STRATEGIES FOR THE EVALUATION OF COMPUTED TOMOGRAPHY IN DIAGNOSTICS AND THERAPEUTICS

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ABSTRACT

The introduction of a new radiologic imaging technology requires an assessment of its proper place in the diagnosis and treatment of specified conditions. In terms of its use in diagnosis, computed tomography must be evaluated with reference to the existing diagnostic process to determine whether its contribution is likely to have any beneficial impact on the patient. In terms of its use in therapy, the special ability of computed tomography to make an image of soft tissue points to its potential use in the initial staging of malignant neoplastic disease.

The objective of this thesis is to propose a methodology of evaluation of Computed Body Tomography that may be carried out in association with normal clinical practice, and to illustrate this with a diagnostic example and a therapeutic example. In both instances there are two steps to the evaluation. First, a comparison of the accuracy of the information of computed tomography against the conventional diagnostic tests. Second, the strategy for evaluating the benefit of the introduction of computed tomography in the diagnostic and therapeutic examples.

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CHAPTER 1

Rationale for Evaluation

"... The body of knowledge that forms the ... practice of medicine is a curious mixture of highly effective technology interspersed with islands of dogma, empiricism, conventional wisdom, and at times, superstition ... The persistence of unvalidated technologies lead not only to serious diagnostic error, but to waste of skilled services and money; it also contributes to the increasing load of medically induced, i.e., iatrogenic disease, and can give rise to untold human anguish and misery." (McDermott, 1977)

1.1 The Issues and The Arguments

In a very provocative fashion McDermott made this plea for the assessment of new and existing diagnostic technologies In the pages that follow a case shall be presented for the systematic evaluation of techniques that yield diagnostic information to the clinician This evaluation is essential to demonstrate the degree to which benefit is being delivered to the patient undergoing investigation.

The Institute of Medicine (1977), in its report on computed tomography (CT), argues that the tradition of medical practice has tended to accept evidence of the value or usefulness of a clinical innovation based on informed judgment and personal observation. They propose that this method, being susceptible to biases which tend to invalid conclusions, be replaced by the more systematic application of clinical trials methodology. This is particularly difficult, they remark, in the case of modern

technologic innovations like computed tomography. The initial period of utilization during which well-designed evaluations might be performed, can be confounded by technical revisions to the basic instrument and by widespread diffusion into clinical practice for use without protocol.

The introduction of technologic innovation to the diagnostic process has been addressed by a number of authors. Wulff (1976) reports that the very fact that such innovation in the diagnostic process has not been subjected to serious scrutiny is noteworthy. He pointed out that the introduction of a new laboratory test or other similar aids to the diagnostic decision making process is not regulated or assessed in a fashion similar to innovative procedures in therapeutics, particularly new drugs. The reasons for this are unclear since both therapeutic decisions and diagnostic decisions can have similarly profound impact on health care costs and on the health and well-being of the patient. The continuing increase in the number of unproven investigative procedures available to the clinician, and the suspicion that patients are often subjected to more diagnostic manoeuvres than is necessary, formed the basis of his argument for the application of rigid standards of evaluation to diagnostic tests.

Murphy's analysis of the place of diagnosis in health care lends some support to Wulff's notion of the problems associated with evaluation:

"Diagnosis is a sequential process in which the facts are non-independently and non-identically distributed, usually collected not singly but in groups and with an end-point constrained by urgency, compassion, cost and redundancy" (Murphy, 1976).

He argues a case for the introduction of rationality into the clinical arts, including diagnosis. Somewhere between the extremes of blind superstition on the one hand, and strict empiricism on the other, he seeks a pragmatic course of action which might promote excellence in the practice of the clinical arts. It is unclear what this middle course is; however, its key characteristic is to be found in the attempt *"... to replace transcendental evaluations and mystical instincts by rational, articulate, and where possible, quantitative argument"* (Murphy, 1976).

The objective of each of the elements of the diagnostic process is clear: it is information - information which must have utility for the clinician in his progress toward the diagnostic decision, and as a consequence, utility to the patient whose condition is being assessed. To be able to discriminate between diseases or between variants of a disease is trivial if it does not affect the prognosis, heritability, or transmission of disease (Murphy, 1976).

Feinstein (1967) makes a contribution to what Murphy has loosely termed the clinical arts. In his schema a key feature is the clinician-as-scientist, an individual who possesses a complement of clinical skills and who has acquired a sense of discrimination in employing them. He is quite clear in defining

the purpose of clinical arts; that is, behaving in such a way that the results are a benefit to the patient: *"A clinician's primary job is to discover what ails the patient not merely to diagnose disease. No matter how scientifically precise or interesting, a diagnosis that does not account for the ailment may be clinically worthless"* (Feinstein, 1967).

Given the proliferation of diagnostic manoeuvres, the skill of the clinician in selecting the appropriate tests and in their appropriate order becomes paramount. Selecting too many manoeuvres tends to be inefficient by providing redundant or misleading information; it represents a less than optimal utilization of diagnostic resources which might be better used with another patient. The selection of too few tests by the clinician increases the risk of missing the true nature of the patient's complaint; this tends to affect therapeutic decisions and prognosis.

Given the widespread diffusion of diagnostic manoeuvres, Feinstein points to the increasing likelihood of iatrogenic consequences for the patient. This risk is of two types: the direct result of the application of an investigative technic, and the indirect result of hospitalization and deterioration of function incurred by the patient undergoing evaluation. Ansell (1976) provides a comprehensive review of complications and ill effects associated with the more invasive diagnostic procedures used in radiology.

Further discussion of the need for a rational assessment in health care is found in Cochrane's (1972) book: Effectiveness and Efficiency. He postulates a need to receive optimal benefits from the health care system, and this is realized ultimately by the application of cost-to-benefit analysis to alternative courses of clinicial action. The prior condition for this procedure is the construction of indexes of effectiveness; these are measures of the effect of a particular medical action in altering the natural history of a particular disease for the better.

The most reliable, though not the most frequently employed, technic for assessing effectiveness in medical care is the experiment - the controlled clinical trial. The most frequent application of the experimental method in clinical research is to test a derivative of the hypothesis that a therapeutic regimen will do more good than harm to the patient. Less well developed is the use of the trial in evaluating the effectiveness of diagnostic procedures. Cochrane proposes the use of the trial in the assessment of tests used in screening as well as those used in diagnosis. In applying a screen of known sensitivity and specificity to an asymptomatic population there are two results: in a small proportion the disease being sought is discovered, and in the majority the disease is excluded. In clinical practice, however, the aim is to assess a patient's symptoms, signs, and complaints. Given the data generated from the history, physical examination and laboratory tests, the clinician poses an answer to the presenting problem, and proceeds to initiate therapeutic plan. In screening,

the likelihood of discovering a disease for which there exists no beneficial treatment should be nil, while in clinical practice this is a very frequent occurrrence.

Despite the noted difficulties of evaluation of diagnostic tests by a sound methodology, Cochrane feels that it is an appropriate course of action. The typical course of evaluation, he says, gives not enough weight to the welfare of the patient.

1.2 Conclusions

A case has been presented for the necessity to evaluate those technics which provide information about a patient's condition. The technic may be diagnostic insofar as it yields information that leads to a therapeutic solution to the patient's presenting problem. It also may be a management technic when applied to assessing the extent of disease or the patient's response to a therapeutic regimen.

The two crucial questions to be answered with regards to the use of any such innovative technics are:

(1) How accurate is the diagnostic information it is providing?

(2) What effect will the use of this new technic have on the patient?

When these questions are addressed to an innovative technic, they must be answered in a comparative framework, i.e., in relation to the existing diagnostic or management process.

Table 1.1 illustrates each authors' position with regard to the problem of appropriate utilization of innovative diagnostic manoeuvres.

Table 1.1

Problems and Solutions of Selected Authors in Respect of Technological Innovation in Health Care

Author	Problem	Solution
McDermott (1977)	persistence of unvalidated technologies	---
Institute of Medicine (1977)	personal and informal evaluation	clinical trials methodology
Murphy (1976)	inherent irrationality in diagnostic process	rationality in clinical arts
Feinstein (1967)	proliferation of diagnostic and therapeutic manoeuvres	clinician as scientist
Cochrane (1972)	suboptimal use of health care manoeuvres	evaluation of effectiveness and efficiency
Wulff (1976)	insufficient scrutiny of diagnostic innovation	follow model of evaluation of therapeutics
Conclusion	problems within the delivery system, particularly in relation to the integration of new diagnostic tests	require evaluation prior to widespread diffusion into clinical practice

CHAPTER 2

Computed Tomography

"Somatic illumination by Electricity ... Two electrical discoverers report about simultaneously new medical and surgical uses for an extremely powerful light ... Professor Roentgen, the well-known professor of Wurzburg University ... is said to have photographed the bones of the hand, all the soft parts being invisible ... (Anonymous, 1896).

2.1 Computed Tomography - The Image

The objective of investigative medical radiology is to obtain an x-ray image of certain parts of the human body. The ability to do this rests on the resolution of natural or artificially induced (e.g., by air or iodine-containing medium) differential densities of the tissues involved. The main liability of this process is in the fact that shadows of surrounding structures are superimposed on the area under investigation.

Conventional tomography has been developed to minimize this liability. By moving the x-ray source and the film in opposite directions about the patient, the image of one anatomical plane is kept in constant focus while the shadows of the other points are blurred across the film. Also called in-focus or blurring tomography, this process results in a shadowgraph which is an essentially clear image of the axis under investigation with the more distant anatomic structures out of the focus.

Computed tomography represents a significant advance in its ability to resolve the absorption of the x-ray beam as it passes through the body. Its ability to distinguish small differences in x-ray attenuation has been explained by Ter-Pogossian (1977):

(1) The reconstruction of sectional image from a series of projections taken at different angles about an object.

(2) The use of a narrow x-ray beam resulting in a decrease of scattered irradiation.

(3) Minimization of noise by utilizing a large number of photons and low noise detectors.

Computed tomography data is acquired in the following way. A beam of x-ray radiation is produced by a conventional tube energized to a potential of about 120-140 KVp with a current of 30 mA, and columnated to a rectangle in the dimension 10 mm. by 15 mm. It is then passed through the body and impinges upon a detector with the capacity to measure direct current. The tube and detector are connected rigidly to a gantry which, after each scan, is rotated 10 degrees; this process is normally repeated eighteen times.

The data generated by this process is a series of profiles of the attenuation of the x-rays in the tissues scanned; an algorithm is applied to these data by computer to transform them to a tomographic section. The images are so accurate because each point in the cross-section is measured 180 times from a different angle. Up to 25,600 points are reconstructed forming a matrix of

160 by 160 points or pictels. The applications of this process have been in two general areas, the head and the rest of the body. The prototype scanner designed by Hounsfield in the United Kingdom was restricted to use in the head. At present, all scanner manufacturers produce a machine that is suited to head and body imaging requirements.

A major difference in scanning the head and body has been the time required for the examination. In the head, movement can be restrained, and with a long scan time of two to five minutes an excellent image can be produced. In the body, faster scan times were required to minimize artefacts due to respiratory, cardiac, and bowel motion.

Body sections are displayed on a screen as though viewed from the bottom so that the patient's right is on the viewer's left. These images are presented on a standard cathode ray tube terminal (CRT) and/or paper hard copy. The CRT image of one section can be manipulated in terms of the amount of grey scale (window level). This allows the investigator to "see" the full range of anatomic structures from air to bone. Polaroid photographs or projection transparencies can be made of the images of the CRT and these then become part of the patient's medical record.

2.2 Diffusion of Computed Tomography Scanners

Perhaps the most significant feature of this technological innovation in roentologic imaging is its relative newness. Scanning of the head was developed by Hounsfield (1973) at E.M.I. Incorporated in the early 1970's, and the first unit was installed at an American institution in 1973. The first unit capable of producing images of other parts of the body has been operational since early 1974 (Ledley, 1974).

Ter-Pogossian (1976) reports that since its introduction into radiology computed tomography has been revolutionary; it has produced socio-economic reverberations in areas remote from its primary site of action. Radiologists' enthusiastic acceptance of computed tomography, based on its vast potential and not on the thorough evaluation indicated for such costly x-ray equipment, has had an impact on the industry. E.M.I. currently produces in the tends of instruments per month, and there are now more than a dozen manufacturers on the scanner marketplace. Ter-Pogossian (1976) finds these actions by the producers to be a "... *natural response to a buying frenzy by the radiologic community*".

In terms of the magnitude of this response, in August 1976 there were 321 CT units installed in the United States; there were 330 on order, and 200 applications were being reviewed by various health planning organizations (Creditor and Garrett, 1977). At that rate there would be 1,400 in America by January 1978 and 2,500 by 1980. Another estimate made earlier in 1976 was that

600 CT units had been sold in the world. In terms of dollars spent for purchasing, the costs of computed tomography represent about 50 per cent of the total American market for radiologic equipment (Ter-Pogossian, 1976).

2.3 Technological Change

Another factor related to the newness of computed tomography is the considerable change in its technical capability over the past few years. Since its initial development the time required to produce a single scan has been the area where the most dramatic change has taken place.

The earliest units were designed for use in cranial disease. In these machines, the head could be firmly secured, the patient might be mildly sedated, and with no intrinsic or transmitted motion within the skull, a five-minute scan time presented no serious difficulty in terms of motion artefact. However, the adaptation of the basic technology for use in the body, the artefacts produced by, for example, respiratory and bowel motion, had to be eliminated. A number of approaches to this problem have been made.

Respiratory motion can be voluntarily suspended by holding of the breath for a period of time while the scan is being performed, but with the very ill, the uncooperative, and the young, the only solution to reducing the motion artefact problem was to continue to decrease the time required for a scan.

Motion of the bowel cannot be controlled by the patient voluntarily, and along with the faster scan time an antiperistaltic agent (glucagon) is often administred intravenously or intramuscularly (Moss et al., 1978; Kreel, 1978). Movement of the heart muscle offers a particular challenge, and the approach to this problem of cardiac CT has been the development of a beam which is gated to the cardiac cycle. This innovation is still in the prototype stage (Berninger, 1978; Pullam et al., 1978).

In meeting the challenge of reducing motion artefact the scan time has been reduced from its initial five minutes to a present twenty seconds or less. To achieve this, the original single detector has been replaced by many which are arranged in a fan configuration (Ter-Pogossian, 1977). Further innovation in this area involves the use of xenon detectors (Fenster, 1978)

The quality of the CT image is being improved upon in other technical areas including the data processing system. Coronal and sagittal views are available in some prototype (Jelden et al., 1977), and at least one research centre the three-dimensional presentation is being developed (Glen, Jr. et al., 1978; Nalcioglu and Cho, 1978).

2.4 Consequences of Technological Change

The main consequence of the considerable change of the technological capabilities of computed tomography over the past few years is the obsolescence of the earlier models of the scanner.

In some instances, the older machines can be updated to deliver a faster scan time. However, these modifications can bring the scan time down to only about one minute; this is clearly not competitive with the state of the art equipment being produced today (Ontario Ministry of Health, undated).

The consequence of this aspect of computed tomography is that the most current reports of its use are generally not applicable to those installations which have the older units. Clinical and physical research is simply not being done with these old units. Therefore, when a clinically efficacious use of CT is described in the literature, careful assessment of the comparability of technical aspects must be undertaken to assure the generalizability of the new technique.

CHAPTER 3

Methodological Requirements for Studies of Innovation in Diagnostics and Therapeutics

"Many uses are suggested to which this ray can be put and the newspapers are full of experimental researches in this country and abroad. We find that many universities ... are making experiments .. Out of all this work must proceed some good" (Bury, 1896)

3.1 CT in Diagnosis

Studies dealing with the introduction of a new procedure in a diagnostic process can be assessed in terms of how they satisfy certain methodological requirements. The purpose of this chapter is to list these requirements, discuss them and the reasons for their inclusion, and then to take a sample of the papers published on Computed Body Tomography and assess how these standards have been met.

3.2 Diagnostic Accuracy

This criterion is composed of two sets of indexes (sensitivity and specificity, and predictive value) which indicate how well a particular diagnostic test performs in indicating disease when it does exist in a patient and indicating that it does not when, indeed, the patient is free from it.

3.2.1 Sensitivity and Specificity

The term sensitivity indicates the proportion of true positives or positive results among those patients who have the disease of interest. Stated another way, it indicates the ability of the diagnostic manoeuvre to detect a certain disease when the patient does have it. The complement to sensitivity is specificity or the proportion of negative test results among patients who do not have the disease of interest. It is the ability of the test or procedure to indicate no disease when the patient does have it.

Typically these indexes are expressed in percentage form; they are calculated on the basis of the information contained in Figure 3.1

Ideally, one desires a diagnostic test to be very sensitive and very specific. Such a test would neither miss a case nor would it indicate disease in its absence. In reality, however, such tests do not exist.

With respect to radiographic diagnostic tests, several technical problems will affect diagnostic accuracy. X-ray imaging techniques depend upon the radiodensity of the tissue under observation, the anatomic form and thickness of the tissue, as well as kilovoltage and exposure time selected by the radiologist (Squire, 1975).

The choice of a test with a higher sensitivity or specificity will depend largely upon the use that the test is to be put. Feinstein (1977) utilizing these indexes, defines three categories of diagnostic tests. The discovery test often used in

Figure 3.1

Calculating the Sensitivity and Specificity of a Diagnostic Test

		Clinical or Pathological Proof of Disease		
		Disease Present	Disease Absent	
Result of Diagnostic Test	Disease Present	True Positives (a)	False Positives (b)	Patients with Positive Test
	Disease Absent	False Negatives (c)	True Negatives (d)	Patients with Negative Test
		Patients with Disease	Patients free of Disease	All Patients Tested

$$\text{SENSITIVITY} = \begin{cases} \dfrac{\text{True Positives}}{\text{All Patients with Disease}} \times 100 = \% \\ \dfrac{a}{a+c} \times 100 = \% \end{cases}$$

$$\text{SPECIFICITY} = \begin{cases} \dfrac{\text{True Negatives}}{\text{All Patients Free of Disease}} \times 100 = \% \\ \dfrac{d}{b+d} \times 100 = \% \end{cases}$$

screening procedures should have a high sensitivity because, if the disease is present, it must be found. In this situation the occasional false positive result is more acceptable than a false negative. The second category is the confirmation test characterized by very high specificity; it will be ordered to verify the findings of a discovery test. The exclusion test is utilized to rule out disease when its presence is suspected on the basis of other tests. Accordingly, it will be very sensitive - close to unity.

As a requirement for the study of a new diagnostic test, therefore, discussion of the sensitivity and specificity is critical. In lieu of this discussion, presentation of data to fill all the cells of the fourfold table (Figure 3.1) is required because sophisticated readers can then calculate these indexes for themselves.

3.2.2 Predictive Value

As Feinstein has indicated, knowledge of the sensitivity and specificity of a diagnostic test or other information generating procedure, is, by itself, inadequate in terms of the information the clinician requires in the management of a particular patient. In the most frequent clinical situation a patient presents a disease problem to the clinician whose task it is to assess his patient's ailment and, where appropriate, initiate a therapeutic plan. When choosing a diagnostic test in these cases the clinician wants to know how likely the positive or negative

test result he has received is correct. Positive predictive value refers to the likelihood that the positive test result (i.e., indicating presence of disease) is correct. Conversely, negative predictive value refers to the likelihood that the negative test is correct.

With reference to Figure 3.2, the positive and negative predictive values are calculated using the number of positive or negative tests as the denominators and the number of true positives and true negatives as the numerators.

In some instances, a summary accuracy index is calculated. In this calculation (Figure 3.3) the total number of correct test results is expressed as a percentage of all test results. However, it is felt that this summary accuracy index tends to gloss over what might be very important differences in positive or negative predictive values, and, therefore, it is recommended that this procedure not be used.

Figure 3.2

Calculating the Predictive Value of a Diagnostic Test

$$\text{Positive Predictive Value} = \begin{cases} \dfrac{\text{True Positives}}{\text{All Patients with Positive Test}} \times 100 = \% \\ \dfrac{a}{a+b} \times 100 = \% \end{cases}$$

Figure 3.3

Calculating the Accuracy of a Diagnostic Test

$$\text{Accuracy} = \begin{cases} \dfrac{\text{True Positives + True Negatives}}{\text{All Patients Tested}} \times 100 = \% \\ \dfrac{a+d}{a+b+c+d} \times 100 = \% \end{cases}$$

3.2.3 Prevalence

Finally, any discussion of diagnostic accuracy is incomplete without mention of disease prevalence or the likelihood that the patient has the disease which the diagnostic test is designed to assess. Sackett (1978), Feinstein (1977) and Galen and Gambino (1975), have stressed the influence that prevalence has on the evaluation of a diagnostic test. Since sensitivity and specificity are the inherent characteristics of a procedure based on confirmed cases, prevalence will not have any influence on them. However, predictive value is affected by prevalence and this must be taken into consideration. With reference to Figure 3.4 prevalence can be determined as follows:

Figure 3.4

Calculation of Disease Prevalence Among Patients Tested

$$\text{Prevalence} = \begin{cases} \dfrac{\text{All Patients with Disease}}{\text{All Patients Tested}} = \% \\ \\ \dfrac{a+c}{a+b+c+d} \times 100 = \% \end{cases}$$

Because of the relationship between prevalence and predictive value, failure to consider both in a study of a diagnostic test is a potentially serious error. Sackett (1978) illustrates this problem in the situation where the clinician, anticipating a predictive value based on a report in the literature, may subject his patient to a certain diagnostic test. If the proportion of diseased patients in his practice is lower than that at the site where the test was developed, the positive predictive value of the test will decline and the negative predictive value will rise. The upshot of this is an increase in the proportion of false positive test results. The implications of this are serious in terms of therapeutic decisions which are based upon them. Since most tests are initially developed in tertiary care research centres where the prevalence of conditions under study is high, it is likely that the uncritical extrapolation of results from such a centre to primary clinical practice may lead to the unfortunate results of decreased positive predictive value and the tests will fall into disrepute.

3.3 Attributes of the Patients Tested

As has been pointed out, tests performed on differing populations will yield different indexes of predictive value. To counteract this development, and to indicate to what groups of patients a certain diagnostic procedure can confidently be applied, a further requirement of the evaluation of a new test is required. Part of the confounding due to prevalence can be

neutralized if a study describes the relevant demographic and clinical attributes of the population tested. These attributes will vary from test to test, but at the very least there must be some evidence indicating the likelihood that the patient tested has the disease. This will vary from, for example, *"all patients with a suspected hepatobiliary disease"*, through *"patients with jaundice thought to be caused by an obstruction"*, and *"patients beyond three months of age with elevated serum bilirubin and serum alkaline phosphatase levels"*. If the condition of interest with these three examples is obstructive jaundice, and if the test is one to differentiate obstructive from non-obstructive jaundice, then clearly, the third descriptive phrase is much more useful to the clinician in terms of generalizability.

3.4 Description of Technic

Another factor upon which the published studies of CT are to be assessed is the description of technic. If the report of a diagnostic test evaluation is to be considered complete, it must include specific detail describing patient preparation and test procedure. Failure to comply with this represents a serious limitation of the repeatability of the manoeuvre.

In the case of the CT scanner, technic is still in the developmental stages, therefore, an investigator is expected to report explicit procedural information. Mention should be made of the manufacturer and make a model of the scanner, whether sedative or antiperistaltic medication was administered to the

patients, and whether contrast enhancing media was used. Other relevant aspects of technic include: slice thickness, smoothing algorithm, window height and width, and scan time.

3.5 Definition of Test and Disease Outcome

For the evaluation of the diagnostic accuracy of a new procedure to be at all useful, specific details of what constitutes a positive and negative test result is an essential component. In computed tomography for example, this necessitates a description of the attenuation values, the displacement of normal anatomy, and other clinical features as appropriate to the particular tissue under observation.

This requirement applies to the confirmation of presence or absence of disease as well. It should be stated whether there is clinical or surgical proof of the presence of the disease. Studies lacking this characteristic, or which group all patient outcomes even though based upon different disease outcome criteria, are less useful than those that meet this requirement.

3.6 Impact on the Diagnostic Process

A further requirement is the discussion of the potential or demonstrated impact the introduction of a new test might have on the current sequence of diagnostic manoeuvres. As stated in Chapter 1, the patient must be assessed by means of the most effective manoeuvres and the process itself should be carried out in the shortest time allowable under the clinical circumstances.

The attributes of this impact requirement are of two parts. First, the effect on the sequence and selection of tests and, secondly, the consequences of this for the patient.

3.6.1 Improvement Over Existing Tests

The new diagnostic test, by definition, is developed to assis the clinician in his effort to discover what ails the patient. Its contribution is in terms of the information about the disease process, and its value in this regard lies in how well the test compares with existing tests. With the exception of a new procedure which yields diagnostic data hitherto unavailable, as assessment of the relative merit of the new versus the existing tests is essential.

Without this requirement it is possible that a test might be introduced which adds no new diagnostic information. A variation on this problem is the new manoeuvre which yields qualitatively superior data but which is in itself diagnostically similar to, or inferior to, that which is currently available. This situation is more likely to be a concern in medical imaging techniques where there is not necessarily a direct correlation between the quality of the image of some anatomic area and a diagnostic usefulness of this new data.

The discussion of comparative usefulness of diagnostic information is phrased in terms of indexes of diagnostic accuracy as discussed under Section 3.1.

3.6.2 Effects on the Patient

The second aspect of impact that an assessment of a new test should include is the effect on the patient. In the evaluation of a diagnostic procedure, therefore, we are concerned about two factors: time and risk. Time is an important factor in that a diagnostic sequence leading to therapy should be as efficient as possible. A new modality which can shorten the length of time from presentation of the problem to initiation of efficacious therapy in a given disease is, by definition, a benefit to the patient. The second factor to be considered is risk to the patient with the introduction of the new manoeuvre. There will be some risk of morbidity or mortality associated with many new tests, and this extra risk must be considered in relation to the diagnostic sequence. A beneficial situation may arise when a new test of relatively low risk is used to replace an existing test which poses greater risk. Risk is of two orders: there is the quantifiable, such as radiation delivered, hypersensitivity reactions to contrast medium, complications of endoscopic techniques, etc. A second order of risk involves the pain, embarrassment and acceptability associated with the performance of the test itself.

In summary, therefore, there are five factors which study of a new diagnostic test must take into consideration. These are:

(1) diagnostic accuracy

(2) population of the patients tested

(3) description of the technic

(4) outcome measures used

(5) impact on process and patient

These criteria will now be applied to all papers dealing with the use of computed tomography in hepatobiliary disease, and, a 25 per cent random sample of all studies of diagnostic uses of Computed Body Tomography listed in the Index Medicus for 19[illegible] This will be laid out in tabular form with the methodologic criteria listed across the top and various studies down the side. At the point of intersection of a particular report and a particular requirement within the table, a cell with a zero indicates no discussion or insufficient discussion of that requirement, and an "x" designates satisfactory discussion. The papers will be presented in two groups, the first includes those dealing with hepatobiliary disease and the second, the 25 per cent sample of other diagnostic body studies.

By observing the cells of Tables 3.1 and 3.2 it can be concluded that there is a satisfactory discussion of population, technical aspects and outcome, but at the same time these studies are deficient in the categories of accuracy and impact.

In the sample of papers representing the general use of CT, only one (Husband et al., 1977) presents data and discussion of diagnostic accuracy. In the biliary group, one paper (Levitt et al., 1977b) deals with these issues, but only insofar as it clearly

Table 3.1

Studies Assessing the Diagnostic Use of CT Among Patients with Hepatobiliary Disease

Anatomic Region	Accuracy	Population	Technic	Outcome		Impact	
				Test	Disease	Process	Patient
Bile Ducts (Alfidi et al., 1975)	0	0	X	X	0	0	0
Bile Ducts (Harrell et al., 1977)	0	0	X	0	0	0	0
Bile Ducts (Stanley et al., 1977)	0	X	X	X	X	0	0
Bile Ducts (Havrilla et al., 1977)	0	X	X	X	0	0	0
Bile Ducts (Levitt et al., 1977b)	X	0	X	X	X	0	0
Bile Ducts (Alfidi et al., 1976)	0	0	X	X	0	0	0
Bile Ducts (Goldberg et al., 1977)	0	X	X	X	X	0	0
Bile Ducts (Di Giacomo et al., 1977)	0	X	X	X	X	0	0
Bile Ducts (Stephens et al., 1977)	0	0	X	X	X	0	0 0
% of Papers Meeting Requirements	11%	44%	67%	78%	56%	0%	0%

Table 3.2

Studies Assessing the General Diagnostic Uses of CT

Anatomic Region	Accuracy	Population	Technic	Outcome		Impact	
				Test	Disease	Process	Patient
Pelvis (Gerson et al., 1977)	0	X	X	X	X	X	X
Liver (MacCarty et al., 1977)	0	X	X	X	0	0	0
Pancreas (Husband et al. 1977)	X	X	X	X	X	X	0
Abdomen (Holm et al., 1977)	0	0	0	0	0	X	0
Abdomen (Boldt et al., 1977)	0	X	X	X	X	0	0
Pelvis (Carter et al., 1976)	0	X	X	X	X	X	0
Pancreas (Kreel et al., 1977a)	0	0	X	X	0	0	0
Pancreas (Levitt et al., 1977a)	0	X	0	0	X	X	0
Pancreas (Barkin et al., 1977)	0	X	X	X	X	X	0
Breast (Gisvold, 1977)	0	X	X	X	X	X	0
Pancreas (Sheedy et al., 1977b)	0	X	X	X	X	0	0
% of Papers Meeting Requirements	9%	82%	82%	82%	73%	64%	9%

states that the data presented was not appropriate for discussion of sensitiyity and specificity.

The second serious limitation in both groups of studies is the lack of discussion of impact on CT on the diagnostic process and on the patient. Although several studies looked at CT in a comparative framework, few measured or estimated the degree to which the sequence of diagnostic procedures might change with the introduction of CT scanning. Similarly, although most every paper uses "non invasive" as an adjective to describe computed tomography, there was only one (Gerson et al. 1977) instance where the benefit to the patient received adequate attention."

One other aspect of this review of the literature that bears mention is related to the newness of the technology as mentioned in Chapter 2. Computed tomography of the body is a very new procedure, and it is reasonable to extend the idea of a "generation" from a description of the technology itself to studies of the use of the technology in medical care (Table 3.3).

Defined in terms of scan time, the scanner is in its second generation and the third generation is currently being developed. The first generation scanner had a time of abour 4 to 6 minutes; this was a considerable source of noise or motion artefact. Normal respiratory or bowel movement seriously impaired the quality of the image and limited its diagnostic utility. The second generation had a scan time of from twenty seconds to two minutes, and with the administration of an antiperistaltic agent, a diagnostic image

could be made on most patients. The next generation of scanner with a scan time of less than 20 seconds will eliminate all motion artefact and will be capable of in vivo imaging of the phases of cardiac cycle.

Studies of the use of CT can be described as improving in a similar progressive fashion. Virtually all of the papers reviewed herein are of the "first generation". These are characterized by extensive discussion of technic and description of the normal and pathologic anatomy. They are important in terms of the role they play in establishing ground work for technical aspects of the use of computed tomography in clinical practice. Nevertheless, they are deficient in terms of providing useful information in respect of relative diagnostic accuracy and impact.

Table 3.3

Generations within Computed Tomography

Generation	Studies	Technology
First (1970-1974)	Technic oriented evaluations of conditions	Slow scan time and limited applicability
Second (1974-1978)	Evaluation of specific clinical applications	Faster scan time and advanced image manipulation
Third (1978-)	Social impact: costs and benefits	Image reconstruction technics and solution of time problem

The next order of studies is beginning to appear in mimeograph form, and from personal report, and should appear in the literature in the near future.[v] These are evaluations of the use of scanning; they are prolective in terms of data collection and cohort in terms of temporal direction. They seek to quantify the impact on the clinician's diagnostic and therapeutic planning behaviour within certain sub-groups of patients.

The third order of study will be directed toward broader social and economic aspects of the use of Computed Body Tomography. This research endeavour will require the development of mechanisms to put a value on the results of scans as well as on the quality of life.

In summary, based on this review of the literature, the direction which research of the use of computed tomography in the diagnostic situation should take, is that which focuses on a particular clinical problem, collects data to assess relative diagnostic usefulness and which evaluates the potential impact on the patient and on the process.

3.7 CT in Therapeutics

Whereas its application to diagnosis has been the most frequently reported use of Computed Body Tomography, there is another aspect of clinical practice that might benefit by the introduction of this technology, i.e., therapeutics. More specifically, because of the ability of computed tomography to resolve soft tissue, its use in the staging of malignant neoplastic

disease has been suggested by several investigators.

Stewart and Simpson (1977) report that as many as one-third of the patients who are placed on a cancer therapy regimen subsequently die because of the failure to control local and regional sites of involvement and two-thirds due to metastic foci. The development of an imaging technic which can outline the geographic boundaries of local spread such that more accurate radiation therapy can be delivered and which can delineate the extent of spread to secondary sites is potentially beneficial to cancer patients.

As is the case of CT in diagnosis, the assessment of the role of computed tomography in staging malignant neoplastic disease must conform to certain methodologic standards. Since it is once again the anatomical information upon which the staging decision is made, the first requirement is for an assessment of comparative accuracy. As we are, by definition, interested in a distinct population of patients, i.e., those with a positive diagnosis of malignant neoplasm, it is required that an evaluation specifically stage what the nature of the disease is in terms of histologic type and degree of spread. Technic is also a factor insofar as it is different from that employed in a diagnostic use of computed tomography. Finally, an assessment of the introduction of CT into staging must consider that area of benefit to the individual cancer patient.

3.8 Accuracy in Staging

The major concern of a new imaging procedure in the staging of a malignant neoplasm is an assessment of its accuracy, i.e., how well it delineates the regional and metastic spread of a tumor in relation to existing procedures. In a diagnostic situation, the degree of accuracy is based upon ultimate clinical or pathological proof of disease. However, this situation is considerably different in that once the staging decision has been reached, a therapeutic plan is immediately undertaken to remove the tumor, to reduce its size or to retard its subsequent growth. It is not recommended that extensive surgical exploration be employed to establish a reference criterion for the comparative accuracy of the staging decisions. However, in those cases where a patient does go to surgery or autopsy, definitive evaluation of accuraty of staging decisions can be undertaken.

3.9 CT Technic

Reports from institutions using CT in cancer therapy indicate that patient preparation and orientation of the patient in the scanner requires special consideration. In essence, the scanner table must be of the same shape as that which the patient lies on in radiation therapy. Without this, the geographic description of the tumor will differ between the two machines and, therefore, a less than optimal radiation dose might be delivered.

3.10 Description of Patients

In the interest of reproducibility of the technic, it is required that adequate clinical description of the patient undergoing staging be presented. In the case of bronchogenic carcinoma, for example, the World Health Organization has delineated four classifications which account for nearly 90 per cent of all cases of lung cancer. The differences among the four histologic types is related to clinical course, and therefore, is relevant to clinical attributes of the population which must be included in any study of the staging process.

3.11 Benefit in Staging

Benefit in this situation is related to the delivery of an appropriate modality of therapy with the minimum discomfort to the patient in a minimum period of time. The principal factor in reaching a therapeutic plan is an accurate assessment of the stage of a disease. Therefore, the use of an innovation to the existing staging process has the potential to be of benefit by leading to a more specific therapeutic plan and could spare the patient the cost and pain of useless surgery or other invasive investigative procedure.

3.12 Conclusions

While there is a dearth of studies assessing the role of CT as a new medical imaging procedure in the staging of a malignant neoplasm, there is a larger number which suggests that this is possible (Alfidi and Haaga, 1976; Dische, 1977; Jelden et al., 1976;

Schaner et al., 1977; Kreel, 1977b). However, most studies of CT in neoplastic disease are concerned with the diagnostic aspects and, while these are useful in determining particular areas for therapeutic scanning, they do not deal with the special technical aspects required for work on staging. In diagnosis, the chief interest is the presence or absence of the tumor, in staging the objective is to carefully delineate the geography of the tumor and the extent of metastic spread.

As outlined in Chapter 1, to be consistent with the principle of delivering effective and efficient medical care, an innovative procedure must be assessed in relation to both a particular clinical problem and to the existing clinical procedure which it might potentially replace. The following two chapters will attempt to meet this standard by outlining a strategy for evaluation of a diagnostic case - the investigation of patients suspected of having cholestatic jaundice, and a therapeutic case - the initial staging of patients with bronchogenic carcinoma.

CHAPTER 4

Computed Body Tomography in a Diagnostic Situation

"... the further fact, that in a general way only the density of the medium penetrated seems to affect them ('the x-rays') .... hints at further valuable physiologic revelations as well as diagnostic aids. It is only a hint however, and whether it is to be even realized to any extent is perhaps open to serious question." (Anonymous, 1896b).

4.1 Introduction

In Chapter 1 a rationale for the evaluation of an innovative diagnostic procedure was presented, and in Chapter 3 a review of the literature indicated that many of the published assessments of this use of CT were methodologically deficient. This Chapter will propose a general strategy for the evaluation of the diagnostic efficacy of CT, and will illustrate the methodology with an example: its use in the diagnostic evaluation of patients suspected of having cholestatic or surgical jaundice.

4.2 Research Questions

The first question that must be answered is: how accurate is CT as compared to the procedures used in the conventional diagnostic sequence? The accepted method for such comparisons of accuracy is as follows: to add the new test to the existing sequence; to perform each test on a pre-determined number of patients from a homogenous population; to apply, independently, standardized criteria to each test result such that each can be

declared either positive or negative; to determine by the most definitive measure available whether each patient has (the positives) or does not have (the negatives), the condition which the sequence is designed to detect (Feinstein, 1977; Sackett, 1978; Vecchio, 1966). This data can be used to calculate the indexes of accuracy, namely: sensitivity, specificity and predictive value. The indexes of the innovative procedure can be compared to those of the conventional procedure by using the methodology presented by Bennett (1972).

Also under the heading of accuracy, the agreement between the diagnostic decision by the conventional sequence versus the decision by CT can be determined.

Apart from the usefulness of CT as a diagnostic manoeuvre, there are other aspects of the evaluation of a new diagnostic procedure; these are categorized under impact. The second research question enquires: what would be the impact of adding this new test to the diagnostic work-up of a defined group of patients? In Chapter 3 impact was defined as having two elements: time - meaning the duration of the diagnostic process, and invasiveness - referring to the risk of morbidity and mortality associated with each procedure and with in-patient status.

Assessment of risk logically follows the assessment of accuracy. It can be argued that until the relative accuracy of a new diagnostic procedure like CT is understood, it should not be freely introduced to clinical practice as a supplement to or replacement for, any test or tests in the established order.

Once the data on accuracy is available, a tentative decision can be made in relation to what diagnostic procedures the innovation might replace. The definitive assessment of impact, therefore, requires a separate enquiry. However, an estimate of potential impact can be made on the basis of the accuracy data plus an indication of the risk of each of the conventional and the innovative procedures.

While the clinician is the key individual in the study of accuracy, the patient is the focal point when addressing the question of impact. The first concern is the time factor; is there potential for the reduction of the length of time taken by the diagnostic process? Theoretically, a reduction in time provides two benefits: first, the therapeutic plan is initiated earlier and, second, the patient experiences fewer days on a hospital ward. The second concern in the evaluation of impact is related to the risk of morbidity or mortality associated with the individual diagnostic procedures employed. A patient stands to benefit if a procedure with higher risk can be replaced by one of lower risk, and if the latter is at least as diagnostically accurate as the former.

In summary, the introduction of CT has raised the question of the accuracy and impact of this innovative radiologic imaging device. In the absence of methodologically sound assessments of these issues, it is proposed that data be collected to provide a definitive assessment of relative accuracy, and subsequently, an

estimate of the potential impact of introducing CT to the diagnostic sequence established for patients suspected of having cholestatic jaundice.

4.3 Research Strategy

To answer the questions posed under Section 4.2, a methodology will be presented which will take into consideration the following details:

(a) to define a homogenous population of patients

(b) to develop a protocol for handling the patients such that each case is treated equally and undergoes each diagnostic procedure

(c) to define standard objective criteria which will differentiate a positive from a negative test result

(d) to define criteria upon which a final diagnosis is made

(e) to determine the number of patients required to permit an inferential statement, and to propose statistical measures which are appropriate for the study design.

4.3.1 Patient Population

To illustrate the methodology for the evaluation of the accuracy of CT in diagnosis, a clinically homogenous series of patients are required. Patients with suspected cholestatic jaundice have been selected as the subjects of this investigation. To qualify for inclusion these patients must exhibit an elevated direct reacting bilirubin (beyond 0.5 mg/dl), an elevated serum alkaline phosphatase (beyond 120 IU/litre) and a clinically normal gamma glutyl transpepsidase (not beyond 30 IU/litre). With this clinical picture, jaundice secondary to haemolytic disorder or hepatocellular disease is essentially rule out, and the consequent diagnostic impression is jaundice secondary to physical blockage of the biliary tree (Dusol and Schiff, 1975; Kanton et al., 1975; Watson, 1975). From this group of patients, infants and pregnant females are excluded on the grounds that (1) the extra radiation or medication associated with the CT examination is not advised, and (2) there is very little indication of the potential use of CT in these two patient groups.

Those remaining patients require further diagnostic evaluation in order to determine visually the location and extent of any physical obstruction of the biliary tree. It has been suggested that CT is a potentially valuable procedure for this investigation (Alfidi, 1976; Alfidi et al., 1976; Havrilla, 1977; Levitt et al., 1977b; Petansic et al., 1976). A number of published descriptive studies and case reports indicate that CT can provide an accurate image of normal and deranged biliary

anatomy, from the hepatocyte to the ampulla of Vater. With regard to the specific causes of obstruction, it has been reported anecdotally that CT is very accurate in detecting choledocholithiasis (Havrilla et al., 1978), the various biliary carcinomata (Biello et al., 1978), metastic liver disease (Biello et al., 1978; Grossman et al., 1977; MacCarty et al., 1977), pancreatitis and carcinoma of the head of the pancreas (Haaga et al., 1976; Haaga et al., 1977; Sheedy et al., 1977a; Wiggans et al., 1976).

Because patients with suspected cholestatic jaundice are admitted to hospital for diagnosis and treatment, and because all patients will undergo radiologic investigation, the point at which assessment of eligibility for inclusion in this study is made is at the time of referral to x-ray. There is the rare instance when a patient will be admitted as a surgical emergency, and where the only course of action is immediate surgical decompression. These patients do not undergo extensive radiologic investigation, and therefore, are not considered for inclusion in the study group. The other patients who ultimately may be shown to have an obstruction of the biliary tree, but who do not complete the study protocol, are of two groups. First, there are those who initially refuse to enjoin when asked; secondly, those who initially consent, but later exercise their perogative to withdraw. While these cases cannot be included in the analysis of data bearing on accuracy or impact, an effort will be made to explain how they differ from those who are fully compliant.

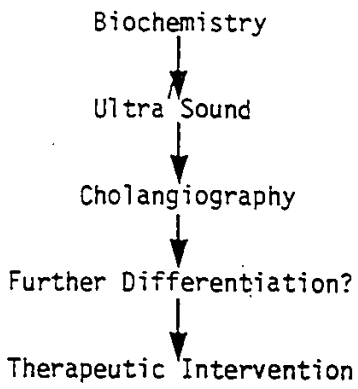
In summary, those patients admitted to hospital and referred to the Radiology Department for investigation of possible obstructive jaundice will be screened by biochemical lab criteria. Those who are picked up by this screen will be asked to consent to undergo CT in addition to those other procedures typically performed on these patients.

4.3.2 Protocol

Typically when the results of diagnostic tests are reported, a tentative diagnostic decision is made: disease x is ruled out, disease y is still a possibility, and so on. The result of this is a sequential certainty of diagnosis. Toward the end of the process the clinicians have fairly solid evidence upon which to frame a "most likely" diagnostic decision and a therapeutic plan. Such is the case with the evaluation of the jaundiced patient as indicated in Figure 4.1

Figure 4.1

Sequence of the Diagnostic Process



Before electing surgical decompression there is evidence indicating whether an obstruction is likely responsible for the jaundice, and, where applicable, the site, nature and extent of the blockage. To introduce CT into the sequence, there is the risk of biasing the conventional diagnostic sequence.

Ransohoff and Feinstein (1978) point out two sources of bias that must be neutralized in studies of diagnostic accuracy. Work-up bias tends to come into play when the result of a test done early in the sequence affects the rigour applied to the selection and interpretation of subsequent tests. In this study, the consequence would be that the results of any radiologic test done prior to CT are likely to influence what the radiologist sees in the CT image. This would compromise the criteria of independent assessment. Incorporation bias operates when the clinical evidence provided by the test being assessed is included with the other data upon which the final diagnosis and therapeutic plan are formulated. To attempt to negate these potential pitfalls, CT will be performed prior to any other radiologic test and the result withheld completely from the conventional clinical sequence. Having done this, independent diagnostic decisions can be made and subsequently compared:

(1) the diagnosis on the basis of CT alone

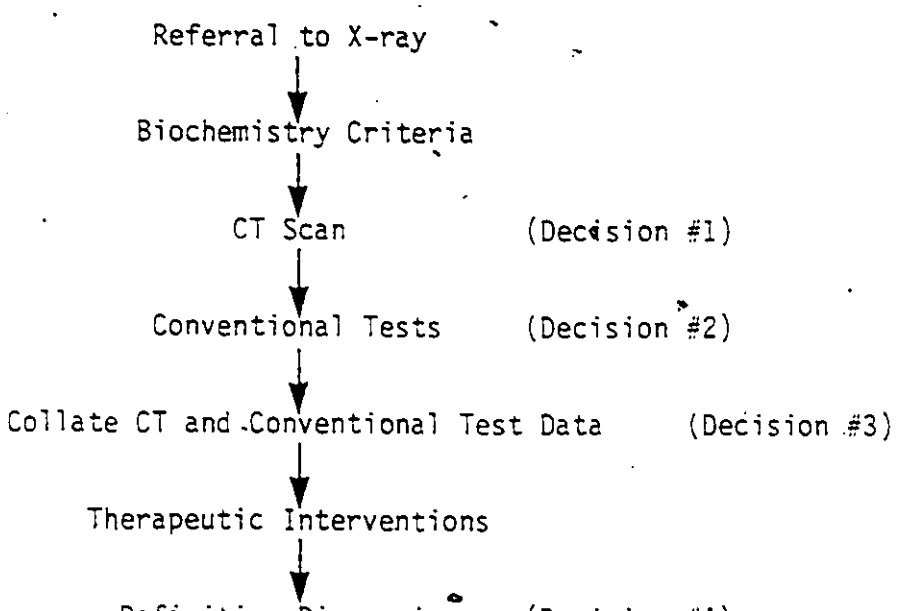
(2) the diagnosis on the basis of the conventional clinical sequence

(3) the diagnosis on the basis of the conventional clinical sequence plus CT

The outline of the study design is depicted in Figure 4.2,

Figure 4.2

Sequence of Diagnostic Study Events



and described as follows:

(a) In-patients referred to radiology for the evaluation of possible obstructive jaundice and who satisfy biochemical criteria will be asked to consent to undergo a CT examination. The risks of this test, as far as they are known, will be described, as will the fact that this test result will not influence, in any way, their clinical course.

(2) For those who consent, a scan will be performed; the results will be withheld until a final diagnosis is reached.

(3) The attending physician who refers the patient will exercise full clinical judgment in reaching a diagnostic decision and therapeutic course.

(4) The therapeutic plan (from (3)) will be implemented.

(5) Data analysis.

4.3.3 Interpretation of CT Results

In this study one radiologist will be responsible for the interpretation of CT scan results and the CT diagnostic decision. The magnetic tapes which store the data used to produce the cross-sectional image shall be kept for the duration of the study. For each patient the interpretation will be phrased as positive or negative for evidence of biliary tract obstruction.

CT technic for the evaluation of the biliary tree, as proposed by Goldberg (1977, 1978), calls for selective use of contrast medium to enhance the capillary beds of the pancreas and liver, and for scanning at 1 cm. intervals in the region of the porta hepatis, the anticipated course of the common bile duct and the head of the pancreas.

4.3.3.1 Evaluation of Intrahepatic Bile Ducts

The first task is to differentiate bile ducts from the portal venous structures (Kressel et al., 1977); this is done with reference to the attenuation coefficients. The liver parenchyma has a mean CT number of 25; the portal vein is normally in the range of 10 to 15 and the bile ducts in the 5 to 10 range. When differentiation is difficult, the intravenous administration of 150 cc. of Conray 30% medium will enhance the image of the portal vein. The second task is to determine whether the ducts are dilated. In the normal adult these ducts are very small, on the average less than 3 mm. in diameter, and just on the threshold of detection by CT. Distended intrahepatic ducts appear as low density tubular structures which course horizontally in the left lobe and appear as oval or semicircular densities in the right lobe.

4.3.3.2 Evaluation of Extrahepatic Bile Ducts

By scanning at 1 cm. intervals in the region of the porta hepatis, one can detect the oval or circular density indicating the common bile duct. This can be differentiated from the duodenal sweep by the administration (per os) of 8 to 12 cc. of 3% Gastrographin and from the portal vein by injection of Conray 30%. A dilated common duct will appear as a low density structure medial to the duodenum in the region of the head of the pancreas.

4.3.3.3 Evaluation of the Site of Obstruction

The most frequently occurring lesions causing obstruction are solid masses or metastases which impinge upon the biliary tree, stones within the duct which block the flow of bile, and the calcifications associated with chronic pancreatitis. Primary and secondary neoplasms in the liver are usually recognized as areas of decreased density having attentuation coefficients in the range of 5 to 10 units lower than surrounding parenchyma. Stones can be readily identified as areas of high density within the low density bile filled ducts. Pancreatitis is normally associated with general decrease in the density of the gland, an increase in its apparent size, and alteration of its contour.

For purposes of comparability, each test performed in the conventional sequence will be interpreted by conventional methods as either positive or negative for obstructive jaundice.

4.3.4 Definite Diagnosis

The report of the surgeon or pathologist will be the source of information for the final diagnosis. This will be recorded in the same way as the results of the diagnostic tests, i.e., either positive or negative for physical obstruction.

4.3.5 Sample Size

When making a decision with respect to the comparative accuracy of CT, two types of errors of logic must be taken into account. The first error, Type I, would be committed if one decided that a true difference in accuarcy existed when in fact it did not. The second error would be committed if one failed to decide that there was a true difference when in fact such a difference really exists.

In planning a study the investigator must decide on the risk he is willing to take with respect to committing each of these types of errors.

In this research the significance level will be set at 0.05. From the review of the literature it was determined that a 20 percent difference in accuracy would be important to detect. The desired probability of committing a type II error, that is, of failing to detect this difference was set at 0.20.

The median value for the accuracy of cholangiography was discovered to be 70 per cent, and for a 20 per cent improvement the accuracy of CT must reach 84 per cent.

These values are applied to the calculation of sample size in Figure 4.3.

Figure 4.3

Sample Size Calculations

		Cholangiography Diagnosis	
		Positive	Negative
CT Diagnosis	Positive	a	b
	Negative	c	d

$Z_\alpha = 1.96$

$Z_\beta = -0.84$

$\pi_a = 0.70$

$\pi_b = 0.84$

$$N = \left[\frac{Z_\alpha \sqrt{\pi_a (1-\pi_a)} - Z_\beta \sqrt{\pi_d (1-\pi_d)}}{\pi_a - \pi_d} \right]^2$$

$$= \left[\frac{1.96 \sqrt{(.7)(.3)} - (-.84) \sqrt{(.84)(.16)}}{.14} \right]^2$$

= 74 patients

4.3.6 Measuring Accuracy

A measure of the agreement of the two diagnostic strategies is proposed using the statistic Kappa (Fleiss, 1973).

For comparisons of the sensitivity, specificity and predictive value of the individual diagnostic tests, the method proposed by Bennett (1972) will be employed. His procedure assumes the knowledge of presence or absence of disease in each of a series of n patients and the diagnostic results (positive or negative) of t diagnostic tests. The method employs the χ^2 tets for homogeneity of the indexes of accuracy (Bennett, 1967). The situation where $t=2$ tests is illustrated for the comparison of sensitivity (ξ).

Test One	Test Two	Final Diagnosis Positive	Negative
+	+	ρ_{11}	ρ_{01}
+	-	ρ_{12}	ρ_{02}
-	+	ρ_{13}	ρ_{03}
-	-	ρ_{14}	ρ_{04}
Total		π	$1-\pi$

The frequencies are distributed as the multinomial:

$$n! \prod_{i=1}^{I} \prod_{j=1}^{4} p_{ij}^{n_{ij}} / n_{ij}!$$

The sensitivity of the two tests is:

$$\text{test one:} \quad \xi_1 = (\rho_{11} + \rho_{12})/\pi$$

$$\text{test two:} \quad \xi_2 = (\rho_{11} + \rho_{13})/\pi$$

The hypothesis H_ξ^0: ξ_2 is equivalent to $H_\xi^0 : \rho_{12} = \rho_{13}$.

The appropriate test statistics for H_ξ^0 is the matched sample χ^2 (Bennett, 1967) given by

$$\chi^2_\xi = \frac{(n_{12} - n_{13})^2}{(n_{12} + n_{13})}$$

with one degree of freedom. The continuity correction is omitted because its use results in poor agreement with χ^2 (Bennett and Underwood, 1970).

4.3.7 Measuring Impact

Studies of the use of CT scanning of the head indicate that the more invasive procedures such as arteriography, cerebral angiography and pneumoencephalography have been replaced by CT which is at least as accurate in its ability to detect and pinpoint neurologic lesions (Ambrose et al., 1976; Reich et al., 1976; Gawler et al., 1976).

Based on this proposal for a study focusing on accuracy, and given existing estimates of relative invasiveness, some indication of the potential impact of CT on the conventional

diagnostic sequence can be made. Table 4.2 presents hypothetical data describing accuracy and relative invasiveness to illustrate the point.

Table 4.2

Relative Accuracy and Invasiveness

Procedure	Accuracy Compared to CT	Invasiveness Compared to CT
Ultrasound	Less	Less
Endoscopic Retrograde Cholangiopancreatography	Similar	More
Abdominal Film	Less	Less
Percutaneous Transhepatic Cholangiography	Similar	More
Exploratory Laparotomy	More	More
Selective Angiography	Similar	More

If the decision criteria for the selection of a diagnostic manoeuvre can be limited to accuracy and safety, then Table 4.2 suggests that CT can likely replace cholangiography and ultrasound with no loss of diagnostic value and a real gain in safety.

With regard to the second element of impact, namely, time required for diagnostic evaluation, Table 4.2 indicates the potential for replacing the less accurate tests with CT. Theoretically, this could reduce the length of stay for the average patient.

This consideration of accuracy is included to show what practical implications a study of diagnostic accuracy can provide.

CHAPTER 5

Computed Tomography in the Staging of Bronchogenic Carcinoma

"Physicians from time immemorial have even had a keen desire to explore the interior of the animal body. Hence arose disection, and later on vivisection ... But none of these methods fully satisfied the wish to know what is actually taking place within ... during life ... No wonder then that the x-ray with its marvelous revelations of the hitherto unseen has excited universal interest" (Morton, 1896).

5.1 Scope and Objectives

The objective of this Chapter is to present a strategy to assess the potential value of the use of CT scanning among patients with histologically diagnosed brochogenic carcinoma. The particular use to be studied is CT as a staging manoeuvre; that is, to determine the extent to which the primary tumor has spread from the initial locus. This is a clinically important question because the stage of the disease is the principal determinant of the therapeutic program to be prescribed for the patient (Laughlin et al., 1977). Therefore, it is in the best interest of the patient that the most accurate physical description of the stage of the disease be made available.

Hansen (1977) describes the three stages of bronchogenic carcinoma:

STAGE A: Regional Disease, which includes patients who technically can undergo radical resection of the primary tumor.

STAGE B: Limited Disease, consisting of inoperable patients with disease limited to one hemithorax with or without involvement of the scalene lymph nodes.

STAGE C: Extensive Disease, including inoperable patients with intrathoracic and extrathoracic disease, which is not included in Stage B.

Each of these stages is normally associated with a particular therapeutic approach. With regional disease, and this represents about 20 per cent of all lung cancer patients, pneumonectomy, lobectomy, wedge resection or sleve resection is the indicated therapeutic approach. However, this is a very invasive procedure wherein postoperative mortality is highly related to the extent of surgery. It is essential, therefore, that before resection is elected, the best possible image of the chest is available. If a patient, on the basis of conventional tomography, is erroneously labeled Stage A, the surgical approach in addition to its inherent risks, will likely have no beneficial impact on prognosis.

With limited disease (Stage B) radiotherapy is the most frequently employed therapeutic approach. The primary impact of this therapy is the palliation of symptoms such as atelectasis secondary to bronchial tumor obstruction, hemoptysis and pain caused by invasion of the ribs and brachial plexus. Only among patients with epidermoid carcinoma has radiotherapy been shown to increase survival, and this increase is in the range of only one

to two months (Roswitt et al., 1968). Radiotherapy combined with chemotherapy in the treatment of limited disease of specific histological types has been shown to be more efficacious than radiotherapy alone (Hansen, 1977). The patient with Stage B disease likely will not benefit from surgical exploration or resection (such as would be the case if erroneously labeled Stage A) and probably will not benefit from any adjuvant chemotherapy.

With regard to extensive disease (Stage C) more than 50 per cent of all lung cancer patients present with metastatic disease beyond the regional lymph nodes. Consequently surgery is inefficacious, and the main thrust in treatment has been the use, either singly or in combinations, of various chemotherapeutic compounds. As in the case with Stage A and Stage B patients, accurate delineation of the extent of the mass is the key to the therapeutic approach. Subjecting a Stage C patient to either surgery or radiotherapy is likely to contribute to pain, discomfort and risk of premature death while having no therapeutic value.

The effect of clinical staging and histological cell type on the 5 and 10 year survival rates are presented in Table 5.1 (Shields et al. 1975).

Table 5.1

Effect of Cell Type and Clinical Stage on Survival (%) in Bronchogenic Carcinoma

Stage	Cell Type					
	Squamous Cell Carcinoma		Adenocarcinoma		Others	
	5 years	10 years	5 years	10 years	5 years	10 years
Stage A	34.3	20.5	34.8	14.9	31.6	24.2
Stage B	17.5	12.1	12.3	4.6	13.3	5.7
Stage C	11.5	5.4	2.9	0.0	6.1	4.1

The staging decision is perhaps the most important aspect of clinical care that the lung cancer patient will receive. On the basis of staging, and other clinical prognostic factors, a therapeutic program tailored to the patient and his disease is planned and initiated. Because of the severity of this carcinoma and the ill effects and risks of morbidity and mortality associated with diagnostic and therapeutic manoeuvres, it is in the overall best interest of the patient that the staging reflect as accurately as possible the true extent of the disease. The patient with regional disease (Stage A) is best served by resection; if falsely staged as limited or extensive not only will his survival be adversely affected, but he will be subjected to unnecessary pain, embarrassment and

discomfort associated with radiotherapeutic and chemotherapeutic regimens. If the inoperable patient is falsely diagnosed as Stage A then he will likely not receive therapy and may be subjected to a risky surgical manoeuvre that will have no beneficial effect.

It is the depiction of the extent of cancer growth by a radiographic technique that is the subject of this proposed research.

5.2 Research Questions

There are two related research questions being asked in this study: first, how accurate is CT as compared to anterior-posterior tomography in the delineation of the site and extent of bronchogenic carcinoma? Second, does the addition of CT to the staging process result in any change in the therapeutic plan?

5.3 Review of Research

The principal question under investigation in this study is the comparison of the staging and therapeutic decisions based upon conventional radiographic tomography to the decision based upon computed tomography in patients with unstaged but histologically proven bronchogenic carcinoma. Short of surgical exploration, the best indication of the extent of neoplastic disease is realized by anterior-posterior tomography (APT) of the thorax. Recently however, CT has been utilized as a staging procedure, but because

no controlled series of patients has been properly studied by both techniques, the evidence reporting utility of CT must be considered essentially anecdotal and of little clinical value.

The literature on this subject suggests that CT may be a more beneficial staging tool than APT. The studies reviewed and the proposed research consider outcome as the clinical staging decision. Stanely et al. (1976) in an early report state that among 11 patients with various chest tumors a CT examination provided more diagnostic information on 4 patients (36 per cent) than was available through conventional chest radiography. Muhm et al. (1977) found CT more diagnostically useful than APT in 10 (34 per cent) of a series of 29 patients in terms of depicting pulmonary nodules. Kreel (1976) reports lymph node enlargement visualized in 8 (58 per cent) of 14 patients with lymphoma. Sternick et al. (1977), comparing therapeutic plans based on CT scanning to those based upon APT, report deviations of up to 10 per cent for tumor dose and 20 per cent for spinal cord dose. Schaner et al.,(1978) report that CT was superior to APT and lateral tomography in that, in addition to visualizing the lesion under scrutiny, CT documented accompanying pathology (percardial extension, sternal destruction) that was relevant to the staging process. They report further that CT was superior in mapping tumor margins for radiotherapy in 9 (100 per cent) of a series of cases. In a previously published study, Schaner et al., 1977) found CT of specific value in detecting additional

unilateral and bilateral nodules once a lesion had been identified, and in providing an accurate means of documenting small nodule growth on successive examination. Emami et al. (1978) report that compared to conventional chest films, CT depicted better the delineation of the tumor in 24 (75 per cent) of 32 patients, provided a more accurate assessment of the size of the tumor in 14 (43 per cent); more adequate coverage of the tumor extent by therapy portals in 9 (28 per cent), and alteration in irradiated volume of normal tissue in 13 (41 per cent) of 32 cases. Only 4 of their series had whole lung APT; in 1 of these CT provided data not found by APT, in another the APT film suggested involvement not visible on the CT scan. Emami et al. (1978) conclude that CT is responsible for the change in clinical staging in 13 (41 per cent) and the change in therapeutic regimen in 5 (16 per cent).

The studies cited indicate that CT has a potentially valuable role to play in the staging of patients with bronchogenic carcinoma. However, due to their inherent methodological deficits, no generalized statement of its utility can be drawn. As was the case with studies assessing the use of CT among jaundiced patients inadequate attention was paid to the methodological requirements for this type of patient series research. Consequently, we cannot presume that results are generalizable to all lung cancer patients. This is particularly problematic given the knowledge that histological typology has a profound effect on the natural history of this disease (Table 5.1). In addition, in each study reviewed there was either evidence of the bias of associating the test result

with the disease or inadequate discussion of the way these biases tend to invalidate studies of diagnostic efficacy (Ransohoff and Feinstein, 1978).

5.4 Research Strategy

Following the general approach adopted in Section 4.3, a strategy will be outlined which defines a homogenous patient population, a standard sequence of manoeuvres, and a plan for the interpretation of data and consequences for the patient.

5.4.1 Patient Population

The patients to be studied must have a histologically proven bronchogenic carcinoma classified according to the World Health Organization (WHO) system (Kreyberg, 1967). The WHO defines four types of carcinoma; epidermoid carcinoma (WHO I), small cell anaplastic carcinoma (WHO II), adenocarcinoma (WHO III) and large cell carcinoma (WHO IV). Secondly, these patients must not be currently under treatment for their disease; they must not have previously received a CT thoracic examination; they must neither be staged nor have a therapeutic plan. Thirdly, the patients must not have a co-morbid condition that would contraindicate evaluation by CT. Fourthly, the patients will be asked to voluntarily consent to undergo CT as an adjunct to their normal work-up.

5.4.2 The Protocol

The object of this study is to obtain a thoracic CT scan from patients prior to the conventional APT, to make a staging decision independently on the basis of each, then to review all data and formulate an ultimate staging decision and therapeutic plan. This design will yield three staging decisions and will provide evidence of the relative benefit with the use of CT.

The staging decisions will be made in accordance with the Tumor Node Metastasis (TNM) classification system (Denoix, 1946; Mountain et al., 1974). The purpose of this schema is to group patients with regard to the severity of disease and to serve as a standardized reporting system for staging decisions. The letter T represents the primary tumor and utilizes subscripts to describe its size. The letter N represents regional nodal involvement, and the subscrips describe the degree of such involvement. The letter M represents distant metastases and its subscripts the increasing degree of tumor dissemination.

The T factor ranges from T_0, designating no evidence of primary tumor, through T_x designating a tumor evidence by the presence of malignant cells but not visualized radiographically; T_1 designates a 3.0 cm. (or less) tumor growth without invasion of lobar branches; T_2 designates a tumor greater than 3.0 cm., but with no pleural effusion; T_3 represents a tumor of any size exhibiting extension into an adjacent structure or any tumor associated with atelectasis, obstructive pneumonitis of an entire lung or pleural effusion.

The N factor ranges from N_0 designating no metastasis to regional lymph nodes, through N_1 designating metastasis to the ipsihilar region, to N_2 designating metastasis to the nodes in the mediastinum.

The M factor ranges from M_0 designating no distant metastasis to M_1 designating any distant metastasis.

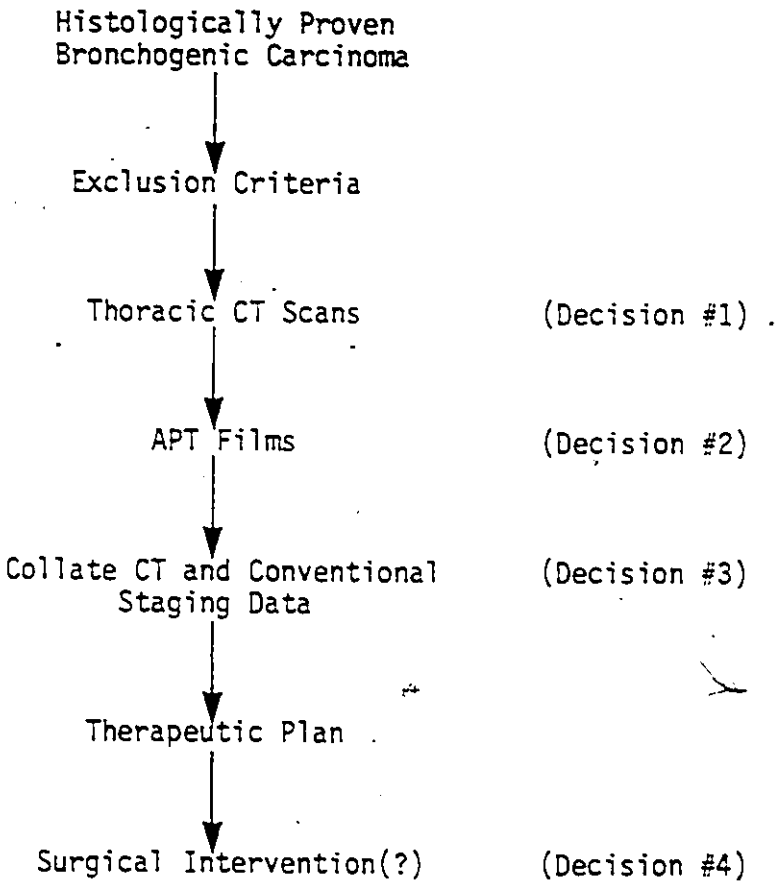
The CT scan will be performed early in the evaluation of the patient and the results will be recorded in terms of the TNM system. By performing the scan prior to the test to which it is to be compared the risk of introducing work-up bias is minimized (Ransohoff and Feinstein, 1978). The conventional staging procedures, including APT, will be interpreted without knowledge of the CT result and will be scored using the TNM classification system.

In this research the criterion staging will be APT or surgery when the latter is carried out. Because exploratory surgery is not to be routinely applied to discover the true stage of each patient the final therapeutic regimen will employ all clinical data, including the CT scan. Figure 5.1 illustrates the sequence of events.

Emami et al. (1978) reported that as a result of CT scanning, 13 of 14 patients' staging was changed to a more severe form of the disease and, therefore, did not undergo any surgical procedure. Even though their CT scans were not validated against a true measure based on surgery it is thought that the evidence is strong enough to support employing CT in the final therapeutic decision.

Figure 5.1

Sequence of Therapeutic Study Events



5.4.3 Sample Size

The assumptions behind this determination are the same as those outlined under 4.3.5. The level of significance was set at 0.05, and the probability of a type II at 0.20 for an anticipated benefit of 16 per cent with respect to changes in treatment policy after CT. Based on Emami's (1978) research, 63 percent of the patients were scheduled to undergo resection based upon conventional staging manoeuvres. In this instance:

$Z_\alpha = 1.96$

$Z_\beta = -0.84$

$\pi_d = 0.63$

$\pi_a = 0.73$

$$N = \left[\frac{Z_\alpha \sqrt{\pi_a(1-\pi_a)} - Z_\beta \sqrt{\pi_d(1-\pi_d)}}{\pi_a - \pi_d}\right]^2$$

$$= \left[\frac{1.96 \sqrt{(.63)(.37)} - (-.84) \sqrt{(.73)(.27)}}{(.63) - (.73)}\right]^2$$

= 174 patients

5.4.4 Analysis

A strategy to assess the agreement between the treatment decisions (dichotomized as either radical or palliative) and the staging decisions (employing the TNM schema) involves the analysis of crosstabulated ordinal data utilizing the Tau "b" or "c" statistic. Table 5.2 illustrates the display of data describing the nodal involvement with and without CT. A similar table will be constructed for the T factor and M factor.

Table 5.2

Nodal Involvement as Indicated by CT and APT

	APT			
CT	N_0	N_1	N_2	Total
N_0				
N_1				
N_2				
Total				

With regard to the therapeutic plan with and without the CT scans, Table 5.3 illustrates the crosstabulation format. The McNemar Chi-square statistic is applicable.

Table 5.3

Therapeutic Plan With CT and Without CT Data

	Plan Without CT		
Plan With CT	Palliative	Radical	Total
Palliative			
Radical			
Total			

Subgroups of special interest from the study are: those for whom a staging based on surgical exploration is available, and those in each of the WHO histological categories.

5.4.5 Impact

When completed, this research will indicate whether CT has provided more staging information compared to the conventional procedure. It will also indicate whether or not its addition to the therapy planning process makes any significant contribution.

The importance of determining the correct stage of bronchogenic carcinoma has been underscored by McNeil and Pauker (1979) and McNeil et al. (1978). They have determined that, when asked to choose between a surgical or radiotherapeutic approach to their operable lung cancer, patients will often give consideration to risk of morbidity, ill effects and convenience

as opposed to the conventional measure - the 5 year survival curve. It follows that if the patient is likely to prefer a situation where immediate risks to well being, such as those associated with thoracotomy, are minimized, then the need to provide the most valid staging information becomes paramount.

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