



# Functional Infrared Imaging of the Breast

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## Historical Perspectives, Current Applications, and Future Considerations

There is general consensus that earlier detection of breast cancer should result in improved survival. Current first-line breast imaging relies primarily on mammography. Despite better equipment and regulation, variability in interpretation and tissue density still affect mammography accuracy. To promote earlier diagnosis, a number of adjuvant functional imaging techniques have recently been introduced, including Doppler ultrasound and gadolinium-enhanced MRI that can detect cancer-induced regional neovascularity. While these are valuable modalities, problems relating to complexity, accessibility, cost, and in some cases the need for intravenous access make them unsuitable as components of a first-line imaging strategy.

In this article, in order to re-assess the potential contribution of infrared (IR) imaging as a first-line component of a multi-imaging strategy using currently available technology, we first review the history of its introduction and clinical application, including the results of the Breast Cancer Detection Demonstration Projects (BCDDP). We then discuss experiments with a new high-resolution, computerized IR station and software program acquired by the Ville Marie Breast Center to assess IR imaging's ability to complement clinical exam and mammography in the early detection of breast cancer. Our goal is to show that high-resolution IR imaging provides additional safe, practical, and objective information when produced and interpreted by sufficiently trained breast physicians.

### Historical Perspectives

In 1961 in the *Lancet*, Williams and Handley [1], using a rudimentary handheld thermopile, reported that 54 of 57 of their breast cancer patients were detectable by IR imaging, and "among these were cases in which the clinical diagnosis was in much doubt." The authors reported that the majority of these cancers had a temperature increase of 1-2°C, and that the IR imaging permitted excellent discrimination between benign and malignant processes. Their protocol at the Middlesex Hospital consisted of having the patient strip to the waist and be exposed to the ambient temperature for 15 min.

The authors demonstrated a precocious understanding of the significance of IR imaging by introducing the concept that increased cooling to 18°C further enhanced the temperature discrepancy between cancer and the normal breast. In a follow-up article the subsequent year,

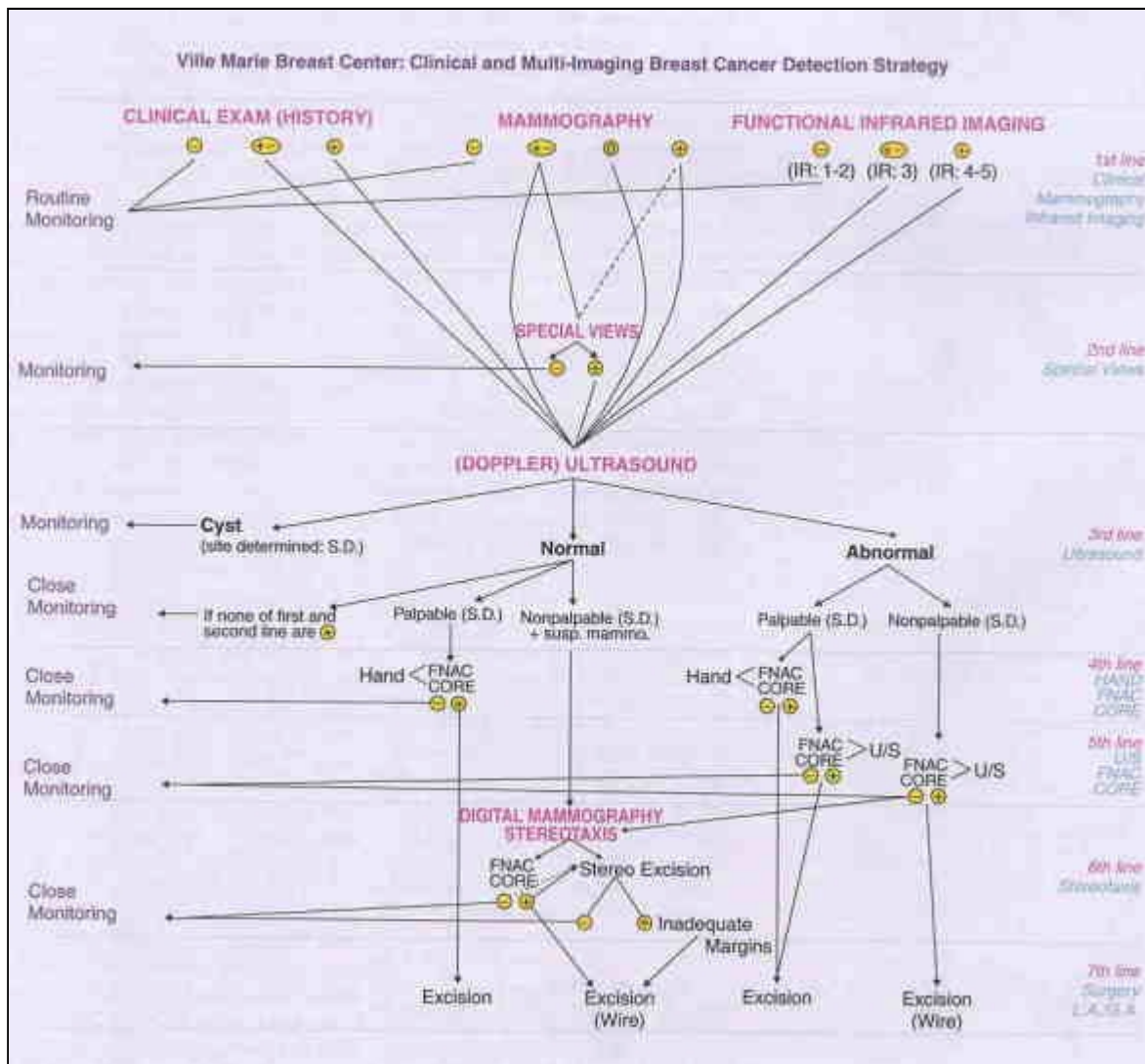
Handley [21] demonstrated a close correlation between the increased thermal pattern and increased recurrence rate. While only four of 35 cancer patients with a 1-2°C discrepancy recurred, five of the six patients with over 3°C rise developed recurrent cancer, suggesting already that the prognosis could be gauged by the amount of rise of temperature in the overlying skin.

In 1963, Lawson and Chughtai [3], two McGill University surgeons, published an elegant intraoperative study demonstrating that the increase in regional temperature associated with breast cancer was related to venous convection. This quantitative experiment added credence to Handley's suggestion that IR findings were related to both increased venous flow and increased metabolism.

In 1965, Gershen-Cohen [4], a radiologist and researcher from the Albert Einstein Medical Center, introduced IR imaging to the United States. Using a Barnes thermograph that required 15 min to produce a single IR image, he reported 4000 cases with a remarkable true positive rate of 94% and a false positive rate of 6%. Those data were included in a review of the then current status of IR imaging published in 1968 in *Ca -A Cancer Journal for Physicians* [5]. The author, JoAnn Haberman, a radiologist from Temple University School of Medicine, reported their local experience with IR imaging, which produced a true positive rate of 84% compared with a concomitant true positive rate of 80% for mammography. In addition, she compiled 16,409 IR imaging cases from the literature between 1964 and 1968, revealing an overall true positive rate of 87% and a false positive rate of 13%.

A similar contemporary review compiled by Jones, consisting of nearly 70,000 cases, revealed an identical true positive rate of 85% and an identical false positive rate of 13%. Furthermore, Jones [6] reported on over 20,000 IR imagings from the Royal Marsden Hospital between 1967 and 1972 and noted that approximately 70% of Stage I and Stage II cancers and up to 90% of Stage III and Stage IV cancers had abnormal IR features. These reports resulted in an unbridled enthusiasm for IR imaging as a front-line detection modality for breast cancer.

Sensing a potential misuse of this promising but unregulated imaging modality, Isard made some sobering comments in 1972 [7] in a publication of the *American Journal of Roentengology*, where he emphasized that, like other imaging techniques, IR imaging does not diagnose cancer but merely indicates the presence of an abnormality. Reporting his radiology division's experience with 10,000 IR studies done concomitantly with mammography between 1967 and 1970, he reiterated a number of important concepts, including the remarkable stability of the IR image from year to year in the otherwise healthy patient, and the importance of recognizing any significant change. Infrared imaging detected 60% of occult cancers in his experience, versus 80% with mammography. The combination of both these modalities increased the sensitivity by approximately 10%, thus underlining the complementarity of both of these processes, since each did not always suspect the same lesion.



1.

**Ville Marie multi-imaging strategy for detecting breast cancer.**

It was Isard's conclusion that, had there been a preliminary selection of his group of 4393 asymptomatic patients by IR imaging, mammography examination would have been restricted to the 1028 patients with abnormal IR imaging (23% of this cohort). This would have resulted in a cancer detection rate of 24.1 per 1000 mammographic examinations, as contrasted to the expected 7 per 1000 by mammographic screening. He concluded that since IR imaging is an innocuous examination, it could be utilized to focus attention upon asymptomatic women who should be examined more intensely.

In 1972, Gerald D. Dodd [8] of the Department of Diagnostic Radiology of the University of Texas presented an update on IR imaging in breast cancer diagnosis at the 7th National Cancer Conference sponsored by the National Cancer Society and the National Cancer Institute. He also suggested that IR imaging would be best employed as a screening agent for mammography and proposed that in any general survey of the female population age 40 and over, 15 to 20% would have positive IR imaging and would require mammograms. Of these, approximately 5% would be recommended for biopsy. He concluded that IR imaging would serve to eliminate 80 to 85% of the potential mammograms. Reporting the Texas Medical School's experience with IR imaging, he reiterated that IR was capable of detecting approximately 85% of all breast cancers. The false positive rate of 15% to 20% did not

concern the author, who stated that these were false positives only in the sense that there was no corroborative evidence of breast cancer at the time of the examination and that they could serve to identify a high-risk population.

Feig, et al. [9], reported the respective abilities of clinical exam, mammography, and IR imaging to detect breast cancer in 16,000 self-selected women. While only 39% of the initial series of overall established cancer patients had an abnormal IR imaging, this increased to 75% in his later cohort, reflecting an improved methodology. Of particular interest was the ability of IR imaging to detect 54% of the smallest tumors, four times that of clinical examination. This potential important finding was not elaborated, but it could reflect IR's ability to detect vascular changes that are sometimes more apparent at the initiation of tumor genesis. The authors suggested that the potential of IR imaging to select high-risk groups for follow-up screening merited further investigation.

Wallace [10] presented an update on IR imaging of the breast to another contemporary cancer conference sponsored by the American College of Radiology, the American Cancer Society, and the Cancer Control Program of the National Cancer Institute. The analysis suggested that the incidence of breast cancer detection per 1000 screenees could increase from 2.72 when using mammography to 19 when using IR imaging. He then underlined that IR imaging poses no radiation burden on the patient; requires no physical contact; and, being an innocuous technique, could concentrate the sought population by a significant factor, selecting those patients that required further investigation. He concluded that "the resulting IR image contains only a small amount of information as compared to the mammogram, so that the reading of the IR image is a substantially simpler task."

Unfortunately, this rather simplistic and cavalier attitude toward the acquisition and interpretation of IR imaging was widely prevalent when it was hastily added to the BCDDP, which was just getting underway. Rather than assess, in a controlled manner, its potential as a complementary first-line detection modality, it was hastily introduced into the BCDDP as a potential replacement for mammography and clinical exam.

Table 1. Ville Marie Infrared (IR) Grading Scale
<b>Abnormal Signs</b>
1) Significant vascular asymmetry.*
2) Vascular anarchy consisting of unusual tortuous or serpiginous vessels that form clusters, loops, abnormal arborization, or aberrant patterns.*
3) A 1°C focal increase in temperature ( $\Delta T$ ) when compared to the contralateral site when associated with the area of clinical abnormality.*
4) A 2°C focal $\Delta T$ versus the contralateral site.*
5) A 3°C focal $\Delta T$ versus the rest of the ipsilateral breast when not present on the contralateral site.*
6) Global breast $\Delta T$ of 1.5°C versus the contralateral breast.*
<b>Infrared Scale</b>
IR1 = Absence of any vascular pattern to mild vascular symmetry
IR2 = Significant but symmetrical vascular pattern to moderate vascular asymmetry, particularly if similar to prior imaging
IR3 = One abnormal sign
IR4 = Two abnormal signs
IR5 = Three abnormal signs
*Unless stable on serial imaging or due to known noncancer causes (e.g., abscess or recent surgery).

## The Breast Cancer Detection Demonstration Projects

A detailed review of the Report of the Working Group of the BCDDP is essential to

understand the subsequent evolution of IR imaging [11]. The scope of this project was issued by the National Cancer Institute (NCI) on 26 March 1973, with six objectives, the second being to determine if a negative IR imaging was sufficient to preclude the use of clinical examination and mammography in the detection of breast cancer. The Working Group, reporting on results of the first four years of this project, gave a short history regarding IR imaging in breast cancer detection. They reported that as of the 1960s, there was intense interest in determining the suitability of IR imaging for large-scale applications, and mass screening was one possibility. The need for technological improvement was recognized and the authors stated that efforts had been made to refine the technique. One of the important objectives behind these efforts had been to achieve a sufficiently high sensitivity and specificity for IR imaging under screening conditions to make it useful as a prescreening device in selecting patients who would then be referred for mammographic examination. It was thought that if successful, this technology would result in a relatively small proportion of women having mammography, a technique that caused concern because of

the possible carcinogenic effects of radiation. The Working Group indicated that the sensitivity and specificity of IR imaging readings from clinical data emanating from interinstitutional studies were close to the corresponding results for physical examination and for mammography. While they noted that these three modalities selected different subgroups of breast cancers, further evaluation of IR imaging as a potential stand-alone screening device in a controlled clinical trial was recommended.

The authors of the BCDDP Working Group then generated a detailed review of mammography and efforts to improve its quality control in image quality and reduction in radiation. They recalled that in the 1960s, the Cancer Control Board of the US Public Health Service had financed a national mammography training program for radiologists and their technologists. Weekly courses in mammography were taught at approximately 10 institutions throughout the country with material supplied by the American College of Radiology. In 1975, shortly after the beginning of this project, the NCI had already funded seven institutions in the United States in a three-year effort aimed at reorienting radiologists and their technologists in more advanced mammographic techniques and interpretation for the detection of early breast cancer.

Age	Clinical Exam	Infrared Grade	Mammography	Histological Size of Tumor (cm)	Grade
65	+ -	4	-	2	2
50	+ -	3	-	1.2	3
32	+	4	-	3	1
45	+ -	-	-	2.5	1
42	+ -	3	-	2	3
43	+	3	-	2.9	2
66	+ -	-	-	0.7	1
53	+	-	-	1	1
38	+ -	3	-	2.8	2
53	+	-	-	0.8	3
45	+	3	-	1.4	3
66	+ -	3	-	1.5	1
48	#	-	-	DCIS	-
46	+	3	-	1.7	3
53	+ -	4	-	0.7	2

+ = suspicious; + - = equivocal; - = nonspecific

In the interim, the American College of Radiology and many interested mammographers and technologists had presented local postgraduate refresher courses and workshops on mammography. Every year for the previous 16 years, the American College of Radiology had supported, planned, and coordinated week-long conferences and workshops aimed at optimizing mammography to promote the early detection and treatment of breast cancer. It was recognized that the well-known primary and secondary mammographic signs of a malignant condition, such as ill-defined mass, skin thickening, skin retraction, marked fibrosis and architectural distortion, obliteration of the retromammary space, and enlarged visible axillary lymph nodes, could detect an established breast cancer. However, the authors emphasized that the more subtle radiographic signs that occur in minimal, clinically occult, and early cancers, such as localized punctate calcifications, focal areas of duct prominence, and minor architectural distortion, could lead to an earlier diagnosis even when the carcinoma was not infiltrating, which was a rare finding when previous mammographic techniques were used.

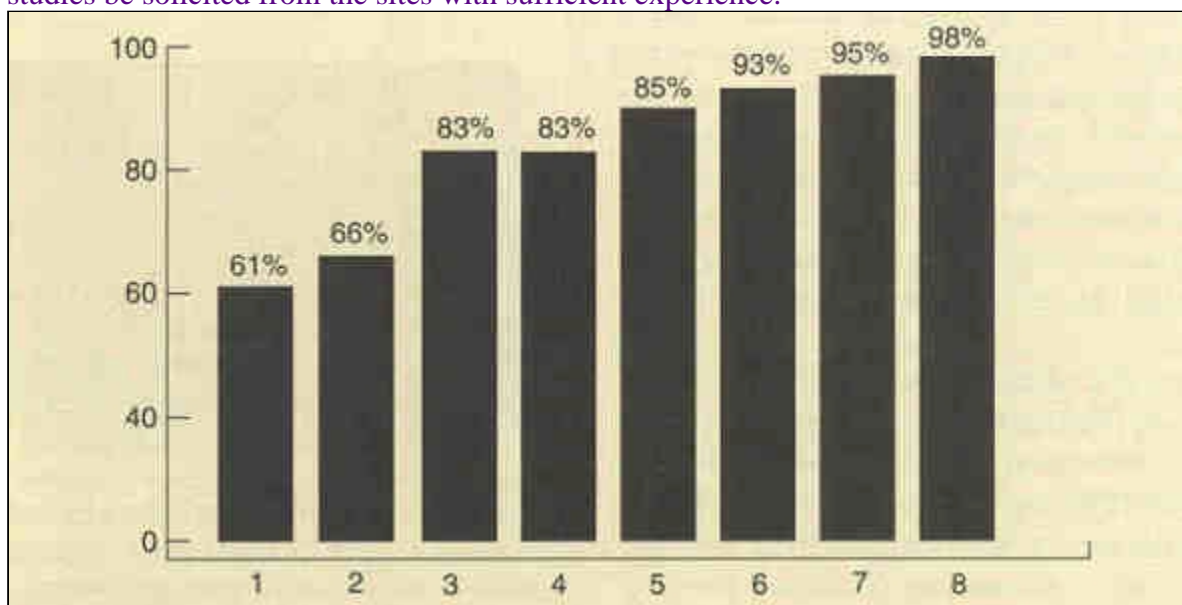
The authors reiterated that the reproduction of early mammography signs required a constant high-quality technique for fine image detail, careful comparison of the two breasts during interpretation, and the search for areas of bilateral parenchymal asymmetry that could reflect underlying cancer. The BCDDP Working Group report stated that mammographies were conducted by trained technicians and that, while some projects utilized radiological technicians for the initial interpretation, most used either a radiologist or a combination of technician and/or radiologist. Quality control for mammography consisted of reviews by the project radiologists and site visits by consultants to identify problems in procedures and the quality of the films.

On the other hand, the entire protocol for IR imaging within this study was summarized in one paragraph, and it indicated that IR imaging was conducted by a BCDDP trained technician. Initial interpretation was made mostly by technicians; some projects used technicians plus radiologists and a few used radiologists and/or physicians with other

specialties for all readings. Quality control relied on review of procedures and interpretations by the project physicians. Positive physical exams and mammographies were reported in various degrees of certainty about malignancy or as suspicious-benign; IR imaging was reported simply as normal or abnormal. While the protocol for the BCDDP required that the three clinical components of this study (physical examination, IR imaging, and mammography) be conducted separately, and initial findings and recommendations be reported independently, it was not possible for the Working Group to assess the extent to which this protocol was adhered to or to evaluate the quality of the examinations.

The detailed extensive results from this Working Group report consisted of over 50 tables. There was, however, only one table that referred to IR imaging, showing that it had detected 41% of the breast cancers during the first screening, while the residual were either normal or unknown. There was no breakdown as far as these two latter groups were concerned. Since 28% of the first screening and 32% of the second screening were picked up by mammography alone, IR imaging was dropped from any further evaluation or consideration. The report stated that it was impossible to determine whether abnormal IR imaging could be predictive of interval (developing between screenings) cancers, since these data were not collected.

By the same token, the Working Group was unable to conclude, with their limited experience, whether the findings were related to the then existing technology of IR imaging or with its application. They did, however, indicate that the decision to dismiss IR imaging should not be taken as a determination of the future of this technique, rather that the procedure continued to be of interest because it does not entail the risk of radiation exposure. In the Working Group's final recommendation, they state that "infrared imaging does not appear to be suitable as a substitute for mammography -for routine screening in the BCDDP" but could not comment on its role as a complementary modality. The report admitted that several individual programs of the BCDDP had results that were more favorable than for the BCDDP as a whole. They also recommended that high priority be given to development and testing of IR imaging under carefully controlled study conditions. They noted that a few suitable sites appeared to be available among the BCDDP and proposed that developmental studies be solicited from the sites with sufficient experience.



**2. Relative sensitivity of clinical exam, mammography, and IR imaging in 100 cases of DCIS, Stage 1 and Stage 2 breast cancer. 1: Positive clinical exam. 2: Positive**

**mammography. 3: Positive clinical or positive mammography. 4: Abnormal IR imaging. 5: Positive or equivocal mammography. 6: Positive clinical or positive or equivocal mammography. 7: Abnormal IR or positive mammography. 8: Abnormal IR or positive mammography or positive clinical.**

Further insight into the inadequate quality control assigned to IR imaging during this program was provided by Haberman, who was a participant in that project [12]. The author reiterated that, while proven expertise in mammography was an absolute requirement for the awarding of a contract to establish a Screening Center, the situation was just the opposite in regard to IR imaging. As no experience was required, when the 27 demonstration projects opened their doors, only five of the centers had pre-existing expertise in IR imaging. Of the remaining screening centers, there was no experience at all in this technology. Finally, more than 18 months after the BCDDP project had begun, the NCI, recognizing this problem, established centers where radiologists and their technicians could obtain further training in IR imaging. Unfortunately, only 11 of the demonstration project directors considered this training of sufficient importance to send their technologists. In some centers, it was reported that there was no effort to cool the patient prior to examination. In other centers, there was complete lack of standardization, and a casual attitude prevailed with reference to interpretation of results. While quality control of this imaging technology could be considered lacking, it was nevertheless subjected to the same stringent statistical analysis as was mammography and clinical breast examination.

### **Post-Breast Cancer Detection Demonstration Projects Era**

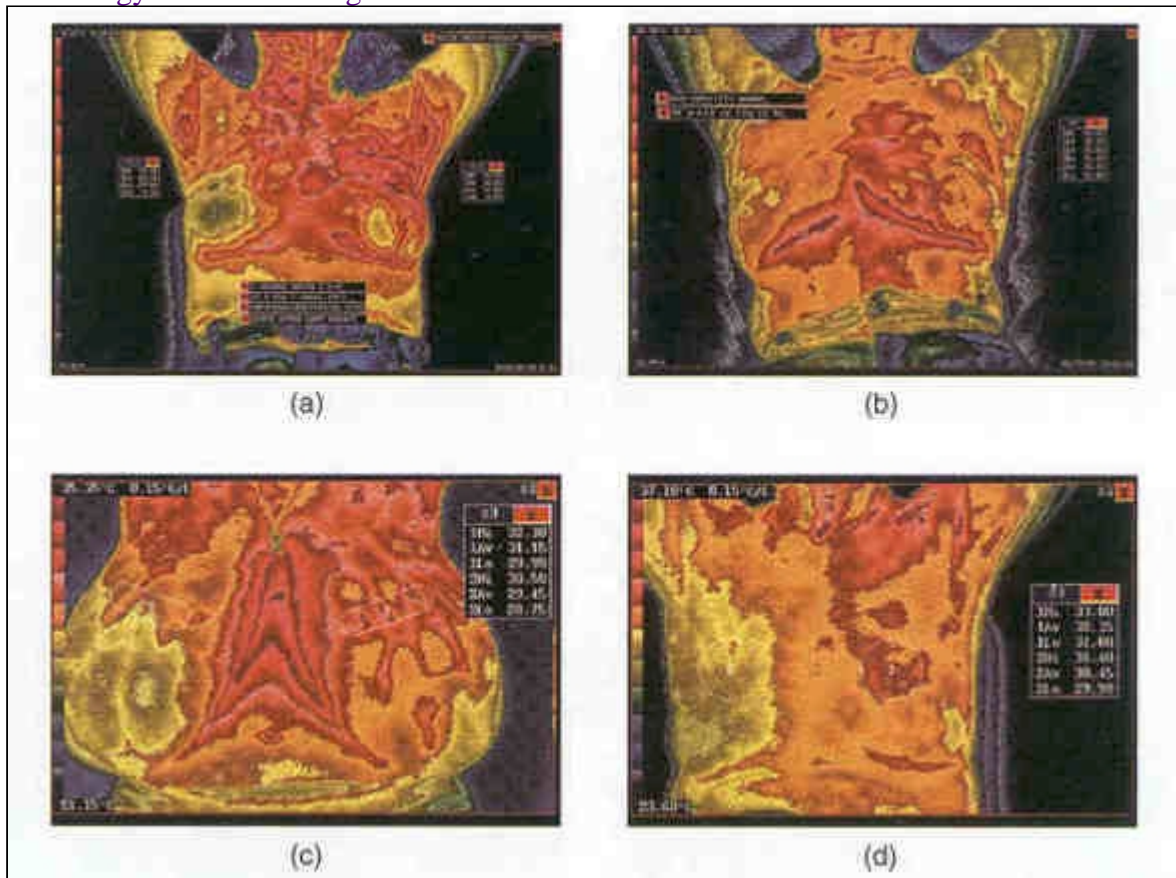
Two small-scale studies carried out in the 1970s by Moskowitz [13] and Threatt [14] reported on the sensitivity and reliability of IR imaging. Both used "experts" to review the images of breast cancer patients. While Moskowitz excluded unreadable images, data from Threatt's study indicated that less than 30% of the images produced were considered good, with the rest being substandard. Both these studies produced poor results, inconsistent with numerous previous multicenter trials, particularly that of Stark [15] who, 16 years earlier, reported an 81% detection rate for preclinical cancers.

Threatt noted that IR imaging demonstrated an increasing accuracy as cancers increased in size or aggressiveness, as did the other testing modalities (i.e., physical examination and mammography). The author also suggested that computerized pattern recognition would help solve the reproducibility problems sometimes associated with this technology and that further investigation was warranted. Moskowitz also suggested that for IR imaging to be truly effective as a screening tool, there needed to be more objective means of interpretation. He proposed that this would be much facilitated by computerized evaluation.

In a more current review of the status of breast imaging, Moskowitz [16] challenged the findings of the recent Canadian National Breast Screening Study (NBSS) that questioned the value of mammography, much in the same way that the Working Group of the BCDDP questioned IR imaging some 20 years previously. Using arguments that could have qualified the disappointing results of the IR imaging used in the BCDDP study, the author explained the poor results of mammography in the NBSS on the basis of inadequate technical quality. He concluded that only 68% of the women received satisfactory breast imaging.

In addition to the usual causes of poor technical quality, failure to use the medial lateral

oblique view resulted in exclusion of the tail of Spence and of much of the upper outer quadrant in many of the subjects screened. There was also a low interobserver agreement in the reading of mammographies, which resulted in a potential diagnostic delay. His review stated that of all noncontrast, nondigital radiological procedures, mammography required the greatest attention to meticulous detail for the training of technologists, selection of the film, contrast monitoring of processing, choosing of equipment, and positioning of the patient. For mammography to be of value, it required dedicated equipment, a dedicated room, dedicated film, and needed to be performed and interpreted by dedicated people. Echoing some of the criticisms that could be pertinent to the BCDDP's use of IR imaging, he indicated that mammography is not a procedure to be performed by the untutored. In rejecting any lack of quality control of infrared imaging during the BCDDP studies by stating that "most of the investigators in the BCDDP did undergo a period of training," the author suggested that the potential of infrared imaging would only increase if there was better standardization of technology and better-designed clinical trials.



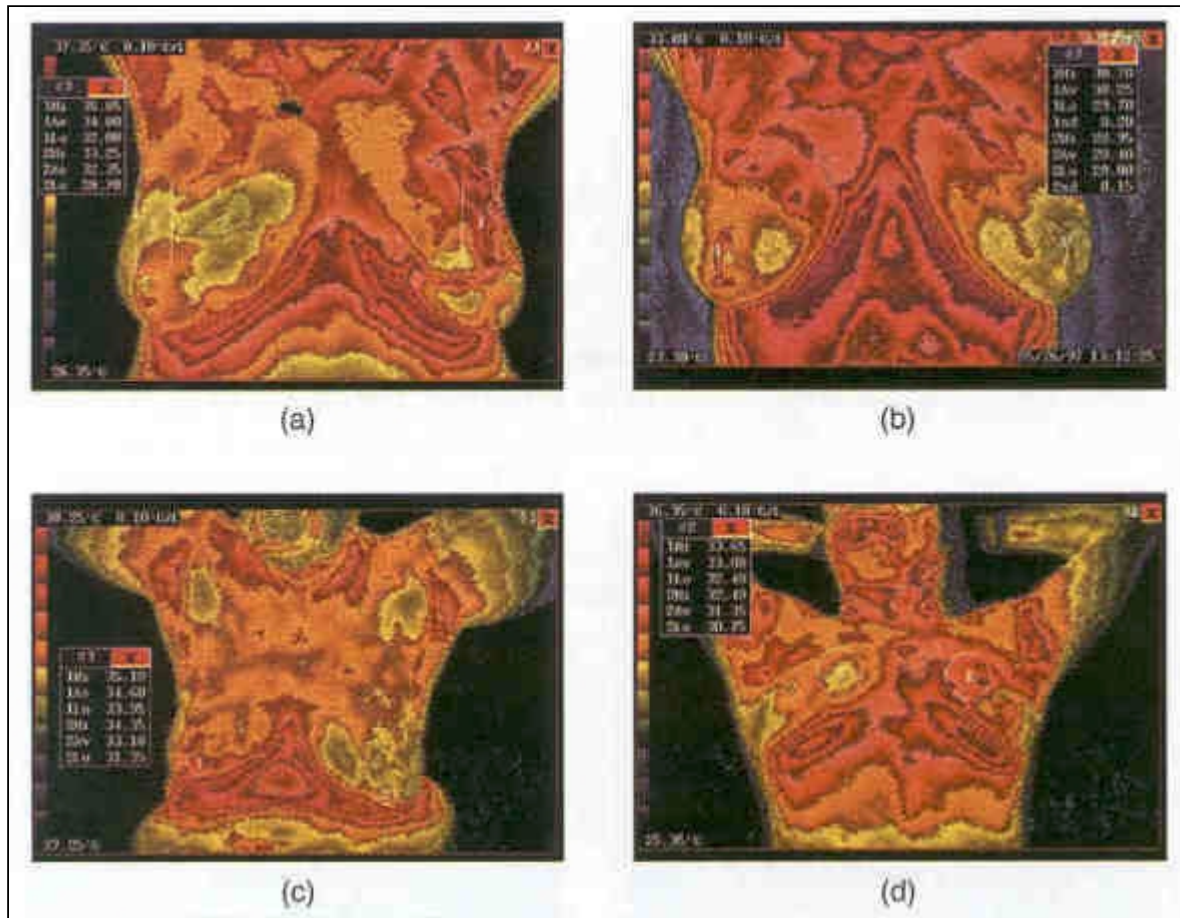
3. (a) 33-year-old with significant vascular asymmetry (SVA) and a temperature difference ( $\Delta T$ ) of 3C (IR-4) in the upper outer quadrant of the left breast. Surgical histology: multifocal ductal carcinoma in situ and early infiltrating ductal carcinoma. (b) 48-year-old with SVA and a  $\Delta T$  of 0.8°C (IR-3) in the lower inner quadrant of the left breast. Surgical histology: 1.6 cm of infiltrating ductal carcinoma. (c) 44-year-old with SVA and a  $\Delta T$  of 1.5°C (IR-4) in the upper inner quadrant of the left breast. Surgical histology: 0.9 cm infiltrating ductal carcinoma. (d) 82-year-old with SVA and a  $\Delta T$  of 1.90°C (IR-4) in the left subareolar area. Surgical histology: 1cm infiltrating ductal carcinoma.

Despite its initial promise, this challenge was not taken up by the medical community, who systematically lost interest in this technique, primarily due to the nebulous BCDDP

experience. Nevertheless, during the 1980s, a number of isolated reports continued to appear, most emphasizing the risk factors associated with abnormal IR imaging. In *Cancer* in 1980, Gautherie and Gros [17] reported their experience with a group of 1245 women who had a mildly abnormal IR image along with either normal or benign disease by conventional means, including physical exam, mammography, ultrasonography, and fine needle aspiration or biopsy. They noted that within five years, more than a third of this group had histologically confirmed cancers. They concluded that IR imaging is useful not only as a predictor of breast cancer risk but also to identify the more rapidly growing neoplasms.

The following year, Amalric, et al. [18], expanded on this concept by reporting that 10% to 15% of patients undergoing IR imaging will be found to be mildly abnormal when the remainder of the examination is essentially unremarkable. They noted that among these "false positive" cases, up to 38% will eventually develop breast cancer when followed closely. In 1981, Mariel [19] carried out a study in France on 655 patients and noted an 82% sensitivity. Two years later, Isard [20] discussed the unique characteristics and respective roles of IR imaging and ultrasonography and concluded that, when used in conjunction with mammography in a multi-imaging strategy, their potential advantages included enhanced diagnostic accuracy, reduction of unnecessary surgery, and improved prognostic ability. The author emphasized that neither of these techniques should be used as a sole screening modality for breast cancer in asymptomatic women but rather as a complementary modality to mammography.

In 1984, Nyirjesy [21] reported in *Obstetrics and Gynecology* a 76% sensitivity for IR imaging of 8767 patients. The same year, Bothmann [22] reported a sensitivity of 68% from a study carried out in Germany on 2702 patients. In 1986, Useki [23] published the results of a Japanese study indicating an 88% sensitivity.



4. (a) 60-year-old with SVA and a  $\Delta T$  of  $1.65^{\circ}\text{C}$  (IR-4) in the upper central area of the left breast. Surgical histology: 2.5 cm infiltrating ductal carcinoma. (b) 59-year-old with a  $\Delta T$  of  $1.85^{\circ}\text{C}$  (IR-3) in the right subareolar area. Surgical histology: 4 cm ductal carcinoma in situ and infiltrating ductal carcinoma. (c) 79-year-old with SVA and a  $\Delta T$  of  $1.5^{\circ}\text{C}$  (IR-4) in the lower mid-portion of the right breast. Surgical histology: multifocal ductal carcinoma in situ. (d) 42-year-old with SVA and a  $\Delta T$  of  $1.65^{\circ}\text{C}$  (IR-4) in the upper inner quadrant of the left breast. Surgical histology: 2.1 cm infiltrating ductal carcinoma.

### Current Application of Infrared Imaging of the Breast

Despite newly available IR technology, due in large part to military research and development, as well as compelling statistics of over 70,000 documented cases showing the contribution of functional IR imaging in a hitherto structurally based strategy to detect breast cancer, few North American centers have shown an interest, and fewer still have published their experience. This is surprising in view of the current consensus regarding the importance of vascular-related events associated with tumor initiation and growth that finally provide a plausible explanation for the IR findings associated with the early development of smaller tumors. The questionable results of the BCDDP and a few small-scale studies are still being referred to by a dwindling authorship that even mention the existence of this imaging modality. This has resulted in a generation of imagers that have neither knowledge of nor training in IR imaging. However, there are a few isolated centers that have continued to

develop an expertise in this modality and have published their results.

In 1993, Head and Elliott [24] reported that improved images of the second-generation of IR systems allowed more objective and quantitative visual analysis. They also reported that growth-rate-related prognostic indicators were strongly associated with the IR results [25]. In 1996, Gamagami [26] studied angiogenesis by IR imaging and reported that hypervascularity and hyperthermia could be shown in 86% of nonpalpable breast cancers. He also noted that in 15% of these cases, this technique helped to detect cancers that were not visible through mammography.

The concept of angiogenesis, suggested by Gamagami as an integral part of early breast cancer, was reiterated in 1996 by Guido and Schnitt [27], whose observations suggested that angiogenesis is an early event in the development of breast cancer. They noted that it may occur before tumor cells acquire the ability to invade the surrounding stroma and even before there is morphologic evidence of an in situ carcinoma.

In contemporary publications, Anbar [28, 29], using an elegant biochemical and immunological cascade, suggested that the empirical observation that small tumors capable of producing notable IR changes could be due to enhanced perfusion over a substantial area of breast surface via tumor-induced nitric oxide vasodilatation. He introduced the importance of dynamic area telethermometry to validate IR's full potential.

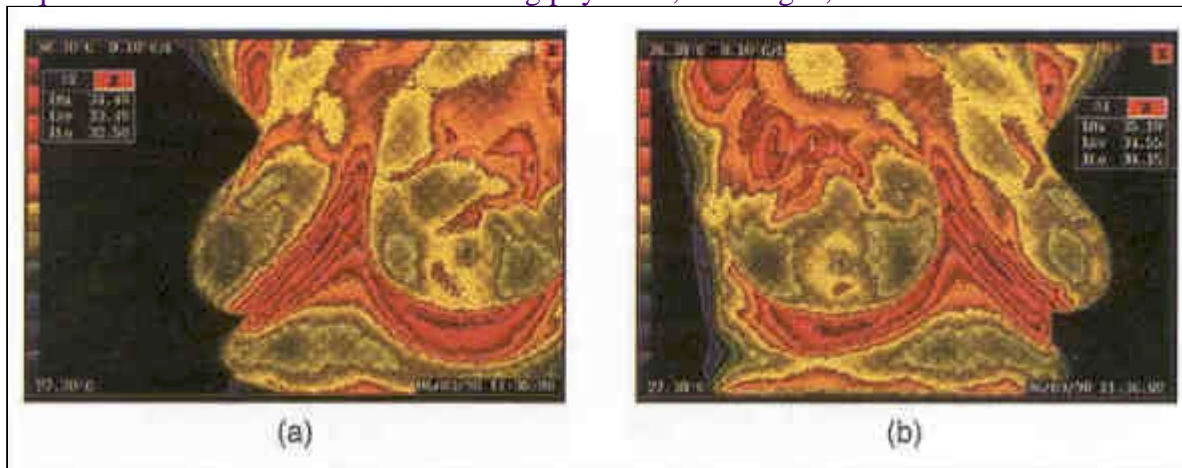
#### **The Ville Marie Initial Experience with Currently Available Infrared Imaging**

There is still a general consensus that the crucial strategy for the first-line detection of breast cancer depends essentially on clinical examination and mammography. Limitation of the former, with its reported sensitivity rate below 65%, is well recognized [30], and even the proposed value of breast self-examination is now being contested [31]. With the current emphasis on earlier detection, there is an increasing reliance on better imaging. Mammography is still recognized as our most reliable and cost-effective imaging modality [16]. However, variable interpretation [32] and tissue density, now proposed as a risk factor itself [33] and seen in both younger patients and those on hormonal replacement [34], prompted us to reassess currently available IR technology spearheaded by military research and development, as a first-line component of a multi-imaging breast cancer detection strategy ([Fig. 1](#)).

This modality is capable of quantifying minute temperature variations and qualifying abnormal vascular patterns, probably associated with regional angiogenesis, neovascularization, and nitric-oxide-induced regional vasodilatation [28], frequently associated with tumor initiation and progression, and potentially an early predictor of tumor growth rate [25, 27]. To replace an older unit, we acquired a new fully integrated, high-resolution, computerized IR imaging station to complement our mammography units. To validate its reported ability to help detect early tumor-related regional metabolic and vascular changes [26], we limited our initial review to a series of 100 successive cases of breast cancer that filled the following three criteria: (a) minimal evaluation included a clinical exam, mammography, and IR imaging; (b) definitive surgical management constituted the preliminary therapeutic modality carried out at one of our affiliated institutions; and (c) the final staging consisted of either noninvasive cancer ( $n = 4$ ), Stage I ( $n = 42$ ), or Stage II ( $n = 54$ ) invasive breast cancer.

While 94% of these patients were referred to our Comprehensive Breast Center for the first time, 65% from family physicians, and 29% from specialists, the remaining 6% had their diagnosis of breast cancer at a follow-up visit. Age at diagnosis ranged from 31 to 84 years, with a mean of 53. The mean histologic tumor size was 2.5 cm. Lymphatic, vascular, or neural invasion was noted in 18% of the patients; and concomitant noninvasive cancer was present, along with the invasive component, in 64%. Of the 89 patients who had axillary lymph node dissection, one-third had involved nodes and 38% of the tumors were histologic Grade III.

While most of these patients underwent standard four-view mammography, with additional views when indicated, using a GE DMR apparatus at our center, in 17 cases we relied on recent and adequate quality outside films. Mammograms were interpreted by our examining physician and radiologist, both having access to the clinical findings. Lesions were considered suspicious if either noted findings indicative of carcinoma. The remainder were considered either contributory but equivocal or nonspecific. A nonspecific mammography required concordance with our examining physician, radiologist, and the authors.



**5. 56-year-old patient is referred with a negative clinical exam, ultrasound, and suspicious mammographic calcifications in the left breast. Infrared imaging in 1998 revealed SVA and a  $\Delta T$  of  $1.15^{\circ}\text{C}$  (IR-4) in the upper outer quadrant of the right breast (b) compared with the left breast (a). The IR abnormality was not pursued and stereotaxic biopsy of the left breast revealed benign cells. One year later, this patient developed a fullness in the upper outer quadrant of the right breast. Core biopsy revealed an infiltrating ductal carcinoma and the patient was started on preoperative chemotherapy.**



**6. The anticipated stability of IR imaging is evident in the images done on the same patient 12 months apart: (a) May 1998; (b) May 1999.**

Our integrated IR station consisted of a scanning-mirror optical system containing a mercury-cadmium-telluride detector (Bales Scientific, CA) with a spatial resolution of 600 optical lines, a central processing unit providing multitasking capabilities, and a high-resolution color monitor capable of displaying 1024 X 768 resolution points and up to 110 colors or shades of gray per image. Infrared imaging took place in a draft-free thermally controlled room, maintained at between 18°C and 20°C, after a 5 min equilibration period during which the patient sat disrobed with her hands locked over her head. We requested that the patients refrain from alcohol, coffee, smoking, exercise, deodorant, and lotions for three hours prior to testing.

Four images (an anterior, an undersurface, and two lateral views) were generated simultaneously on the video screen. The examining physician would digitally adjust them to minimize noise and enhance detection of more subtle abnormalities prior to exact on-screen computerized temperature reading and IR grading. Images were then electronically stored on retrievable laser discs. Our grading scale relies on pertinent clinical information, comparing current IR images of both breasts with previous images. An abnormal IR image required the presence of at least one abnormal sign ([Table 1](#)). To assess the false positive rate, we reviewed, using similar criteria, our last 100 consecutive patients who underwent an open breast biopsy that produced a benign histology. We used the Carefile Data Analysis Program to evaluate the detection rate of variable combinations of clinical exam, mammography, and IR imaging.

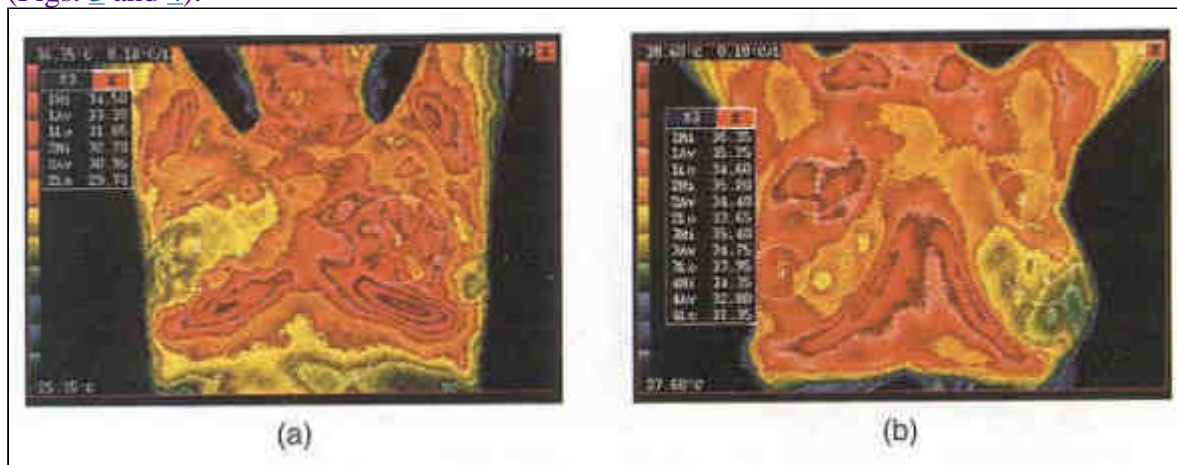
### **Results and Discussion of the Ville Marie Infrared Series**

Of this series, 61% presented with a suspicious palpable abnormality, while the remainder had either an equivocal (34%) or a nonspecific clinical exam (5%). Similarly, mammography was considered suspicious for cancer in 66%, while 19% were contributory but equivocal, and 15% were considered nonspecific. Infrared imaging revealed minor variations (IR- 1 or IR-2) in 17% of our patients while the remaining 83% had at least one (34%), two (37%), or three (12%) abnormal IR signs. Of the 39 patients with either a nonspecific or equivocal clinical exam, 31 had at least one abnormal IR sign, with this modality providing pertinent indication of a potential abnormality in 14 of these patients who, in addition, had an equivocal or nonspecific mammography

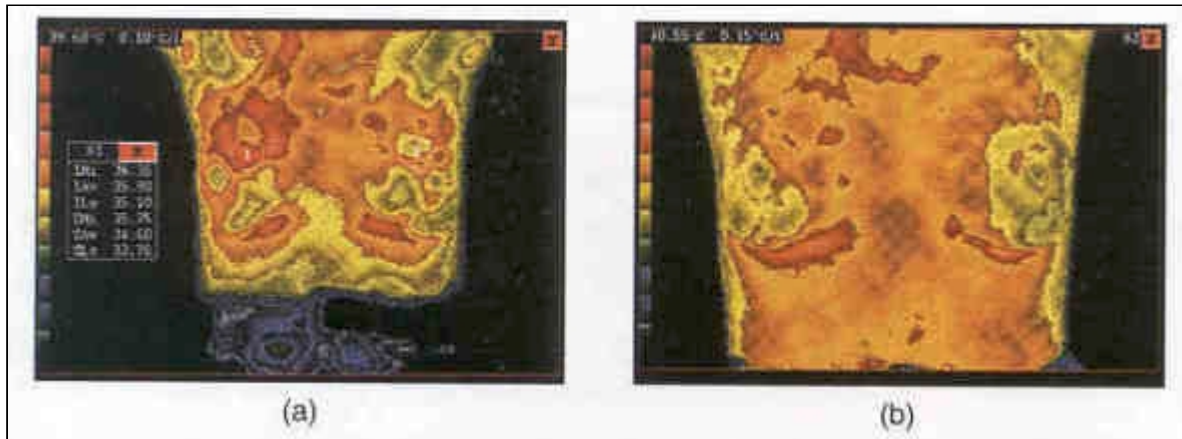
Among the 15 patients with a nonspecific mammography, there were 10 patients (mean age of 48; five years younger than the full sample) who had an abnormal IR image. This abnormal finding constituted a particularly important indicator in six of these patients who also had only equivocal clinical findings (Table 2). While 61 % of our series presented with a suspicious clinical exam, the additional information provided by the 66 suspicious mammographies resulted in an 83% detection rate. The combination of only suspicious mammograms and abnormal IR imaging increased the sensitivity to 93%, with a farther increase to 98% when suspicious clinical exams were also considered (Fig. 2).

The mean histologically measured tumor size for those cases undetected by mammography was 1.66 cm, while those undetected by IR imaging averaged 1.28 cm. In a concurrent series of 100 consecutive eligible patients who had an open biopsy that produced benign histology, 19% had an abnormal IR image and 30% had an abnormal preoperative mammography that was the only indication for surgery in 16 cases.

The 83% sensitivity of IR imaging in this series is higher than the 70% rate for similar Stage I and 11 patients tested from the Royal Marsden Hospital two decades earlier [6]. Although our results might reflect an increased index of suspicion associated with a referred population, this factor should apply equally to both clinical exam and mammography, maintaining the validity of our evaluation. Additional factors could include our standard protocol, our physicians' prior experience with IR imaging, their involvement in both image production and interpretation, as well as their access to much improved image acquisition and precision (Figs. 3 and 4).



7. (a) 50-year-old patient had an IR imaging with significant SVA and a  $\Delta T$  of 2.35°C in the left breast (IR-5). Surgical histology: multifocal aggressive invasive carcinoma with five positive lymph nodes requiring a total mastectomy. (b) A 50-year-old patient had an IR imaging showing SVA and a  $\Delta T$  of 3.4°C (IR-5) in the right breast. Surgical histology: extensive multifocal infiltrating ductal carcinoma and 15 positive lymph nodes requiring a total mastectomy.



**8. (a) A 32-year-old with core biopsy-proven extensive carcinoma of the upper aspect of the right breast. Infrared imaging prior to preoperative chemotherapy revealed SVA, tortuous vascular pattern, and a  $\Delta T$  of  $1.3^{\circ}\text{C}$  (IR-5) in the right breast. (b) Post-chemotherapy and preoperative IR imaging revealed near complete resolution of prior findings (IR-2). Surgical histology: revealed absence of any residual cancer of the breast and axillary dissection revealed five positive nodes.**

While most previous IR cameras had 8-bit (one part in 256) resolution, current cameras are capable of one part in 4096 resolution, providing enough dynamic range to capture all images with  $0.05^{\circ}\text{C}$  discrimination without the need for range switching. With the advancement of video display and enhanced gray and colors, multiple high-resolution views can be compared simultaneously on the same monitor. Faster computers now allow processing functions such as image subtraction and digital filtering techniques for image enhancement. New algorithms provide soft tissue imaging by characterizing dynamic heat-flow patterns. These and other innovations have made vast improvements in the medical IR technology available today.

The detection rate in a series where half the tumors were under 2 cm would suggest that tumor-induced thermal patterns detected by currently available IR technology are more dependent on early vascular and metabolic changes. These changes possibly are induced by regional nitric oxide diffusion and ferritin interaction, rather than strictly on tumor size [28]. This hypothesis agrees with the concept that angiogenesis may precede any morphological changes [27]. Although both initial clinical exam and mammography are crucial in signaling the need for further investigation, equivocal and nonspecific findings can still result in a combined delayed detection rate of 10% [16].

When eliminating the dubious contribution of our 34 equivocal clinical exams and 19 equivocal mammograms, which is disconcerting to both physician and patient, the alternative information provided by IR imaging increased the index of concern of the remaining patients with suspicious mammograms by 27% and the combination of suspicious clinical exams or suspicious mammograms by 15% (Fig. 2). An imaging-only strategy, consisting of both suspicious and equivocal mammography and abnormal IR imaging, also detected 95% of these tumors even without the input of the clinical exam. Infrared imaging's most tangible contribution in this series was to signal an abnormality in a younger cohort of breast cancer patients who had noncontributory mammograms and also nonspecific clinical exams who conceivably would not have been passed on for second-line evaluation (Table 2).

While 17% of these tumors were undetected by IR imaging, either due to insufficient production or detection of metabolic or vascular changes, the 19% false positive rate in

histologically proven benign conditions, in part a reflection of our current grading system, suggests sufficient specificity for this modality to be used in an adjuvant setting.

Our initial reappraisal would also suggest that IR imaging, based more on process than structural changes and requiring neither contact, compression, radiation, or venous access, can provide pertinent and practical complementary information to both clinical exam and mammography, our current first line detection modalities. Quality-controlled abnormal IR imaging heightened our index of suspicion in cases where clinical or mammographic findings were equivocal or nonspecific, thus signaling further investigation rather than observation (Fig. 1).

### **Future Considerations Concerning Infrared Imaging**

Mammography, our current standard first-line imaging modality, cannot make the diagnosis of breast cancer but only reflect an abnormality that could then prompt the clinician to intervene rather than to observe. This decision is crucial since it is at this first level that sensitivity and specificity are most vulnerable. There is a clear consensus that we have not yet developed the ideal breast imaging technique, and this is reflected in the flurry of new modalities that have recently appeared. While progress in imaging and better training have resulted in the gradual decrease in the average size of breast tumors over the previous decade, the search for improved imaging continues in an attempt to further reduce the false negative rate and promote earlier diagnosis.

Digital mammography is being developed to further advance the contribution of structural imaging such as mammography and ultrasound. However, there is now new emphasis on developing functional imaging that can exploit early vascular and metabolic changes associated with tumor initiation that often predate morphological changes that most of our current structural imaging modalities still depend on; thus, the enthusiasm in the development of sestamibi scanning, Doppler ultrasound, and MRI of the breast [ 16]. Unfortunately, as promising as these modalities are, they are often too cumbersome, costly, inaccessible, or require intravenous access to be used as first-line detection modalities alongside clinical exam and mammography.

On the other hand, integrating IR imaging, a safe and practical modality, into the first-line strategy, can increase the sensitivity at this crucial stage by providing an early warning of an abnormality that in some cases is not evident in the other components (Fig. 5). Combining IR imaging and mammography in an IR-assisted mammography strategy is particularly appealing in the current era of increased emphasis on screening by imaging and less reliance on palpation as tumor size further decreases.

Intercenter standardization of a protocol concerning patient preparation, temperature-controlled environment, digital image production, enhanced grading, and archiving, as well as data collection and sharing, are all important factors that are beginning to be addressed. New technology could permit real-time image acquisition that could be submitted to computerized image reading, which will further enhance the physician's ability to detect subtle abnormalities.

Physician training is an essential component for this imaging modality to realize its full

potential. A thorough knowledge of all aspects of benign and malignant breast pathology and familiarity with image acquisition and the interpretation protocol are important features. In addition, access to the full clinical history, mammography, other imaging modalities, and to prior IR images that should remain stable (Fig. 6) are all contributory features. This modality needs to benefit from the same quality control recently applied to mammography. This is especially important since there are no current IR regulations, as it poses no health threat and does not use radiation, and could thus fall victim to untrained personnel who could misuse it on unsuspecting patients as was previously the case.



**9. (a) A 52-year-old patient with a core biopsy-proven extensive carcinoma of the right breast. Infrared imaging prior to preoperative chemotherapy revealed SVA over an extensive area and a  $\Delta T$  of  $1.2^{\circ}\text{C}$  (IR-5). (b) Post-chemotherapy and preoperative infrared imaging reveals complete resolution of prior findings (IR-1). Surgical histology: reveals no residual tumor in the resected breast specimen and all 21 lymph nodes were negative.**

Its future promise, however, resides primarily in its ability to qualify and quantify vascular and metabolic changes related to early tumor genesis. The proposals that a higher temperature difference ( $\Delta T$ ) and increased vascular asymmetry are potential prognostic factors of tumor aggressivity need to be validated by further research (Fig. 7). The same applies to the possibility that the reduction in IR changes often seen following preoperative chemotherapy reflect reduction in neoangiogenesis and thus treatment efficiency (Figs. 8 and 9). They remain, at the very least, extremely interesting and promising areas for future research, particularly in view of the current interest in new angiogenesis-related therapeutic strategies. Its contribution to monitoring postoperative patients [Fig. 10(a)] and its ability to recognize recurrent cancer [Fig. 10(b)] are other areas for further clinical trials.



**10. (a) An infrared imaging five years following a left partial mastectomy and radiotherapy for cancer in a patient showing no evidence of any infrared abnormality and no clinical evidence of any recurrence (IR-1). (b) A 52-year-old patient, five years following right partial mastectomy, radiation, and chemotherapy for breast cancer. A follow-up infrared image now shows new SVA and a  $\Delta T$  of  $1.5^{\circ}\text{C}$  (IR-4) in the area of the previous surgery. Surgical histology: revealed recurrent infiltrating ductal carcinoma.**

As is the case for all current imaging modalities, the fact that this modality does not detect all tumors should not detract from its contribution as a reliable functional adjuvant addition to our current first-line imaging strategy that is still based on mammography, a structural modality. A good first-line imaging modality must be safe, convenient, and able to help detect primarily the more aggressive tumors where early intervention can have a greater impact on survival.

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