit to radiotherapy [after lumpectomy] and that it should be a rare patient with a very low risk of recurrence or a very short expected life span for whom it should be eliminated," said Christy Russell, MD, chair of the American Cancer Society's Breast Cancer Advisory Group and co-director of the University of Southern California Norris Breast Center, Los Angeles.

According to this analysis, among the 7,300 women treated with breast-conserving surgery, radiation reduced the risk of having a relapse in the next 5 years from 26 percent to just 7 percent. This confirmed radiation's undisputed ability to reduce the risk of recurrences. More surprising was the conclusion that the risk of dying from breast cancer over the next 15 years dropped from 35.9 percent to 30.5 percent, a 5.4 percent difference.

For the 8,500 women who had a mastectomy, radiotherapy reduced the 5-year risk of local recurrence to just 6 percent. It also reduced the 15-year risk of death from breast cancer from 60.1 to 54.7 percent, also a 5.4 percent difference.

The benefits were greatest for women whose cancer had spread to the lymph nodes, and those with larger tumors or higher-grade tumors.

There were certain unusual features to this study, however. This was a statistical

projection based on pooled data from a heterogeneous group of papers. If you don't know this, there is a tendency to think that one is reading an exciting new RCT, when in fact this is a **reinterpretation of equivocal data that has been provided in previous studies**, and that had yielded contradictory conclusions in the past. I have heard this type of analysis humorously referred to as "torturing the data until it confesses."

Second, some of the most pivotal questions were not addressed in this article. If one accepts that adjuvant radiation *does* improve 15-year breast cancer mortality by approximately 5 percent, one is still confronted with the question of precisely **how** it supposedly does this. How and why does improving local control of tumor growth (all that radiation admittedly does in this context) translate into increased long-term survival?

This central issue of the physiological or pathological mechanism is seldom if ever addressed. At every turn, we are simply told that radiation improves local control and thereby imparts a modest improvement in long-term survival. We are therefore left wondering exactly how this comes about. I think this is a major deficiency of the paper. The word 'metastasis' (the source of most breast cancer mortality) is never even mentioned in this article.

The paper also fails address the question of whether - and if so, in how many cases - the size of the recurrence exceeded the size of the original primary. According to the argument of Richard Evans, MD (see above), if the recurrence is detected while it is still smaller than, or the same size as, the original cancer, this represents no increased risk to life. "These cases may well explain all the excess deaths among unirradiated patients," Evans said. "In fact, they may explain why unirradiated patients did not live longer than irradiated patients" (Evans 2006).

In addition, the average reader will be unaware of the *theoretical* nature of the arguments. For example, the article concludes:

> "These trials of radiotherapy and of the extent of surgery show that in the *hypothetical* absence of other causes of death, about one breast cancer death over the next fifteen years would be avoided for every four local recurrences avoided" (EBCTCG 2006, emphasis added).

Yet the article itself enumerates many ways in which other causes of death, some of them related directly to radiation itself, are at work here, particularly in the 15-year survivors, who are now getting into their 60s and 70s. By omitting this possibility, the figures have in my opinion been skewed in favor of radiation.

The paper itself seems to allude to this, albeit in very difficult-to-interpret terms:

> "For example, if additional local treatment led to an estimated reduction in the 5-year local recurrence risk of, say, about 12 percent, then from the general four-to one- relationship between effects on local recurrence and on breast cancer mortality, it could reasonably be inferred that the 15-year reduction in breast

> cancer mortality would be about 3 percent, even though directly randomized proof of such a small mortality difference would be difficult to obtain."

This torturous paragraph is based on several conjectures, namely that additional treatment logically leads to an "estimated reduction" and that this "estimated reduction" in turn leads to a reasonable inference that breast cancer deaths rates will decline…by about three percent! Aware that even this small putative advantage is based on a string of hypotheticals, the authors backtracks by adding that direct proof through RCTs "would be difficult to obtain."

Instead of straightforward conclusions derived from well-designed RCTs we are asked to rely on this exercise in logical inferences. I for one am uneasy with that method of decision making.

Another issue, as the authors themselves point out, is that there have been many changes in screening, diagnosis, pathology, surgery and adjuvant therapy of breast cancer in the time since many of the pooled trial data were first obtained. Such advances mean that 5-year risks of local recurrence might already be lower than they were at the time the figures used for this meta-analysis were obtained.

The authors state:

> "The absolute risks of local recurrence in these trials and the absolute benefits and hazards of radiotherapy in these trials **cannot be generalized** because of the continuing changes in practice since the trials began" (emphasis added).

Nevertheless, they then claim that "the quantitative relationship in these trials between local disease control and 15-year breast cancer mortality should still be relevant to current and future treatment decisions." But the provisos 'cannot be generalized' and 'should still be relevant' contradict one another. Either risks and benefits can be generalized, or they can't. Logically, one cannot have it both ways.

Another problem is that this study based its analysis on what happened at a maximum of 15 years. Yet the chances of iatrogenic (medically-caused) cardiovascular disease and second cancers, historically, continue up to and well beyond the 15-year point. As the authors themselves acknowledge, there is a somewhat higher death rate during the period after 15 years from causes other than breast cancer, related to radiation's after effects.

Many of the women included in this meta-analysis were not followed to year 15, much less beyond it, so it was too early to become sanguine about a long-term reduction in mortality. Many of the worst late after effects of radiation emerge several decades after exposure (as the survival data from the Hiroshima and Nagasaki bombings showed). The authors themselves project the following:

> "At 20 years, the reduction in breast cancer mortality remains unchanged at 5.4 percent…while that for all-cause mortality, although still significant, is only 3.5

> percent…, indicating a continuing excess of non-breast-cancer mortality long after treatment with the older radiotherapy regimens" (EBCTCG 2006).

In other words, the number of deaths continues to creep upward as the years progress. To ascribe it only to "the older radiotherapy regimens" is excessively optimistic, as the 2007 JNCI article (discussed above) shows.

The excess of iatrogenic deaths is another area of this study that really bears scrutiny. The authors say that there was an excess of cancer incidence among women who were given radiotherapy, and that this mainly involved contralateral breast and lung cancers, but also esophageal cancer, leukemia, soft tissue sarcoma, and pulmonary embolisms.

The excess of contralateral breast cancer (i.e., in the initially unaffected breast) began emerging, apparently, after the 5-year mark, and certainly extended past the arbitrary 15-year mark. An increasing incidence of iatrogenic deaths can be clearly seen in the post-mastectomy trials. That is because mastectomy is the older of the two treatments and therefore the data is more mature. But will it also show up eventually in the post-breast conserving surgery (BSC) trials? The authors state: "There is as yet, however, little follow-up beyond year 15—indeed, *many women have not yet been followed to year 15*" (EBCTCG 2006, emphasis added).

Notice the implications of that last sentence: the optimistic projections heralded by the ACS and others include results in "many women" who have not even been studied for 15 years, much less 20 or more. It is therefore possible that an excess of iatrogenic deaths – already seen in the post-mastectomy patients – will increasingly be seen as the BSC-treated patients grow older, and are followed beyond the present 5-, 10- or 15-year mark.[*]

Radiation in early-stage, node-negative breast cancer

It bears repeating that as medical understanding of the complexity of breast cancer has grown, so it has become increasingly apparent that generalizations and "one size fits all" prescriptions concerning the best treatment following surgery are inappropriate at best, and may in some instances be directly damaging.

For example, a 2004 study looked at 163 women who had undergone breast conserving surgery but who did *not* receive adjuvant radiation. The overwhelming majority of these women were postmenopausal, with small (T1), low-grade tumors, no positive nodes, and clear surgical resection margins.

[*] The authors say that the excess mortality from causes other than breast cancer is significant both for women younger than 50 years and for those older than 50, which effectively rules out the possibility that this is an age-related effect and that older women develop more secondary cancers (EBCTCG 2006)

At follow-up, 20 patients (12 percent) had experienced a recurrence. In 17 of these patients the recurrence was an invasive new cancer; in 3 of the patients it was DCIS. The authors concluded:

> "A defined ideal subset of older breast cancer patients with smaller, lower-grade cancers and adequate excision margins can be treated with lumpectomy without irradiation and with minimal local recurrence" (Lee 2004).

Another area of great contention in making the radiation decision concerns women with early-stage, node-negative disease who undergo mastectomies. Should such women accept radiation treatment after their surgery? For such women, the authors state, the 5-year local recurrence risk after mastectomy and axillary node clearance was 6 percent in the absence of radiation therapy.

Radiation therapy then reduces the recurrence rate to 2 percent, for an absolute 5-year gain in these women of just 4 percent. The EBCTCG 2006 authors then admit that there is no significant reduction in 15-year breast cancer mortality in such women, and then added the parenthetical phrase: "Indeed, there appears if anything to be a slight increase, but the numbers of events are small" (EBCTCG 2006)

Of course, for the women and their families adversely affected, that "slight increase" in the death numbers was anything but small. In none of the vast publicity surrounding this paper did I see any mention of the fact that in this subgroup there actually was a 3.6 percent *reduced* breast-cancer specific survival among the irradiated patients. This is strange and alarming. Doctors irradiated these women, reduced their local breast cancer recurrence rate (by 4.0 percent at 5 years) and yet *more* of these women subsequently died of metastatic breast cancer. Here is a phenomenon crying out for detailed explanation: it should not be swept under the rug with a parenthetical remark about how "small" the absolute numbers are.

Talking about small effects, the authors also state: "The absolute reduction in breast cancer mortality also appears somewhat larger for women with node-positive disease, but the numbers are too small for this finding to be statistically reliable." I detect a bias here. Small and statistically non-significant reductions in breast cancer mortality are ballyhooed in the media with handy catchphrases ("One life saved for every four recurrences prevented!") But increases in breast cancer mortality in other groups of radiation recipients are summarily dismissed as irrelevant.

The EBCTCG 2006 study concludes with the following guarded statement, which, as you will see, is loaded with hypothetical and conditional qualifiers:

> "Differences in local treatment that substantially affect local recurrence rates *would, in the hypothetical absence of any other causes of death,* avoid about one breast cancer death for every four local recurrences and *should* reduce 15-year overall mortality. Although the management of early breast cancer continues to change, it is *reasonable to assume* that this approximate four-to-one relationship

> will continue to apply and will still be of relevance to future treatment choices." (emphasis added)

In fact, the historical experience has been quite the opposite: iatrogenic deaths continue to creep upward from the 15-year point. These have been particularly cancers in the contralateral breast, cardiovascular disease, as well as immune and pulmonary damage. Admittedly, there is greater awareness of these dangers among radiotherapists today but as the JNCI article (Hooning 2007) showed, this has not eliminated the danger by any means.

The use of potentially cardiotoxic chemotherapy, especially Adriamycin and Herceptin, has grown exponentially since most of the studies included in the EBCTCG 2006 meta-analysis were conducted. It is known that a combination of radiation with Adriamycin, Herceptin and other drugs is likely to *increase*, not *decrease*, the frequency of heart damage seen in years to come. Thus, conjectures about what is likely to happen to today's patient based on projections from older trials are unreliable. Even if we grant the general accuracy of the EBCTCG 2006 figures, the differences in actual overall survival, between those irradiated and those not are so small that they could be reversed by even a small countervailing trend toward increased iatrogenic disease and mortality. And that is the direction in which oncology is presently heading. Only time will tell which trend is in fact stronger.

Accelerated Partial Breast Irradiation (Hypofractionated Radiation)

Until recently, the only available method of radiation treatment for breast cancer was one or other form of whole breast external beam radiation (WB-EBRT). The arrival of a new modality – accelerated partial breast irradiation (APBI) – has altered the landscape somewhat.

APBI differs from traditional whole breast irradiation in some important ways. First, rather than including the whole breast in the radiation field, APBI targets only a small area surrounding the tumor bed (hence the "partial"). Since the majority of local recurrences arise in or close to the site of the original tumor, APBI targets the most vulnerable areas of the breast in much the same way as the standard "boost" does.

Second, while standard whole breast radiation typically involves a protracted course of daily treatments lasting several weeks (50 Gy delivered in 25 fractions (doses) over a period of 35 days), APBI can take as little as as5 or 6 days to complete (hence the "accelerated"). There are many in the oncology and radiology profession who feel that just as lumpectomy revolutionized the surgical approach to breast cancer, making the more drastic mastectomy a much less common procedure, so APBI stands to reduce the difficulties associated with standard radiation therapy, making it speedier and much less onerous for the patient.

There are several ways of delivering APBI. These include **interstitial brachytherapy** (in which tiny radioactive seeds are implanted and withdrawn via multiple catheters inserted

into the breast); **balloon or intracavitary brachytherapy** (also known under the trade names Mammosite® and Axxent®), which involves the insertion of a small inflatable balloon into the tumor cavity via a catheter, as a vehicle for the radioactive seed implants; **intraoperative radiation** (IORT), which is delivered in the operating room at the same time as surgery; and 3-dimensional **conformal external beam radiation**, which uses very sophisticated computer modeling techniques to deliver very accurately targeted radiation to the precise outlines of the tumor cavity. Treatment can take as little as 1 day (with IORT) but with most other methods typically takes 5 days.

Currently the various methods of delivering APBI are being evaluated by researchers at different academic centers, including Stanford University, to determine whether the methods are equivalent, or whether one method emerges as clearly more effective than the others. Although interstitial brachytherapy has been in use longer than the other methods, the fact that it requires the insertion of multiple catheters can be very daunting to patients. By comparison, some of the newer techniques, particularly intracavitary brachytherapy (Mammosite®, Axxent®) are simpler and potentially less invasive.

One advantage of APBI is its convenience. Currently, at least in part because of the tremendous inconvenience of a 6-7 week regimen of daily treatment, a high proportion - as many as 40 percent by one estimate – of women with early breast cancer choose to forego this treatment entirely (Malin 2002). Committing to a daily treatment for 6-7 weeks is particularly difficult for women living in rural areas, where travel to and from the treatment center can take up an entire day. The economic impact of protracted treatment under these circumstances can be absolutely devastating. With the duration of treatment condensed into as little as 1 day (for IORT) to 5 days (for brachytherapy techniques), many more women may opt to take the treatment.

Another advantage with APBI is that should a tumor recur, or should a new tumor arise in the same breast, the opportunity for a further breast conserving surgery is still present in most cases, whereas with standard radiation techniques a recurrence would almost invariably necessitate mastectomy.

As with traditional radiation treatment, some subsets of patients will benefit more than others from APBI. The technique is particularly useful for patients with early breast cancer, with tumors no larger than 2-3 cm and no more than 3 positive lymph nodes. In addition, it is important for the surgical excision to have left clean margins: those patients for whom this has not been possible may not be such good candidates for APBI.

Although initial results of several clinical trials of APBI have been published, this technology is very much still in its youth (if not actually still in its infancy). There are as yet only preliminary data on its long term efficacy. Patients will need to be followed up for a minimum of 8-10 years before it will be possible to draw any firm conclusions in a head-to-head comparison with the effectiveness of standard radiation protocols.

However, the clinical data that has emerged so far has been on the whole favorable. Data from several trials has borne out the radiobiological premise that a higher dose of

radiation, delivered over a shorter period, can be just as effective as a lower dose per fraction delivered over a longer period. A 2002 paper published in the Journal of the National Cancer Institute compared 5-year results of randomized trials comparing standard radiation with accelerated protocols in women with early breast cancer treated by lumpectomy. The study showed no significant difference in recurrence rates or overall survival between the two groups (Whelan 2002).

At the San Antonio Breast Cancer Conference in December 2007, the same group of Canadian researchers which published this study presented data on a new study directly comparing a 3-week long schedule of hypofractionated (accelerated) radiation with a standard 6-7 week long schedule. The researchers studied more than 1200 patients over a median follow-up of 12 years. They discovered that patients receiving standard radiation had a 6.7 percent risk of recurrence, while those receiving the foreshortened, accelerated regimen had a recurrence risk of 6.2 percent. While this study did not look specifically at APBI, it does have relevance as a measure of the effectiveness of accelerated schedules as compared to standard regimens.

Until the data on this method are considerably more mature, there will continue to be unsettled controversies. For example, there are those who feel that the whole breast is potentially vulnerable to recurrence, and that by focusing solely on the tumor bed instead of delivering radiation to the whole breast, APBI risks reducing the protective effect of radiation against same-breast recurrence. Others point out that statistically the majority of tumor recurrences (around 71 percent) occur close to the site of the original tumor, and that therefore APBI does not leave the breast as a whole at increased risk of recurrence (Kuerer 2004).

Further reading on APBI

Arthur DW, Vicini FA. Accelerated partial breast irradiation as part of breast conservation therapy. J Clin Oncol 2005;23(8) 1726-1735

Kuerer HM, Julian TB, Strom EA, et al. Accelerated partial breast irradiation after conservative surgery for breast cancer. Ann Surg 2004;239(3):338-351

Conclusions

In my opinion, the data so far supports the following conclusions:

1. Postoperative radiation *does* considerably decrease the chances of a local-regional recurrence in the same breast after surgery.

2. This positive effect is especially noteworthy in patients who are at high risk of local recurrence. Certain high-risk patients who are also receiving chemo- or hormonal therapy may actually benefit in terms of life prolongation.[1]

3. Adjunctive radiation is probably unnecessary for women who have a low risk of a recurrence. Unfortunately, there remains a great deal of uncertainty about where to draw the line between the high and low risk groups.

4. Because of its harmful effect primarily on the heart, but also on the lungs and immune system, radiation has caused the premature death of some patients. As a result, radiation historically has not resulted in an appreciable increase in overall survival in most studies. That is because an excess of deaths from other causes counterbalanced the decrease in breast cancer deaths in patients who received radiation therapy. (However, see the discussion of the 2006 *Lancet* meta-analysis for a contrary view.)

5. It seemed plausible that today's more accurate delivery systems for radiation would decrease the adverse effects of radiation on the heart. And, indeed, this seems to be true of radiation delivered directly to the tumor bed and the remaining breast tissue. But overall, there was still a danger to the heart from modern forms of adjuvant radiation (Hooning 2007). **Newer techniques shifted the pattern of harm, but did not remove the danger**. Furthermore, adding chemotherapy, and especially the drugs Adriamycin and Herceptin, to radiation might independently increase the degree of cardiac toxicity.

While everyone would like clear-cut guidelines in this matter, there is an element of personal selection or subjectivity in the radiation decision. You have to ask yourself: How important is it to avoid a recurrence at any cost—even if there is increased risk of death later on from other causes? As a generalization, I believe that doctors tend to emphasize the need to prevent recurrences, while patients may erroneously see the prevention of recurrence as synonymous with prolongation of survival (which is by no means always the case). They may not become aware in time of the potential for radiation to contribute to a reduction in long term survival by causing damage to the heart, resulting in increased cardiac-associated mortality.

Cohn KE, et al. Heart disease following radiation. *Medicine* 1967;46:281-298.

Correa CR, Litt HI, Hwang WT, et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol*. 2007 20;25:3031-3037.

[1] A meta-analysis of 18 randomized trials comparing local regional radiation therapy after surgery with surgery alone in women with *node-positive* breast cancer who received systemic therapy revealed a decrease in overall mortality in women who received radiation therapy (Whelan 2000).

References

Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005 Dec 17;366(9503):2087-106.

Crile G, Jr. *What Women Should Know About the Breast Cancer Controversy*. New York: Macmillan, 1973.

Cuzick J, Stuart H, Rutquist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol*. 1994;12:447-453.

Cuzik J, et al. Overview of randomized trials of post-operative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep*. 1987;71:15-29.

Deutsch M, Safyan E, Angiosarcoma of the breast occurring soon after lumpectomy and breast irradiation for infiltrating ductal carcinoma: a case report. *Am J Clin Oncol*. 2003; 26:471-472.

DeVita VJ, Hellman S, Rosenberg SA, Eds. *Cancer: Principles & Practice of Oncology*, 5th Ed., Philadelphia: Lippincott-Raven, 1997.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials.. *Lancet*. 2000;355:1757-1770.

Evans RA. Host resistance to carcinoma of the breast. *South Medical Journal*. 1980;73:1261-1262.

Evans RA. *The Cancer Breakthrough You Never Heard Of*. Houston: Texas Cancer Center, 2001.

Evans RA. Unpublished notes to his paper on "Host Resistance to Carcinoma of the Breast," 2000.

Fajardo LF. Pathological effects of hyperthermia in normal tissues. *Cancer Res*. 1984;44:4826s–4835s.

Fajardo LF and Stewart JR. Experimental radiation-induced heart disease. I. Light microscopic studies. *Am J Pathol.* 1970;59:299-316.

Fajardo LF, et al. Morphology of radiation-induced heart disease. *Arch Pathol.* 1968;86:512-519.

Fajardo LF, Berthrong M, Anderson RE. *Radiation Pathology*. Oxford: Oxford University Press, 2001.

Fisher B, Anderson S, Bryant J. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002 347:1233-1241.

Fisher B, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer. *Cancer.* 1977;39:2827-2839.

Fisher B, et al. Postoperative radiotherapy in the treatment of breast cancer. Results of the NSABP clinical trial. *Ann Surg*. 1970;172:711-730.

Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med.* 1995;333:1456-1461.

Fisher B. The importance of clinical trials. *News from the Commission on Cancer of the American College of Surgeons,* 1991;2(2). Accessed March 7, 2002 at: http://www.asri.edu/bfisher/clinical_trials.html

Gauthier ML, Berman HK, Miller C, et al. Abrogated response to cellular stress identifies DCIS associated with subsequent tumor events and defines basal-like breast tumors. Cancer Cell 2007;12(5):479-91

Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. *Radiother Oncol.* 1998;48:185-190.

Gyenes G, Fornander T, Carlens P, Rutqvist LE. Morbidity of ischemic heart disease in early breast cancer 15-20 years after adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys.* 1994;28:1235-1241.

Harris Jay R. *Breast Diseases*, 2nd Ed. Philadelphia: Lippincott, 1991.

Højris I, Overgaard M, Christensen JJ, et al. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Lancet. 1999;354:1425-1430.

Haagensen, CD. *Diseases of the Breast*, 2nd ed. Philadelphia: Saunders, 1971.

Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst.* 2007;99:365-375.

Host H, et al. Post-operative radiotherapy in breast cancer—Long-term results from the Oslo study. *Int J Radiat Oncol Biol Phys.* 1986;12:727-732.

Huston TL, Simmons RM. Locally recurrent breast cancer after conservation therapy. *Am J Surg*. 2005;189:229-235.

Jensen BV. Cardiotoxic consequences of anthracycline-containing therapy in patients with breast cancer. *Semin Oncol*. 2006;33S8:S15-21.

Kuerer HM, Julian TB, Strom EA, et al. Accelerated partial breast irradiation after conservative surgery for breast cancer. *Ann Surg.* 2004:239:338-351.

Keynes G. Conservative treatment of cancer of the breast. *Br Med J*. 1937;2:643-649.

Kurtz JM. Which patients don't need a tumor-bed boost after whole-breast radiotherapy? *Strahlenther Onkol*. 2001;177(1):33-6.

Lee SH, Chung MA, Chelmow D, et al. Avoidance of adjuvant radiotherapy in selected patients with invasive breast cancer. *Ann Surg Oncol.* 2004:11:316–321.

Malin JL, Schuster MA, Kahn KA, et al. Quality of breast cancer care: what do we know? *J Clin Oncol.* 2002;20:4381-4393.

Micheletti E, et al. Postmastectomy radiotherapy and concomitant adjuvant chemotherapy versus adjuvant chemotherapy alone in premenopausal breast cancer patients with positive axillary nodes. *Tumori.* 1998;84:652-658.

Miller AB, Howe GR, Sherman GJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. *New Engl J Med.* 1989;321:1285-1289.

Mustakallio S. Conservative treatment of breast carcinoma–review of 25 years of follow-up. *Clin Radiol.* 1972;23:110-116.

Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med*. 1997;337:949-955.

Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet*. 1999;353:1641-1648.

Paterson R and Russell MH. Clinical trials in malignant disease. Part III. Breast cancer: evaluation of post-operative radiotherapy. *J Facult Radiol*. 1959;10:175-180.

Perez CA and Brady LW, Eds. *Principles and Practice of Radiation Oncology,* 4rd Ed. Philadelphia: Lippincott-Raven, 2003.

Prosnitz RG, Marks LB. Radiation-induced heart disease: vigilance is still required. *J Clin Oncol.* 2005;23:7391-7394.

Ragaz J, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med.* 1997;337:956-962.

Romestaing P, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol.* 1997;15:963-968.

Rutqvist LE ,et al. Radiotherapy, chemotherapy and tamoxifen as adjuncts to surgery in early stage breast cancer: A summary of three randomized trials. *Int J Radiat Oncol Biol Phys.* 1989;16:629-639.

Rutqvist LE, et al. Randomized trial of adjuvant tamoxifen combined with postoperative radiotherapy or adjuvant chemotherapy in postmenopasual breast cancer. *Cancer.* 1990;66:89-96.

Spitalier JM, et al. Traitements curatifs à espérance conservatrice des cancers du sein-généralités-résultats d'ensemble à 5 et 10 ans. *Méditer Méd.*1978;170S:3.

Valagussa P, et al. Cardiac effects following adjuvant chemotherapy and bresat irradiation in operable breast cancer. *Ann Oncol.* 1994;5:209-216.

Veronesi U, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. *Eur J Cancer*. 1995;31A:1574-1579.

Veronesi U, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med.* 1993;328:1587-1591.

Vin-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst.* 2004;96:115-121.

Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol*. 2001;19:1688-1697.

Whelan T, Julian J, Wright J, et al. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol. 2000;18(6):1220-9

Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst*. 2002;94:1143-1150.