

THE BIOMEDICAL ENGINEERING HANDBOOK

THIRD EDITION

Medical Devices and Systems

EDITED BY

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Taylor & Francis
Taylor & Francis Group

The Biomedical Engineering Handbook

Third Edition

Medical Devices and Systems

The following is Chapter 25 of the 2006 edition of *The Biomedical Engineering Handbook, Third Edition, Medical Devices and Systems* published by CRC Press.

Joseph D. Bronzino, editor of the handbook, comments that “Medical Devices and Systems is an authoritative reference text and is considered the “bible” of biomedical engineering. This latest volume presents new and updated material contributed by a team of world-renowned experts. The text reflects the most recent advances in both research and practice, and authoritatively covers sensor and imaging technologies, signal analysis, and medical instrumentation. This Third Edition presents an excellent summary of the status of knowledge and activities of biomedical engineers in the beginning of the 21st century.”

The principle author of this chapter, Dr. William Amalu, is joined by three other world-renowned experts in this field to present the state-of-the-art in infrared breast imaging. The following chapter contains a review of the literature along with a presentation of infrared physics, imaging system standards, a brief historical background, laboratory and patient imaging standards and protocols, and a look at the future of this lifesaving technology.

The following is a brief highlight of the chapter that follows:

- **In 1982, the FDA approved breast thermography as an adjunctive breast cancer screening procedure.**
- **Breast thermography has undergone extensive research since the late 1950's.**
- **Over 30 years of research comprising over 800 peer-reviewed studies on breast thermography exist in the index-medicus literature.**
- **In this database, well over 300,000 women have been included as study participants.**
- **The numbers of participants in many studies are very large -- 10K, 37K, 60K, 85K ...**
- **Some of these studies have followed patients up to 12 years.**
- **Strict standardized interpretation protocols have been established for over 15 years.**
- **Breast thermography has an average sensitivity and specificity of 90%.**
- **An abnormal thermogram is 10 times more significant as a future risk indicator for breast cancer than a first order family history of the disease.**
- **A persistent abnormal thermogram carries with it a 22x higher risk of future breast cancer.**
- **An abnormal infrared image is the single most important marker of high risk for developing breast cancer.**
- **Breast thermography has the ability to detect the first signs that a cancer may be forming up to 10 years before any other procedure can detect it.**
- **Research has shown that breast thermography significantly augments the long-term survival rates of its recipients by as much as 61%.**
- **When used as part of a multimodal approach (clinical examination + mammography + thermography) 95% of early stage cancers will be detected.**

25

Infrared Imaging of the Breast — An Overview

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Prologue

The use of infrared imaging in health care is not a recent phenomenon. Its utilization in breast cancer screening, however, is seeing renewed interest. This attention is fueled by research that clearly demonstrates the value of this procedure and the tremendous impact it has on the mortality of breast cancer.

Infrared imaging of the breast has undergone extensive research since the late 1950s. Over 800 papers can be found in the indexed medical literature. In this database, well over 300,000 women have been included as study participants. The number of participants in many studies are very large and range from 10,000 to 85,000 women. Some of these studies have followed patients up to 12 years in order to establish the technology's ability as a risk marker.

With strict standardized interpretation protocols having been established for over 15 years, infrared imaging of the breast has obtained an average sensitivity and specificity of 90%. As a future risk indicator for breast cancer, a persistent abnormal thermogram carries a 22 times higher risk and is 10 times more

significant than a first order family history of the disease. Studies clearly show that an abnormal infrared image is the single most important risk marker for the existence of or future development of breast cancer.

25.1 Introduction

The first recorded use of thermobiological diagnostics can be found in the writings of Hippocrates around 480 B.C. [1]. A mud slurry spread over the patient was observed for areas that would dry first and was thought to indicate underlying organ pathology. Since this time, continued research and clinical observations proved that certain temperatures related to the human body were indeed indicative of normal and abnormal physiologic processes.

In the 1950s, military research into infrared monitoring systems for nighttime troop movements ushered in a new era in thermal diagnostics. Once declassified in the mid-1950s, infrared imaging technology was made available for medical purposes. The first diagnostic use of infrared imaging came in 1956 when Lawson discovered that the skin temperature over a cancer in the breast was higher than that of normal tissue [2–4]. He also showed that the venous blood draining the cancer is often warmer than its arterial supply.

The Department of Health Education and Welfare released a position paper in 1972 in which the director, Thomas Tiernery, wrote, “The medical consultants indicate that thermography, in its present state of development, is beyond the experimental state as a diagnostic procedure in the following 4 areas: (1) Pathology of the female breast. (2)...” On January 29, 1982, the Food and Drug Administration published its approval and classification of thermography as an adjunctive diagnostic screening procedure for the detection of breast cancer. Since the late 1970s, numerous medical centers and independent clinics have used thermography for a variety of diagnostic purposes.

Since Lawson’s groundbreaking research, infrared imaging has been used for over 40 years as an adjunctive screening procedure in the evaluation of the breast. In this time significant advances have been made in infrared detection systems and the application of sophisticated computerized image processing.

25.2 Fundamentals of Infrared Breast Imaging

Clinical infrared imaging is a procedure that detects, records, and produces an image of a patient’s skin surface temperatures and thermal patterns. The image produced resembles the likeness of the anatomic area under study. The procedure uses equipment that can provide both qualitative and quantitative representations of these temperature patterns.

Infrared imaging does not entail the use of ionizing radiation, venous access, or other invasive procedures; therefore, the examination poses no harm to the patient. Classified as a functional imaging technology, infrared imaging of the breast provides information on the normal and abnormal physiologic functioning of the sensory and sympathetic nervous systems, vascular system, and local inflammatory processes.

25.2.1 Physics

All objects with a temperature above absolute zero (-273 K) emit infrared radiation from their surface. The Stefan-Boltzmann Law defines the relation between radiated energy and temperature by stating that the total radiation emitted by an object is directly proportional to the object’s area and emissivity and the fourth power of its absolute temperature. Since the emissivity of human skin is extremely high (within 1% of that of a black body), measurements of infrared radiation emitted by the skin can be converted directly into accurate temperature values. This makes infrared imaging an ideal procedure to evaluate surface temperatures of the body.

25.2.2 Equipment Considerations

Infrared rays are found in the electromagnetic spectrum within the wavelengths of $0.75\ \mu\text{m}$ to $1\ \text{mm}$. Human skin emits infrared radiation mainly in the $2\text{--}20\ \mu\text{m}$ wavelength range, with an average peak at $9\text{--}10\ \mu\text{m}$ [5]. With the application of Planck's equation and Wein's Law, it is found that approximately 90% of emitted infrared radiation in humans is in the longer wavelengths ($6\text{--}14\ \mu\text{m}$).

There are many important technical aspects to consider when choosing an appropriate clinical infrared imaging system (The majority of which is outside the scope of this chapter). However, minimum equipment standards have been established from research studies, applied infrared physics, and human anatomic and physiologic parameters [6,7]. Absolute, spatial, and temperature resolution along with thermal stability and adequate computerized image processing are just a few of the critical specifications to take into account. However, the most fundamental consideration in the selection of clinical infrared imaging equipment is the wavelength sensitivity of the infrared detector. The decision on which area in the infrared spectrum to select a detector from depends on the object one wants to investigate and the environmental conditions in which the detection is taking place. Considering that the object in question is the human body, Planck's equation leads us to select a detector in the $6\text{--}14\ \mu\text{m}$ region. Assessment of skin temperature by infrared measurement in the $3\text{--}5\ \mu\text{m}$ region is less reliable due to the emissivity of human skin being farther from that of a blackbody in that region [8,9]. The environment under which the examination takes place is well controlled, but not free from possible sources of detection errors. Imaging room environmental artifacts such as reflectance can cause errors when shorter wavelength detectors (under $7\ \mu\text{m}$) are used [10]. Consequently, the optimum infrared detector to use in imaging the breast, and the body as a whole, would have a sensitivity in the longer wavelengths spanning the $9\text{--}10\ \mu\text{m}$ range [7–14].

The problems encountered with first generation infrared camera systems, such as incorrect detector sensitivity (shorter wavelengths), thermal drift, calibration, analog interface, and so on, have been solved for almost two decades. Modern computerized infrared imaging systems have the ability to discern minute variations in thermal emissions while producing extremely high-resolution images that can undergo digital manipulation by sophisticated computerized analytical processing.

25.2.3 Laboratory and Patient Preparation Protocols

In order to produce diagnostic quality infrared images, certain laboratory and patient preparation protocols must be strictly adhered to. Infrared imaging must be performed in a controlled environment. The primary reason for this is the nature of human physiology. Changes from a different external (noncontrolled room) environment, clothing, and the like, produce thermal artifacts. In order to properly prepare the patient for imaging, the patient should be instructed to refrain from sun exposure, stimulation or treatment of the breasts, cosmetics, lotions, antiperspirants, deodorants, exercise, and bathing before the exam.

The imaging room must be temperature and humidity-controlled and maintained between 18 and 23°C , and kept to within 1°C of change during the examination. This temperature range insures that the patient is not placed in an environment in which their physiology is stressed into a state of shivering or perspiring. The room should also be free from drafts and infrared sources of heat (i.e., sunlight and incandescent lighting). In keeping with a physiologically neutral temperature environment, the floor should be carpeted or the patient must wear shoes in order to prevent increased physiologic stress.

Lastly, the patient must undergo 15 min of waist-up nude acclimation in order to reach a condition in which the body is at thermal equilibrium with the environment. At this point, further changes in the surface temperatures of the body occur very slowly and uniformly; thus, not affecting changes in homologous anatomic regions. Thermal artifacts from clothing or the outside environment are also removed at this time. The last 5 min of this acclimation period is usually spent with the patient placing their hands on top of their head in order to facilitate an improved anatomic presentation of the breasts for imaging. Depending

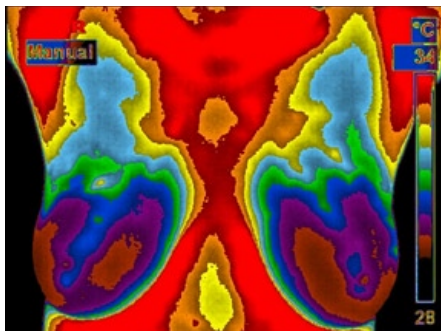


FIGURE 25.1 Bilateral frontal.

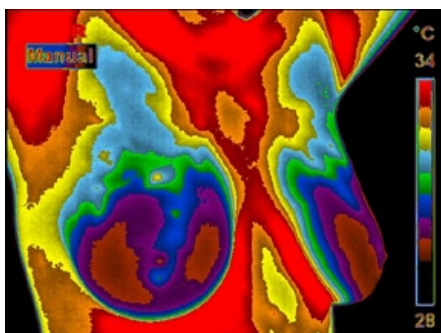


FIGURE 25.2 Right oblique.

on the patient's individual anatomy, certain positioning maneuvers may need to be implemented such that all of the pertinent surfaces of the breasts may be imaged. In summary, adherence to proper patient and laboratory protocols is absolutely necessary to produce a physiologically neutral image, free from artifact and ready for interpretation.

25.2.4 Imaging

The actual process of imaging is undertaken with the intent to adequately detect the infrared emissions from the pertinent surface areas of the breasts. As with mammography, a minimum series of images is needed in order to facilitate adequate coverage. The series includes the bilateral frontal breast along with the right and left oblique views (a right and left single breast close-up view may also be included). The bilateral frontal view acts as a scout image to give a baseline impression of both breasts. The oblique views (approximately 45° to the detector) expose the lateral and medial quadrants of the breasts for analysis. The optional close-up views maximize the use of the detector allowing for the highest thermal and spatial resolution image of each breast. This series of images takes into consideration the infrared analyses of curved surfaces and adequately provides for an accurate analysis of all the pertinent surface areas of the breasts (see Figure 25.1 to Figure 25.5).

Positioning of the patient prior to imaging facilitates acclimation of the surface areas and ease of imaging. Placing the patient in a seated or standing posture during the acclimation period is ideal to facilitate these needs. In the seated position, the patient places their arms on the arm rests away from the body to allow for proper acclimation. When positioning the patient in front of the camera, the use of a rotating chair or having the patient stand makes for uncomplicated positioning for the necessary views.

Because of differing anatomy from patient to patient, special views may be necessary to adequately detect the infrared emissions from the pertinent surface areas of the breasts. The most common problem

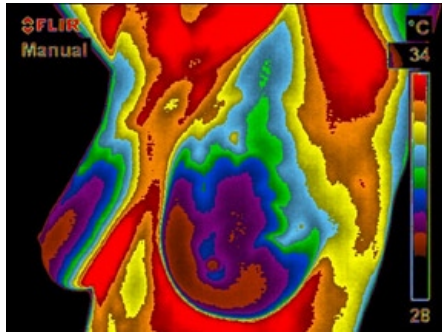


FIGURE 25.3 Left oblique.

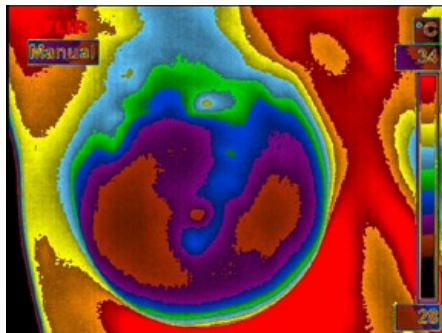


FIGURE 25.4 Right close-up.

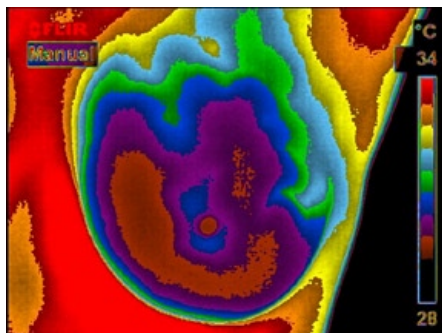


FIGURE 25.5 Left close-up.

encountered is inadequate viewing of the inferior quadrants due to nipple ptosis. This is easily remedied by adding “lift views.” Once the baseline images are taken, the patient is asked to “lift” each breast from the Tail of Spence exposing the inferior quadrants for detection. Additional images are then taken in this position in order to maintain the surface areas covered in the standard views.

25.2.5 Special Tests

In the past, an optional set of views may have been added to the baseline images. Additional views would be taken after the patient placed their hands in ice cold water as a thermoregulatory cold challenge. It was hoped that this dynamic methodology would increase the sensitivity and specificity of the thermographic procedure.

In order to understand the hopes placed on this test, one needs to understand the underlying physiologic mechanisms of the procedure. The most common and accepted method of applied thermoregulatory challenge involves ice water immersion of the hands or feet (previous studies investigating the use of fans or alcohol spray noted concerns over the creation of thermal artifacts along with the methods causing a limited superficial effect). The mechanism is purely neurovascular and involves a primitive survival reflex initiated from peripheral neural receptors and conveyed to the central nervous system. To protect the body from hypothermia, the reflex invokes a sympathetically mediated blood vessel constriction in the periphery in an attempt to maintain the normal core temperature set point. This stress test is intended to increase the sensitivity of the thermogram by attempting to identify nonresponding blood vessels such as those involved in angiogenesis associated with neoplasm. Blood vessels produced by cancerous tumors are simple endothelial tubes devoid of a muscular layer and the neural regulation afforded to embryologic vessels. As such, these new vessels would fail to constrict in response to a sympathetic stimulus. In the normal breast, test results would produce an image of relative cooling with attenuation of vascular diameter. A breast harboring a malignancy would theoretically remain unchanged in temperature or demonstrate hyperthermia with vascular dilation. However, to date it has not been found that the stress test offers any advantage over the baseline images [15].

For well over a decade, leading experts and researchers in the field of infrared breast imaging have discontinued the use of the cold challenge. Yet, in a 2004 detailed review of the literature combined with an investigational study, Amalu [15] explored the validity of the cold challenge test. Results from 23 patients with histologically confirmed breast cancers along with 500 noncancer cases were presented demonstrating positive and negative responses to the challenge. From the combined literature review and study analysis it was found that the test did not alter the clinical decision-making process for following up suspicious thermograms, nor did it enhance the detection of occult cancers found in normal thermograms. In summary, it was found that there was no evidence to support the use of the cold challenge. The study noted insufficient evidence to warrant its use as a mandated test with all women undergoing infrared breast imaging. It also warned that it would be incorrect to consider a breast thermogram “substandard” if a cold challenge was not included. In conclusion, Amalu stated that “Until further studies are performed and ample evidence can be presented to the contrary, a review of the available data indicates that infrared imaging of the breast can be performed excluding the cold challenge without any known loss of sensitivity or specificity in the detection of breast cancers.”

25.2.6 Image Interpretation

Early methods of interpretation of infrared breast images was based solely on qualitative (subjective) criteria. The images were read for variations in vascular patterning with no regard to temperature variations between the breasts (Tricore method) [16]. This led to wide variations in the outcomes of studies performed with inexperienced interpreters. Research throughout the 1970s proved that when both qualitative and quantitative data were incorporated in the interpretations, an increase in sensitivity and specificity was realized. In the early 1980s, a standardized method of thermovascular analysis was proposed. The interpretation was composed of 20 discrete vascular and temperature attributes in the breast [17,18]. This method of analysis was based on previous research and large scale studies comprising tens of thousands of patients. Using this methodology, thermograms would be graded into 1 of 5 TH (thermobiological) classifications. Based on the combined vascular patterning and temperatures across the two breasts, the images would be graded as TH1 (normal nonvascular), TH2 (normal vascular), TH3 (equivocal), TH4 (abnormal), or TH5 (severely abnormal) (see Figure 25.6 and Figure 25.7). The use of this standardized interpretation method significantly increased infrared imaging’s sensitivity, specificity, positive and negative predictive value, and inter/intra-examiner interpretation reliability. Continued patient observations and research over the past two decades have caused changes in some of the thermovascular values; thus, keeping the interpretation system up-to-date. Variations in this methodology have also been adopted with great success. However, it is recognized that, as with any other imaging procedure, specialized training and experience produces the highest level of screening success.

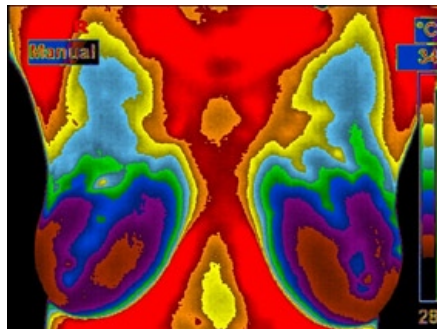


FIGURE 25.6 TH1 (Normal non-vascular).

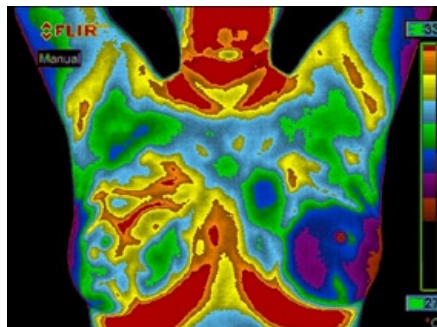


FIGURE 25.7 Right TH5 (Severely Abnormal).

25.3 Correlation Between Pathology and Infrared Imaging

The empirical evidence that an underlying breast cancer alters regional skin surface temperatures was investigated early on. In 1963, Lawson and Chughtai, two McGill University surgeons, published an elegant intra-operative study demonstrating that the increase in regional skin surface temperature associated with breast cancer was related to venous convection [19]. This early quantitative experiment added credence to previous research suggesting that infrared findings were linked to increased vascularity.

Infrared imaging of the breast may also have critical prognostic significance since it may correlate with a variety of pathologic prognostic features such as tumor size, tumor grade, lymph node status, and markers of tumor growth [20]. Continued research is underway investigating the pathologic basis for these infrared findings. One possibility is increased blood flow due to vascular proliferation (assessed by quantifying the microvascular density [MVD]) as a result of tumor associated angiogenesis. Although in one study [21], the MVD did not correlate with abnormal infrared findings. However, the imaging method used in that study consisted of contact plate technology (liquid crystal thermography [LCT]), which is not capable of modern computerized analysis. Consequently, LCT does not possess the discrimination and digital processing necessary to begin to correlate histological and discrete vascular changes [22].

In 1993, Head and Elliott reported that improved images from second generation infrared systems allowed more objective and quantitative analysis [20], and indicated that growth-rate related prognostic indicators were strongly associated with the infrared image interpretation.

In a 1994 detailed review of the potential of infrared imaging [23], Anbar suggested using an elegant biochemical and immunological cascade, and that the previous empirical observation that small tumors were capable of producing notable infrared changes could be due to enhanced perfusion over a substantial area of the breast surface via regional tumor induced nitric oxide (NO) vasodilatation. NO is synthesized by nitric oxide synthase (NOS), found both as a constitutive form of NOS, especially in

endothelial cells, and as an inducible form of NOS, especially in macrophages [24]. NOS has been demonstrated in breast carcinoma [25] using tissue immunohistochemistry, and is associated with a high tumor grade.

Nitric oxide is a molecule with potent vasodilating properties. It is a simple highly reactive free radical that readily oxidizes to form nitrite or nitrate ions. It diffuses easily through both hydrophilic and hydrophobic media. Thus, once produced, NO diffuses throughout the surrounding tissues, inside and outside the vascular system, and induces a variety of biochemical changes depending on the specific receptors involved. NO exerts its influence by binding to receptor sites in the endothelium of arteries or arterioles. This causes inhibition of sympathetic vasoconstriction. The end result is NO induced vasodilatation, which in turn may produce an asymmetrical thermovascular infrared image.

The largest body of evidence surrounding the physiologic mechanism by which infrared imaging detects precancerous and malignant states of the breast lies in the recruitment of existing blood vessels and the formation of new ones (angiogenesis). The process of angiogenesis begins with the release of angiogenesis factors (AF) from precancerous or cancerous cells. In the early stages of tumor growth, the majority of neoplasms exhibit a lower cellular metabolic demand. As such, the release of AF causes the existing vessels to resist constriction in order to maintain a steady supply of nutrients to the growing mass. As the tumor increases in size the need for nutrients becomes greater. AF begins to exert its influence by opening the dormant vessels in the breast. Once this blood supply becomes too little to maintain the growth of the neoplasm, AF causes the formation of new blood vessels. These new vessels are simple endothelial tubes connecting the tumor to existing nearby arteries and arterioles. This augmented blood supply produces the increase in heat and vascular asymmetry seen in infrared images.

The concept of angiogenesis, as an integral part of early breast cancer, was emphasized in 1996 by Guido and Schnitt. Their observations suggested that it is an early event in the development of breast cancer and 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 [26]. In 1996, in his highly reviewed textbook entitled Atlas of Mammography — New Early Signs in Breast Cancer, Gamagami studied angiogenesis by infrared 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 infrared imaging helped to detect cancers that were not visible on mammography [27].

The greatest evidence supporting the underlying principle by which infrared imaging detects precancerous growths and cancerous tumors surrounds the well documented recruitment of existing vascularity and angiogenesis, which is necessary to maintain the increased metabolism of malignant cellular growth and multiplication. The biomedical engineering evidence of infrared imaging's value, both in model *in vitro* and clinically *in vivo* studies of various tissue growths, normal and neoplastic, has been established [28–34].

25.4 The Role of Infrared Imaging in the Detection of Cancer

In order to determine the value of infrared imaging, two viewpoints must be considered: first, the sensitivity of thermograms taken preoperatively in patients with known breast carcinoma; and second, the incidence of normal and abnormal thermograms in asymptomatic populations (specificity) and the presence or absence of malignancy in each of these groups.

In 1965, Gershon-Cohen et al. [35], a radiologist and researcher from the Albert Einstein Medical Center, introduced infrared imaging to the United States [35]. Using a Barnes thermograph, he reported on 4000 cases with a sensitivity of 94% and a false-positive rate of 6%. This data was included in a review of the then current status of infrared imaging published in 1968 in *CA — A Cancer Journal for Physicians* [36].

In prospective studies, Hoffman first reported on thermography in a gynecologic practice. He detected 23 carcinomas in 1924 patients (a detection rate of 12.5 per 1000), with an 8.4% false-negative (91.6% sensitivity) and a 7.4% false-positive (92.6% specificity) rate [37].

Stark and Way [38] screened 4621 asymptomatic women, 35% of whom were under 35 years of age, and detected 24 cancers (detection rate of 7.6 per 1000), with a sensitivity and specificity of 98.3 and 93.5%, respectively.

In a study comprising 25,000 patients screened and 1,878 histologically proven breast cancers, Amalric and Spitalier reported on their results with infrared imaging. From this group a false-negative and false-positive rate of 9% (91% sensitivity and specificity) was found [39].

In a mobile unit examination of rural Wisconsin, Hobbins screened 37,506 women using thermography. He reported the detection of 5.7 cancers per 1,000 women screened with a 12% false-negative and 14% false-positive rate. His findings also corroborated with others that thermography is the sole early initial signal in 10% of breast cancers [17,40].

Reporting his Radiology division's experience with 10,000 thermographic studies done concomitantly with mammography over a 3-year period, Isard reiterated a number of important concepts including the remarkable thermal and vascular stability of the infrared image from year to year in the otherwise healthy patient and the importance of recognizing any significant change [41]. In his experience, combining these modalities increased the sensitivity rate of detection by approximately 10%; thus, underlining the complementarity of these procedures since each one did not always suspect the same lesion. It was Isard's conclusion that, had there been a preliminary selection of his group of 4393 asymptomatic patients by infrared imaging, mammographic examination would have been restricted to the 1028 patients with abnormal infrared imaging, or 23% of this cohort. This would have resulted in a cancer detection rate of 24.1 per 1000 combined infrared and mammographic examinations as contrasted to the expected 7 per 1000 by mammographic screening alone. He concluded that since infrared imaging is an innocuous examination, it could be utilized to focus attention upon asymptomatic women who should be examined more intensely. Isard emphasized that, like mammography and other breast imaging techniques, infrared imaging does not diagnose cancer, but merely indicates the presence of an abnormality.

Spitalier and associates screened 61,000 women using thermography over a 10-year period. The false-negative and positive rate was found to be 11% (89% sensitivity and specificity). Thermography also detected 91% of the nonpalpable cancers (T0 rating). The authors noted that of all the patients with cancer, thermography alone was the first alarm in 60% of the cases [42].

Two small-scale studies by Moskowitz (150 patients) [43] and Treatt (515 patients) [44] reported on the sensitivity and reliability of infrared imaging. Both used unknown experts to review the images of breast cancer patients. While Moskowitz excluded unreadable images, data from Treatt's study indicated that less than 30% of the images produced were considered good, the rest being substandard. Both of these studies produced poor results; however, this could be expected considering the lack of adherence to accepted imaging methods and protocols. The greatest error in these studies is found in the methods used to analyze the images. The type of image analysis consisted of the sole use of abnormal vascular pattern recognition. At the time these studies were performed, the accepted method of infrared image interpretation consisted of a combined vascular pattern and quantitative analysis of temperature variations across the breasts. Consequently, the data obtained from these studies is highly questionable. Their findings were also inconsistent with numerous previous large-scale multicenter trials. The authors suggested that for infrared imaging to be truly effective as a screening tool, there needed to be a more objective means of interpretation and proposed that this would be facilitated by computerized evaluation. This statement is interesting considering that recognized quantitative and qualitative reading protocols (including computer analysis) were being used at the time.

In a unique study comprising 39,802 women screened over a 3-year period, Haberman and associates used thermography and physical examination to determine if mammography was recommended. They reported an 85% sensitivity and 70% specificity for thermography. Haberman cautioned that the findings of thermographic specificity could not be extrapolated from this study as it was well documented that long-term observation (8 to 10 years or more) is necessary to determine a true false-positive rate. The authors noted that 30% of the cancers found would not have been detected if it were not for thermography [45].

Gros and Gautherie reported on a large scale study comprising 85,000 patients screened. Culmination of the data resulted in a 90% sensitivity and 88% specificity for thermography [46–49].

In a large-scale multicenter review of nearly 70,000 women screened, Jones reported a false-negative and false-positive rate of 13% (87% sensitivity) and 15% (85% sensitivity) respectively for thermography [50].

In a study performed in 1986, Usuki reported on the relation of thermographic findings in breast cancer diagnosis. He noted an 88% sensitivity for thermography in the detection of breast cancers [51].

Parisky and associates published a study from a multicenter 4-year clinical trial using infrared imaging to evaluate mammographically suspicious lesions. Data from a blinded subject set was obtained in 769 women with 875 biopsied lesions resulting in 187 malignant and 688 benign findings. The index of suspicion resulted in a 97% sensitivity in the detection of breast cancers [52].

In a study comparing clinical examination, mammography, and thermography in the diagnosis of breast cancer, three groups of patients were used: 4,716 patients with confirmed carcinoma, 3,305 patients with histologically diagnosed benign breast disease, and 8,757 general patients (16,778 total participants). This paper also compared clinical examination and mammography to other well-known studies in the literature including the National Cancer Institute (NCI)-sponsored Breast Cancer Detection and Demonstration Projects. In this study, clinical examination had an average sensitivity of 75% in detecting all tumors and 50% in cancers less than 2 cm in size. This rate is exceptionally good when compared to many other studies at between 35 and 66% sensitivity. Mammography was found to have an average 80% sensitivity and 73% specificity. Thermography had an average sensitivity of 88% (85% in tumors less than 1 cm in size) and a specificity of 85%. An abnormal thermogram was found to have a 94% predictive value. From the findings in this study, the authors suggested that “none of the techniques available for screening for breast carcinoma and evaluating patients with breast related symptoms is sufficiently accurate to be used alone. For the best results, a multimodal approach should be used” [53].

In a series of 4,000 confirmed breast cancers, Thomassin and associates observed 130 subclinical carcinomas ranging in diameter of 3 to 5 mm. Both mammography and thermography were used alone and in combination. Of the 130 cancers, 10% were detected by mammography only, 50% by thermography alone, and 40% by both techniques. Thus, there was a thermal alarm in 90% of the patients and the only sign in 50% of the cases [54].

In a simple review of over 15 large-scale studies from 1967 to 1998, infrared imaging of the breast has showed an average sensitivity and specificity of 90%. With continued technological advances in infrared imaging in the past decade, some studies are showing even higher sensitivity and specificity values. However, until further large-scale studies are performed, these findings remain in question.

25.5 Infrared Imaging as a Risk Indicator

As early as 1976, at the Third International Symposium on Detection and Prevention of Cancer held in New York, thermal imaging was established by consensus as the highest risk marker for the possibility of the presence of an undetected breast cancer. It had also been shown to predict such a subsequent occurrence [55–57]. The Wisconsin Breast Cancer Detection Foundation presented a summary of its findings in this area, which has remained undisputed [58]. This, combined with other reports, has confirmed that an abnormal infrared image is the highest risk indicator for the future development of breast cancer and is 10 times as significant as a first order family history of the disease [48].

In a study of 10,000 women screened, Gautherie found that, when applied to asymptomatic women, thermography was very useful in assessing the risk of cancer by dividing patients into low and high risk categories. This was based on an objective evaluation of each patient’s thermograms using an improved reading protocol that incorporated 20 thermopathological factors [59].

A screening of 61,000 women using thermography was performed by Spitalier over a 10-year period. The authors concluded that “in patients having no clinical or radiographic suspicion of malignancy, a persistently abnormal breast thermogram represents the highest known risk factor for the future development of breast cancer” [42].

From a patient base of 58,000 women screened with thermography, Gros and associates followed 1527 patients with initially healthy breasts and abnormal thermograms for 12 years. Of this group, 44%

developed malignancies within 5 years. The study concluded that “an abnormal thermogram is the single most important marker of high risk for the future development of breast cancer” [49].

Spitalier and associates followed 1416 patients with isolated abnormal breast thermograms. It was found that a persistently abnormal thermogram, as an isolated phenomenon, is associated with an actuarial breast cancer risk of 26% at 5 years. Within this study, 165 patients with nonpalpable cancers were observed. In 53% of these patients, thermography was the only test which was positive at the time of initial evaluation. It was concluded that (1) A persistently abnormal thermogram, even in the absence of any other sign of malignancy, is associated with a high risk of developing cancer, (2) This isolated abnormal also carries with it a high risk of developing interval cancer, and as such the patient should be examined more frequently than the customary 12 months, (3) Most patients diagnosed as having minimal breast cancer have abnormal thermograms as the first warning sign [60,61].

In a study by Gautherie and associates, the effectiveness of thermography in terms of survival benefit was discussed. The authors analyzed the survival rates of 106 patients in whom the diagnosis of breast cancer was established as a result of the follow-up of thermographic abnormalities found on the initial examination when the breasts were apparently healthy (negative physical and mammographic findings). The control group consisted of 372 breast cancer patients. The patients in both groups were subjected to identical treatment and followed for 5 years. A 61% increase in survival was noted in the patients who were followed-up due to initial thermographic abnormalities. The authors summarized the study by stating that “the findings clearly establish that the early identification of women at high risk of breast cancer based on the objective thermal assessment of breast health results in a dramatic survival benefit” [62,63].

Infrared imaging provides a reflection of functional tumor induced angiogenesis and metabolic activity rather than structurally based parameters (i.e., tumor size, architectural distortion, microcalcifications). Recent advances in cancer research have determined that the biological activity of a neoplasm is far more significant an indicator of aggressiveness than the size of the tumor. As a direct reflection of the biological activity in the breast, infrared imaging has been found to provide a significant biological risk marker for cancer.

25.6 Infrared Imaging as a Prognostic Indicator

Studies exploring the biology of cancers have shown that the amount of thermovascular activity in the breast is directly proportional to the aggressiveness of the tumor. As such, infrared imaging provides the clinician with an invaluable tool in prognosis and treatment monitoring.

In a study of 209 breast cancers, Dilhuydy and associates found a positive correlation between the degree of infrared abnormalities and the existence of positive axillary lymph nodes. It was reported that the amount of thermovascular activity seen in the breast was directly related to the prognosis. The study concluded that infrared imaging provides a highly significant factor in prognosis and that it should be included in the pretherapeutic assessment of a breast cancer [64].

Amalric and Spitalier reported on 25,000 patients screened and 1,878 histologically proven breast cancers investigated with infrared imaging. The study noted that the amount of infrared activity in the breast was directly proportional to the survival of the patient. The “hot” cancers showed a significantly poorer prognosis with a 24% survival rate at 3 years. A much better prognosis with an 80% survival rate at 3 years was seen in the more biologically inactive or “cooler” cancers. The study also noted a positive association between the amount of thermal activity in the breast and the presence of positive axillary nodes [65].

Reporting on a study of breast cancer doubling times and infrared imaging, Fournier noted significant changes in the thermovascular appearance of the images. The shorter the tumor doubling time, the more thermographic pathological signs were evident. It was concluded that infrared imaging served as a warning signal for the faster-growing breast cancers [66].

A retrospective analysis of 100 normal patients, 100 living cancer patients, and 126 deceased cancer patients was published by Head. Infrared imaging was found to be abnormal in 28% of the normal patients, compared to 65% of the living cancer patients and 88% of the deceased cancer patients. Known

prognostic indicators related to tumor growth rate were compared to the results of the infrared images. The concentration of tumor ferritin, the proportion of cells in DNA synthesis and proliferating, and the expression of the proliferation-associated tumor antigen Ki-67 were all found to be associated with an abnormal infrared image. It was concluded that “The strong relationships of thermographic results with these three growth rate-related prognostic indicators suggest that breast cancer patients with abnormal thermograms have faster-growing tumors that are more likely to have metastasized and to recur with a shorter disease-free interval” [20].

In a paper by Gros and Gautherie, the use of infrared imaging in the prognosis of treated breast cancers was investigated. The authors considered infrared imaging to be absolutely necessary for assessing pretherapeutic prognosis or carrying out the follow-up of breast cancers treated by exclusive radiotherapy. They noted that before treatment, infrared imaging yields evidence of the cancer growth rate (aggressiveness) and contributes to the therapeutic choice. It also indicates the success of radiosterilization or the suspicion of a possible recurrence or radio-resistance. The authors also noted a weaker 5-year survival with infrared images that showed an increase in thermal signals [67].

In a recent study by Keyserlingk, 20 women with core biopsy-proven locally advanced breast cancer underwent infrared imaging before and after chemohormonotherapy. All 20 patients were found to have abnormal thermovascular signs prior to treatment. Upon completion of the final round of chemotherapy, each patient underwent curative-intent surgery. Prior to surgery, all 20 patients showed improvement in their initial infrared scores. The amount of improvement in the infrared images was found to be directly related to the decrease in tumor size. A complete normalization of prechemotherapy infrared scores was seen in five patients. In these same patients there was no histological evidence of cancer remaining in the breast. In summary, the authors stated that “Further research will determine whether lingering infrared detected angiogenesis following treatment reflects tumor aggressiveness and ultimately prognosis, as well as early tumor resistance, thus providing an additional early signal for the need of a therapeutic adjustment” [68].

25.7 Breast Cancer Detection and Demonstration Project

The breast cancer detection and demonstration project (BCDDP) is the most frequently quoted reason for the decreased interest in infrared imaging. The BCDDP was a large-scale study performed from 1973 through 1979, which collected data from many centers around the United States. Three methods of breast cancer detection were studied: physical examination, mammography, and infrared imaging.

Just before the onset of the BCDDP, two important papers appeared in the literature. In 1972, Gerald D. Dodd of the University of Texas Department of Diagnostic Radiology presented an update on infrared imaging in breast cancer diagnosis at the 7th National Cancer Conference sponsored by the National Cancer Society and the National Cancer Institute [69]. In his presentation, he suggested that infrared imaging would be best employed as a screening agent for mammography. He proposed that in any general survey of the female population aged 40 and over, 15 to 20% of these subjects would have positive infrared imaging and would require mammograms. Of these, approximately 5% would be recommended for biopsy. He concluded that infrared imaging would serve to eliminate 80 to 85% of the potential mammograms. Dodd also reiterated that the procedure was not competitive with mammography and, reporting the Texas Medical School’s experience with infrared imaging, noted that it was capable of detecting approximately 85% of all breast cancers. Dodd’s ideas would later help to fuel the premise and attitudes incorporated into the BCDDP.

Three years later, J.D. Wallace presented to another Cancer Conference, sponsored by the American College of Radiology, the American Cancer Society, and the Cancer Control Program of the National Cancer Institute, an update on infrared imaging of the breast [70]. The author’s analysis suggested that the incidence of breast cancer detection per 1000 patients screened could increase from 2.72 when using mammography to 19 when using infrared imaging. He then underlined that infrared 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 who required further investigation. He concluded that, “the resulting infrared image contains only a small amount of information as compared to the mammogram, so that the reading of the infrared image is a substantially simpler task.”

Unfortunately, this rather simplistic and cavalier attitude toward the generation and interpretation of infrared images was prevalent when it was hastily added and then prematurely dismissed from the BCDDP, which was just getting underway. Exaggerated expectations led to the ill-founded premise that infrared imaging might replace mammography rather than complement it. A detailed review of the Report of the Working Group of the BCDDP, published in 1979, is essential to understand the subsequent evolution of infrared imaging [71].

The work scope of this project was issued by the NCI on the 26th of March 1973 with six objectives, the second being to determine if a negative infrared image 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 4 years of this project, gave a short history regarding infrared imaging in breast cancer detection. They wrote that, as of the sixties, there was intense interest in determining the suitability of infrared 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 infrared imaging in order to make it useful as a prescreening device in selecting patients for referral for mammographic examination. It was thought that, if successful, the incorporation of this technology would result in a relatively small proportion of women having mammography (a technique that had caused concern at that time because of the carcinogenic effects of radiation). The Working Group indicated that the sensitivity and specificity of infrared imaging readings, with clinical data emanating from interinstitutional studies, were close to the corresponding results for physical examination and mammography. They noted that these three modalities selected different subgroups of breast cancers, and for this reason further evaluation of infrared imaging as a screening device in a controlled clinical trial was recommended.

25.7.1 Poor Study Design

While the working group describes in detail the importance of quality control of mammography, the entire protocol for infrared imaging was summarized in one paragraph and simply indicated that infrared imaging was conducted by a BCDDP trained technician. The detailed extensive results from this report, consisting of over 50 tables, included only one that referred to infrared imaging showing that it had detected only 41% of the breast cancers during the first screening while the residual were either normal or unknown. There is 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, infrared imaging was dropped from any further evaluation and consideration. The report stated that it was impossible to determine whether abnormal infrared images could be predictive of interval cancers (cancers developing between screenings) since they did not collect this data.

By the same token, the Working Group was unable to conclude, with their limited experience, whether the findings were related to the then available technology of infrared imaging or with its application. They did, however, conclude that the decision to dismiss infrared 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.” The report admitted that several individual programs of the BCDDP had results that were more favorable than what was reported for the BCDDP as a whole. They encouraged investment in the development and testing of infrared imaging under carefully controlled study conditions and suggested that high priority be given to these studies. They noted that a few suitable sites appeared to be available within the BCDDP participants and proposed that developmental studies should be solicited from sites with sufficient experience.

25.7.2 Untrained Personnel and Protocol Violations

JoAnn Haberman, who was a participant in this project [72], provided further insight into the relatively simplistic regard assigned to infrared imaging during this program. The author reiterated that expertise in mammography was an absolute requirement for the awarding of a contract to establish a screening center. However, the situation was just the opposite with regard to infrared imaging — no experience was required at all. When the 27 demonstration project centers opened their doors, only 5 had any preexisting expertise in infrared imaging. Of the remaining screening centers, there was no experience at all in this technology. Finally, more than 18 months after the project had begun, the NCI established centers where radiologists and their technicians could obtain sufficient training in infrared imaging. Unfortunately, only 11 of the demonstration project directors considered this training of sufficient importance to send their technologists to learn proper infrared technique. The imaging sites also disregarded environmental controls. Many of the project sites were mobile imaging vans, which had poor heating and cooling capabilities and often kept their doors open in the front and rear to permit an easy flow of patients. This, combined with a lack of adherence to protocols and preimaging patient acclimation, lead to unreadable images.

In summary, with regard to infrared imaging, the BCDDP was plagued with problems and seriously flawed in five critical areas (1) The study was initiated with an incorrect premise that infrared imaging might replace mammography. A functional imaging procedure that detects metabolic thermovascular aberrations cannot replace a test that looks for specific areas of structural changes in the breast, (2) Completely untrained technicians were used to perform the scans, (3) The study used radiologists who had no experience or knowledge in reading infrared images, (4) Proper laboratory environmental controls were completely ignored. In fact, many of the research sites were mobile trailers with extreme variations in internal temperatures, (5) No standardized reading protocol had yet been established for infrared imaging. It was not until the early 1980s that established and standardized reading protocols were adopted. Considering these facts, the BCDDP could not have properly evaluated infrared imaging. Since the termination of the BCDDP, a considerable amount of published research has demonstrated the true value of this technology.

25.8 Mammography and Infrared Imaging

From a scientific standpoint, mammography and infrared imaging are completely different screening tests. As a structural imaging procedure, mammography cannot be compared to a functional imaging technology such as infrared imaging. While mammography attempts to detect architectural tissue shadows, infrared imaging observes for changes in the subtle metabolic milieu of the breast. Even though mammography and infrared imaging examine completely different aspects of the breast, research has been performed that allows for a statistical comparison of the two technologies. Since a review of the research on infrared imaging has been covered, data on the current state of mammography is presented.

In a study by Rosenberg, 183,134 screening mammograms were reviewed for changes in sensitivity due to age, breast density, ethnicity, and estrogen replacement therapy. Out of these screening mammograms 807 cancers were discovered at screening. The results showed that the sensitivity for mammography was 54% in women younger than 40, 77% in women aged 40–49, 78% in women aged 50–64, and 81% in women older than 64 years. Sensitivity was 68% in women with dense breasts and 74% in estrogen replacement therapy users [73].

Investigating the cumulative risk of a false-positive result in mammographic screening, Elmore and associates performed a 10-year retrospective study of 2400 women, 40 to 69 years of age. A total of 9762 mammograms were investigated. It was found that a woman had an estimated 49.1% cumulative risk of having a false-positive result after 10 mammograms. Even though no breast cancer was present, over one-third of the women screened were required to have additional evaluations [74].

In a review of the literature, Head investigated the sensitivity, specificity, positive predictive value, and negative predictive values for mammography and infrared imaging. The averaged reported performance

for mammography was: 86% sensitivity, 79% specificity, 28% positive predictive value, and 92% negative predictive value. For infrared imaging the averaged performance was: 86% sensitivity, 89% specificity, 23% positive predictive value, and 99.4% negative predictive value [75].

Keyserlingk and associates published a retrospective study reviewing the relative ability of clinical examinations, mammography, and infrared imaging to detect 100 new cases of ductal carcinoma *in situ*, stage I and 2 breast cancers. Results from the study found that the sensitivity for clinical examination alone was 61%, mammography alone was 66%, and infrared imaging alone was 83%. When suspicious and equivocal mammograms were combined the sensitivity was increased to 85%. A sensitivity of 95% was found when suspicious and equivocal mammograms were combined with abnormal infrared images. However, when clinical examination, mammography, and infrared images were combined a sensitivity of 98% was reached [76].

From a review of the cumulative literature database, it can be found that the average sensitivity and specificity for mammography is 80 and 79% respectively for women over the age of 50 [77–79]. A significant decrease in sensitivity and specificity is seen in women below this age. This same research also shows that mammography routinely misses interval cancers (cancers that form between screening exams) [80], which may be detected by infrared imaging. Taking into consideration all the available data, mammography leaves much to be desired as the current gold standard for breast cancer screening. As a stand alone screening procedure, it is suggested that mammography may not be the best choice. In the same light, infrared imaging should also not be used alone as a screening test. The two technologies are of a complimentary nature. Neither used alone are sufficient, but when combined each builds on the deficiencies of the other. In reviewing the literature it seems evident that a multimodal approach to breast cancer screening would serve women best. A combination of clinical examination, mammography, and infrared imaging would provide the greatest potential for breast conservation and survival.

25.9 Current Status of Breast Cancer Detection

Current first-line breast cancer detection strategy still depends essentially on clinical examination and mammography. The limitations of the former, with its reported sensitivity rate often below 65% [76,81] is well-recognized, and even the proposed value of self-breast examination is being contested [82]. While mammography is accepted as the most cost-effective imaging modality, its contribution continues to be challenged with persistent false-negative rates ranging up to 30% [73,83,84]; with decreasing sensitivity in younger patients and those on estrogen replacement therapy [73,85]. In addition, there is recent data suggesting that denser and less informative mammography images are precisely those associated with an increased cancer risk [86]. Echoing some of the shortcomings of the BCDDP concerning their study design and infrared imaging, Moskowitz indicated that mammography is also not a procedure to be performed by the inexperienced technician or radiologist [87].

With the current emphasis on earlier detection, there is now renewed interest in the parallel development of complimentary imaging techniques that can also exploit the precocious metabolic, immunological, and vascular changes associated with early tumor growth. While promising, techniques such as scintimammography [88], doppler ultrasound [89], and MRI [90] are associated with a number of disadvantages that include exam duration, limited accessibility, need of intravenous access, patient discomfort, restricted imaging area, difficult interpretation, and limited availability of the technology. Like ultrasound, they are more suited to use as second-line options to pursue the already abnormal screening evaluations. While practical, this stepwise approach currently results in the nonrecognition, and thus delayed utilization of second-line technology in approximately 10% of established breast cancers [87]. This is consistent with a study published by Keyserlingk [76].

As an addition to the breast health screening process, infrared imaging has a significant role to play. Owing to infrared imaging's unique ability to image the metabolic aspects of the breast, extremely early warning signals (up to 10 years before any other detection method) have been observed in long-term studies. It is for this reason that an abnormal infrared image is the single most important marker of high

risk for the existence of or future development of breast cancer. This, combined with the proven sensitivity, specificity, and prognostic value of the technology, places infrared imaging as one of the major frontline methods of breast cancer screening.

25.10 Future Advancements in Infrared Imaging

Modern high-resolution uncooled focal plane array cameras coupled with high speed computers running sophisticated image analysis software are commonplace in today's top infrared imaging centers. However, research in this field continues to produce technological advancements in image acquisition and digital processing.

Research is currently underway investigating the possible subtle alterations in the blood supply of the breast during the earliest stages of malignancy. Evidence suggests that there may be a normal vasomotor oscillation frequency in the arterial structures of the human body. It is theorized that there may be disturbances to the normal vascular oscillatory rate when a malignancy is forming. Research using infrared detection systems capturing 200 frames per second with a sensitivity of 0.009 of a degree centigrade may be able to monitor alterations in this vasomotor frequency band.

Another unique methodology is investigating the possibility of using infrared emission data to extrapolate depth and location of a metabolic heat source within the body. In the case of cancer, the increased tissue metabolism resulting from rapid cellular multiplication and growth generates heat. With this new approach in infrared detection, it is theorized that an analysis based on an analogy to electrical circuit theory — termed the thermal-electric analog — may possibly be used to determine the depth and location of the heat source.

New breast cancer treatments are also exploring methods of targeting the angiogenic process. Due to a tumor's dependence on a constant blood supply to maintain growth, antiangiogenesis therapy is becoming one of the most promising therapeutic strategies and has been found to be pivotal in the new paradigm for consideration of breast cancer development and treatment [91]. The future may see infrared imaging and antiangiogenesis therapy combined as the state of the art in the biological assessment and treatment of breast cancer.

These and other new methodologies in medical infrared imaging are being investigated and may prove to be significant advancements. However, a great deal of research will need to be performed before new technologies can be adopted for medical use.

25.11 Conclusion

The large patient populations and long survey periods in many of the above clinical studies yield a high significance to the various statistical data obtained. This is especially true for the contribution of infrared imaging to early cancer diagnosis, as an invaluable marker of high-risk populations, and in therapeutic decision making.

Currently available high-resolution digital infrared imaging technology benefits greatly from enhanced image production, computerized image processing and analysis, and standardized image interpretation protocols. Over 40 years of research and 800 indexed papers encompassing well over 300,000 women participants has demonstrated infrared imaging's abilities in the early detection of breast cancer. Infrared imaging has distinguished itself as the earliest detection technology for breast cancer. It has the ability to signal an alarm that a cancer may be forming up to 10 years before any other procedure can detect it. In 7 out of 10 cases, infrared imaging will detect signs of a cancer before it is seen on a mammogram. Clinical trials have also shown that infrared imaging significantly augments the long-term survival rates of its recipients by as much as 61%. And when used as part of a multimodal approach (clinical examination, mammography, and infrared imaging) 95% of all early stage cancers will be detected. Ongoing research into the thermal characteristics of breast pathologies will continue to investigate the relationships between neoangiogenesis, chemical mediators, and the neoplastic process.

It is unfortunate, but many clinicians still hesitate to consider infrared imaging as a useful tool in spite of the considerable research database, steady improvements in both infrared technology and image analysis, and continued efforts on the part of the infrared imaging societies. This attitude may be due in part to the average clinician's unfamiliarity with the physical and biological basis of infrared imaging. The other methods of cancer investigations refer directly to topics of medical teaching. For instance, radiography and ultrasonography refer to structural anatomy. Infrared imaging, however, is based on thermodynamics and thermokinetics, which are unfamiliar to most clinicians; though man is experiencing heat production and exchange in every situation he undergoes or creates.

Considering the contribution that infrared imaging has demonstrated thus far in the field of early breast cancer detection, all possibilities should be considered for promoting further technical, biological, and clinical research along with the incorporation of the technology into common clinical use.

References

- [1] Adams, F., *The Genuine Works of Hippocrates*, Williams and Wilkins, Baltimore, 1939.
- [2] Lawson, R.N., Implications of surface temperatures in the diagnosis of breast cancer. *Can. Med. Assoc. J.*, 75, 309, 1956.
- [3] Lawson, R.N., Thermography — a new tool in the investigation of breast lesions. *Can. Serv. Med.*, 13, 517, 1957.
- [4] Lawson, R.N., A new infrared imaging device. *Ca. Med. Assoc. J.*, 79, 402, 1958.
- [5] Archer, F. and Gros, C., Classification thermographique des cancers mammaires. *Bulletin du Cancer*, 58, 351, 1971.
- [6] Amalu, W., et al., Standards and protocols in clinical thermographic imaging. *International Academy of Clinical Thermology*, September 2002.
- [7] Kurbitz, G., Design criteria for radiometric thermal-imaging devices, in *Thermological Methods*, VCH mbH, pp. 94–100, 1985.
- [8] Houdas, Y. and Ring E.F.J., Models of thermoregulation, in *Human Temperature: Its Measurement and Regulation*, Plenum Press, New York, pp. 136–141.
- [9] Flesch, U., Physics of skin-surface temperature, in *Thermological Methods*, VCH mbH, pp. 21–33, 1985.
- [10] Anbar M., *Quantitative Dynamic Telethermometry in Medical Diagnosis and Management*, CRC Press, Florida, p. 106, 1994.
- [11] Anbar, M., Potential artifacts in infrared thermographic measurements. *Thermology*, 3, 273, 1991.
- [12] Friedrich, K. (Optic research laboratory, Carl Zeiss — West Germany), Assessment criteria for infrared thermography systems. *Acta Thermographica*, 5, 68–72.
- [13] Engel, J.M., Thermography in locomotor diseases. *Acta Thermographica*, 5, 11–13.
- [14] Cuthbertson, G.M., The development of IR imaging in the United Kingdom, in *The Thermal Image in Medicine and Biology*, Uhlen-Verlag, Wien, pp. 21–32, 1995.
- [15] Amalu, W., The validity of the thermoregulatory stress test in infrared imaging of the breast, presented at the 31st annual symposium of the American Academy of Thermology, Auburn University, Alabama, 2004.
- [16] Gautherie, M., Kotewicz, A. and Gueblez, P., Accurate and objective evaluation of breastthermograms: Basic principles and new advances with special reference to an improved computer-assisted scoring system, in *Thermal assessment of Breast Health*, MTP Press Limited, pp. 72–97, 1983.
- [17] Hobbins, W.B., Abnormal Thermogram — Significance in Breast Cancer. *Interamer. J. of Rad.*, 12, 337, 1987.
- [18] Gautherie, M., New protocol for the evaluation of breast thermograms, in *Thermological Methods*, VCH mbH, pp. 227–235, 1985.
- [19] Lawson, R.N. and Chughtai, M.S., Breast cancer and body temperatures. *Can. Med. Assoc. J.*, 88, 68, 1963.

- [20] Head, J.F., Wang, F. and Elliott, R.L., Breast thermography is a noninvasive prognostic procedure that predicts tumor growth rate in breast cancer patients. *Ann. N.Y. Acad. Sci.*, 698, 153, 1993.
- [21] Sterns, E.E., Zee, B., Sen Gupta, J. and Saunders, F.W., Thermography: Its relation to pathologic characteristics, vascularity, proliferative rate and survival of patients with invasive ductal carcinoma of the breast. *Cancer*, 77, 1324, 1996.
- [22] Head, J.F. and Elliott, R.L., Breast Thermography. *Cancer*, 79, 186, 1995.
- [23] Anbar M., in *Quantitative Dynamic Telethermometry in Medical Diagnosis and Management*, CRC Press, pp. 84–94, 1994.
- [24] Rodenberg, D.A., Chaet, M.S., Bass, R.C., et al., Nitric oxide: An overview. *Am. J. Surg.* 170, 292, 1995.
- [25] Thomsen, L.L., Miles, D.W., Happerfield, L., et al., Nitric oxide synthase activity in human breast cancer. *Br. J. Cancer*, 72, 41, 1995.
- [26] Guidi, A.J. and Schnitt, S.J., Angiogenesis in pre-invasive lesions of the breast. *The Breast Journal*, 2, 364, 1996.
- [27] Gamagami, P., Indirect signs of breast cancer: Angiogenesis study, in *Atlas of Mammography*, Blackwell Science, Cambridge, Mass., pp. 231–26, 1996.
- [28] Love, T., Thermography as an indicator of blood perfusion. *Proc. N.Y. Acad. Sci. J.*, 335, 429, 1980.
- [29] Chato, J., Measurement of thermal properties of growing tumors. *Proc. N.Y. Acad. Sci.*, 335, 67, 1980.
- [30] Draper, J., Skin temperature distribution over veins and tumors. *Phys. Med. Biol.*, 16, 645, 1971.
- [31] Jain, R. and Gullino, P., Thermal characteristics of tumors: Applications in detection and treatment. *Ann. N.Y. Acad. Sci.*, 335, 1, 1980.
- [32] Gautherie, M., Thermopathology of breast cancer; measurement and analysis of *in vivo* temperature and blood flow. *Ann. N.Y. Acad. Sci.*, 365, 383, 1980.
- [33] Gautherie, M., Thermobiological assessment of benign and malignant breast diseases. *Am. J. Obstet. Gynecol.*, 147, 861, 1983.
- [34] Gamigami, P., *Atlas of Mammography: New Early Signs in Breast Cancer*, Blackwell Science, 1996.
- [35] Gershen-Cohen, J., Haberman, J. and Brueschke, E., Medical thermography: A summary of current status. *Radiol. Clin. North Am.*, 3, 403, 1965.
- [36] Haberman, J., The present status of mammary thermography. *CA: A Cancer Journal for Clinicians*, 18, 314, 1968.
- [37] Hoffman, R., Thermography in the detection of breast malignancy. *Am. J. Obstet. Gynecol.*, 98, 681, 1967.
- [38] Stark, A. and Way, S., The screening of well women for the early detection of breast cancer using clinical examination with thermography and mammography. *Cancer*, 33, 1671, 1974.
- [39] Amalric, D., et al., Value and interest of dynamic telethermography in detection of breast cancer. *Acta Thermographica*, 1, 89–96.
- [40] Hobbins, W., Mass breast cancer screening. *Proceedings, Third International Symposium on Detection and Prevention of Breast Cancer*, New York, NY, 637, 1976.
- [41] Isard, H.J., Becker, W., Shilo, R., et al., Breast thermography after four years and 10,000 studies. *Am. J. Roentgenol.*, 115, 811, 1972.
- [42] Spitalier, H., Giraud, D., et al., Does infrared thermography truly have a role in present-day breast cancer management? *Biomedical Thermology*, Alan R. Liss, New York, NY, 269–278, 1982.
- [43] Moskowitz, M., Milbrath, J., Gartside, P., et al., Lack of efficacy of thermography as a screening tool for minimal and stage I breast cancer. *N. Engl. J. Med.*, 295, 249, 1976.
- [44] Threatt, B., Norbeck, J.M., Ullman, N.S., et al., Thermography and breast cancer: An analysis of a blind reading. *Ann. N.Y. Acad. Sci.*, 335, 501, 1980.
- [45] Haberman, J., Francis, J. and Love, T., Screening a rural population for breast cancer using thermography and physical examination techniques. *Ann. N.Y. Acad. Sci.*, 335, 492, 1980.

- [46] Sciarra, J., Breast cancer: Strategies for early detection, in *Thermal Assessment of Breast Health (Proceedings of the International Conference on Thermal Assessment of Breast Health)*, MTP Press LTD, pp. 117–129, 1983.
- [47] Gautherie, M., Thermobiological assessment of benign and malignant breast diseases. *Am. J. Obstet. Gynecol.*, 147, 861, 1983.
- [48] Louis, K., Walter, J. and Gautherie, M., Long-term assessment of breast cancer risk by thermal imaging, in *Biomedical Thermology*, Alan R. Liss Inc., pp. 279–301, 1982.
- [49] Gros, C. and Gautherie, M., Breast thermography and cancer risk prediction. *Cancer*, 45, 51, 1980.
- [50] Jones, C.H., Thermography of the female breast, in *Diagnosis of Breast Disease*, C.A. Parsons (Ed.), University Park Press, Baltimore, pp. 214–234, 1983.
- [51] Useki, H., Evaluation of the thermographic diagnosis of breast disease: Relation of thermographic findings and pathologic findings of cancer growth. *Nippon Gan Chiryō Gakkai Shi*, 23, 2687, 1988.
- [52] Parisky, Y.R., Sardi, A., et al., Efficacy of computerized infrared imaging analysis to evaluate mammographically suspicious lesions. *AJR*, 180, 263, 2003.
- [53] Nyirjesy, I., Ayme, Y., et al., Clinical evaluation, mammography, and thermography in the diagnosis of breast carcinoma. *Thermology*, 1, 170, 1986.
- [54] Thomassin, L., Giraud, D., et al., Detection of subclinical breast cancers by infrared thermography, in *Recent Advances in Medical Thermology (Proceedings of the Third International Congress of Thermology)*, Plenum Press, New York, NY, pp. 575–579, 1984.
- [55] Amalric, R., Gautherie, M., Hobbins, W. and Stark, A., The future of women with an isolated abnormal infrared thermogram. *La Nouvelle Presse Medicale*, 10, 3153, 1981.
- [56] Gautherie, M. and Gros, C., Contribution of infrared thermography to early diagnosis, pre-therapeutic prognosis, and post-irradiation follow-up of breast carcinomas. Laboratory of Electroradiology, Faculty of Medicine, Louis Pasteur University, Strasbourg, France, 1976.
- [57] Hobbins, W., Significance of an “isolated” abnormal thermogram. *La Nouvelle Presse Medicale*, 10, 3155, 1981.
- [58] Hobbins, W., Thermography, highest risk marker in breast cancer. *Proceedings of the Gynecological Society for the Study of Breast Disease*, 267–282, 1977.
- [59] Gautherie, M., Improved system for the objective evaluation of breast thermograms, in *Biomedical Thermology*. Alan R. Liss, Inc., New York, NY, pp. 897–905, 1982.
- [60] Amalric, R., Giraud, D., et al., Combined diagnosis of small breast cancer. *Acta Thermographica*, 1984.
- [61] Spitalier, J., Amalric, D., et al., The Importance of infrared thermography in the early suspicion and detection of minimal breast cancer, in *Thermal Assessment of Breast Health*, MTP Press Ltd., pp. 173–179, 1983.
- [62] Gautherie, M., et al., Thermobiological assessment of benign and malignant breast diseases. *Am. J. Obstet. Gynecol.*, 147, 861, 1983.
- [63] Jay, E. and Karpman, H., Computerized breast thermography, in *Thermal Assessment of Breast Health*, MTP Press Ltd., pp. 98–109, 1983.
- [64] Dilhuydy, M.H., et al., The importance of thermography in the prognostic evaluation of breast cancers. *Acta Thermographica*, 130–136.
- [65] Amalric, D., et al., Value and interest of dynamic telethermography in detection of breast cancer. *Acta Thermographica*, 89–96.
- [66] Fournier, V.D., Kubli, F., et al., Infrared thermography and breast cancer doubling time. *Acta Thermographica*, 107–11.
- [67] Gros, D., Gautherie, M. and Warter, F., Thermographic prognosis of treated breast cancers. *Acta Thermographica*, 11–14.
- [68] Keyserlingk, J.R., Ahlgren P.D., et al., Preliminary evaluation of high resolution functional infrared imaging to monitor pre-operative chemohormonotherapy-induced changes in neo-angiogenesis

- in patients with locally advanced breast cancer. Ville Marie Oncology Center/St. Mary's Hospital, Montreal, Canada. In submission for publication, 2003.
- [69] Dodd, G.D., Thermography in breast cancer diagnosis, in *Abstracts for the Seventh National Cancer Conference Proceedings*. Lippincott Philadelphia, Los Angeles, Calif., 267, 1972.
- [70] Wallace, J.D., Thermographic examination of the breast: An assessment of its present capabilities, in *Early Breast Cancer: Detection and Treatment*, Gallagher, H.S. (Ed.). American College of Radiology, Wiley, New York, pp. 13–19, 1975.
- [71] Report of the Working Group to Review the National Cancer Institute Breast Cancer Detection Demonstration Projects. *J. Natl Cancer Inst.*, 62, 641, 1979.
- [72] Haberman, J., An overview of breast thermography in the United States, in *Medical Thermography*, Margaret Abernathy and Sumio Uematsu (Eds.), American Academy of Thermology, Washington, 218–223, 1986.
- [73] Rosenberg, R.D., Hunt, W.C., et al., Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: Review of 183,134 screening mammograms in Albuquerque, New Mexico. *Radiology*, 209, 511, 1998.
- [74] Elmore, J., et al., Ten-year risk of false positive screening mammograms and clinical breast examinations. *N. Engl. J. Med.*, 338, 1089, 1998.
- [75] Head, J.F., Lipari, C.A. and Elliot, R.L., Comparison of mammography, and breast infrared imaging: Sensitivity, specificity, false negatives, false positives, positive predictive value and negative predictive value. *IEEE*, 1999.
- [76] Keyserlignk, J.R., Ahlgren, P.D., et al., Infrared imaging of the breast; initial reappraisal using high-resolution digital technology in 100 successive cases of stage 1 and 2 breast cancer. *Breast J.*, 4, 1998.
- [77] Schell, M.J., Bird, R.D. and Desrochers, D.A., Reassessment of breast cancers missed during routine screening mammography. *Am. J. Roentgenol.*, 177, 535, 2001.
- [78] Poplack, S.P., Tosteson, A.N., Grove, M., et al., The practice of mammography in 53,803 women from the New Hampshire mammography network. *Radiology*, 217, 832, 2000.
- [79] Pullon, S. and McLeod, D., The early detection and diagnosis of breast cancer: A literature review. General Practice Department, Wellington School of Medicine, December 1996.
- [80] Gilliland, F.D., Joste, N., Stauber, P.M., et al., Biologic characteristics of interval and screen-detected breast cancers. *J. Natl Cancer Inst.*, 92, 743, 2000.
- [81] Sickles, E.A., Mammographic features of “early” breast cancer. *Am. J. Roentgenol.*, 143, 461, 1984.
- [82] Thomas, D.B., Gao, D.L., Self, S.G., et al., Randomized trial of breast self-examination in Shanghai: Methodology and preliminary results. *J. Natl Cancer Inst.*, 5, 355, 1997.
- [83] Moskowitz, M., Screening for breast cancer. How effective are our tests? *CA Cancer J. Clin.*, 33, 26, 1983.
- [84] Elmore, J.G., Wells, C.F., Carol, M.P., et al., Variability in radiologists interpretation of mammograms. *N.E.J.M.*, 331, 1493, 1994
- [85] Laya, M.B., Effect on estrogen replacement therapy on the specificity and sensitivity of screening mammography. *J. Natl Cancer Inst.*, 88, 643, 1996.
- [86] Boyd, N.F., Byng, J.W., Jong, R.A., et al., Quantitative classification of mammographic densities and breast cancer risk. *J. Natl Cancer Inst.*, 87, 670, 1995.
- [87] Moskowitz, M., Breast imaging, in *Cancer of the Breast*, Donegan, W.L. and Spratt, J.S. (Eds.), Saunders, New York, 206–239, 1995.
- [88] Khalkhali, I., Cutrone, J.A., et al., Scintimammography: The complementary role of Tc-99m sestamibi prone breast imaging for the diagnosis of breast carcinoma. *Radiol.*, 196, 421, 1995.
- [89] Kedar, R.P., Cosgrove, D.O., et al., Breast carcinoma: Measurement of tumor response in primary medical therapy with color doppler flow imaging. *Radiol.*, 190, 825, 1994.
- [90] Weinreb, J.C. and Newstead, G., MR imaging of the breast. *Radiol.*, 196, 593, 1995.
- [91] Love, S.M. and Barsky, S.H., Breast cancer: An interactive paradigm. *Breast J.*, 3, 171, 1996.