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Choice of treatment: Application of decision analysis

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Case Western Reserve University, 1994
CHOICE OF TREATMENT
-- APPLICATION OF DECISION ANALYSIS

by

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Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

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GRADUATE STUDIES

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CHOICE OF TREATMENT
-- APPLICATION OF DECISION ANALYSIS

Abstract

by

XI PENG YIN

Three studies that are related to the choice of treatment have been done.

In Chapter I, the treatment of hyperthyroidism has been analyzed. There are three different treatments for hyperthyroidism: medical, surgical, and radiation therapy. It is rather difficult to choose the best treatment for every given patient with the disease. Trade-offs among these various treatment modalities foster disagreement over the patient's indication for choice of one of the various therapeutic modalities over the others for treatment of hyperthyroidism. The three treatment strategies, their respective trade-offs and outcome preferences were modeled using SMLTREE, a microcomputer program for clinical decision analysis. The results of utility analysis show that radiation therapy is the preferable choice although the expected
value of the three therapies are quite close. The sensitivity analysis and cost-effectiveness analysis were also done.

Chapter II is a study of treatment for gallbladder cancer. The medical records of 121 patients with the diagnosis of gallbladder carcinoma during the years 1960 to 1989 were reviewed retrospectively. The survival rate for the five different operations were calculated using Kaplan-Meier survival analysis. Cox's survival analysis was also applied. There was no statistically significant increase in survival rate between cholecystectomy alone and cholecystectomy with hepatic wedge resection. Simple cholecystectomy with postoperative chemotherapy could be the best treatment choice for patients with Nevin Stage I, II, or III disease. Cholecystectomy with an accompanying bypass procedure will be the best choice for more extensive diseases.

In Chapter III, a comparison of outcome and cost for open cholecystectomy and laparoscopic cholecystectomy was done. One hundred patients with laparoscopic cholecystectomy and one hundred patients with open cholecystectomy as control group were studied. Both groups were comparable with regard to
height, weight, and severity of the disease. Statistical analysis has been performed using t-test, analysis of covariance, and logistic regression. The results of this study support that laparoscopic cholecystectomy is a safe and effective alternative to open cholecystectomy and results in significantly shorter hospital stay with considerable cost savings.
To

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INTRODUCTION

Given a patient with several complaints and symptoms, a physician must often decide which diagnostic procedures should be performed to reach a correct diagnosis. For example, should a special blood test be ordered for a patient with acute abdominal pain? Should an X-ray film be taken for a patient with possible bone fractures from a car accident? Should CT scans be taken on a patient after suffering one month of severe headache? Before ordering a biochemical test or other diagnostic examination procedures, a physician considers the severity of the symptoms and the likelihood of the diagnosis. A physician should also be concerned about the sensitivity and specificity of the diagnostic procedure, the risk of the procedure, and the cost of the procedure.

Once a diagnosis is made, a physician must make another more important decision -- choosing an effective method of treatment. For some diseases, the choice of treatment is relatively easy. In the case of pneumonia, for example, choosing treatment is relatively easy. Antibacterial, supportive, and anti-
Symptomatic therapies are very effective and suitable for most of the cases. Even in surgical practice, some clinical decisions are straightforward and require little analysis. For example, given a patient with probable acute appendicitis, a physician usually can select laparotomy with impunity because the risk is low and the potential benefits are high.

Unfortunately, all clinical decisions are not easy to make. For instance, given a patient with coronary artery disease, a physician must decide between coronary by-pass surgery and conservative medical therapy. This complex decision involves balancing the risk of operative complications against the potential long-term benefit of decreasing disability and increasing life expectancy. Thus, the selection of optimal therapy for an individual patient is not straightforward. Consequently, both the skill of the prospective surgeon and the preferences of the individual patient may strongly influence the choice of the therapy.

Traditionally, clinical decision making is a global subjective judgment based on experiences. A physician accumulates experience during and following medical school. Students in medical school study text
books which is the crystallization of their mentors' experiences.

Most people believe that the more experienced physician is the better physician. Nevertheless, with the rapid development of science, new knowledge rapidly replaces old knowledge for describing and understanding disease. New procedures for diagnosis and methods for treatment are developed and being developed continuously. These voluminous and rapid changes make decision making difficult, even for the very experienced physician.

Decision analysis is a method that can help the physician to optimize selection for the diagnosis and treatment of complicated clinical problems like coronary artery disease. Briefly, decision analysis includes consideration of all possible outcomes of therapy, both the probability of each outcome and the utility or the relative worth of each outcome. These probabilities and utilities are then combined to determine which therapeutic option can be expected to be of greater value to the patient.

In this project, treatments of some medical or surgical diseases will be evaluated. In study I, utility analysis, sensitivity analysis and cost-
effectiveness analysis will be applied to assess the choice of the treatments of hyperthyroidism. In study II, five different surgical procedures for gallbladder cancer are studied. The outcomes of these surgical procedures will be compared using survival analysis. In study III, the efficacy of a new procedure for removing gallbladder -- laparoscopic cholecystectomy surgical procedure will be compared with the classical open cholecystectomy in terms of operating time, complications, and length of hospital stay. Cost-effectiveness analysis will also be done for these two operations.
Chapter I.

Treatment of Hyperthyroidism

-- The Use of Decision Analysis

Hyperthyroidism -- Review of Literature

General Description of the Disease

Hyperthyroidism (also called thyrotoxicosis) is a thyroid-related disturbance in which there is an increased total daily output of thyroid hormones and a sustained rise in the plasma level. Hyperthyroidism is not in itself a disease, but a syndrome of complex findings that result when the peripheral tissues are presented with and respond to an excess of thyroid hormone. From a functional view, hyperthyroidism is the final common pathway through which various abnormal states that lead to hormone excess express themselves. Hence, the manner in which hyperthyroidism is manifested is indeterminant, although it may be modified somewhat by that cause as well as by factors intrinsic to the patient, such as age, gender, or
the presence of underlying disease in some other organ system.

The Epidemiology of Hyperthyroidism

Hyperthyroidism is a common disease. A United Kingdom Survey covering 106 general practices suggested a prevalence of hyperthyroidism of 25 to 30 cases per 10,000 females and a hospital inpatient inquiry calculated 3 cases per 10,000 hospital discharges (Hoffenberg, 1974). In the United States, an annual incidence of 3 cases per 10,000 females was suggested (Furszyfer, 1970). More recently, a cross-sectional study of the community of Whickham found a prevalence of hitherto undiagnosed hyperthyroidism of 4.7 per 1,000 females and prevalence of previously diagnosed and treated hyperthyroidism of 20 per 1,000 females (Werner, 1978). The prevalence of established hyperthyroidism was 10 times more common in women than in men and the mean age at diagnosis was 48 years (ranged from 25 to 70).
Treatment of Hyperthyroidism by Medicine

1. Antithyroid Drugs

The observation about 40 years ago, that compounds related to thiourea caused goiter in experimental animals led to the development of present-day antithyroid drugs. The response of the patient with hyperthyroidism to thionamide drug therapy is exactly what might be anticipated, in view of the fact that these agents inhibit thyroid hormone synthesis but not thyroid hormone release. A single dose of drug is not followed by immediate reduction in metabolic rate because residual colloid stores within the gland continue to be drawn upon for secretory purposes. With prolonged therapy, however, the colloid supply which is already low becomes exhausted. Within a few days, as a rule, the excessive secretion of thyroid hormone then begins to diminish.

Several factors affect the duration of the interval to the first clinically evident improvement and the rate of improvement. These factors include: 1) the quantity of hormone stored in the gland; 2) the gland's secretory rate; 3) the initial degree of hyperthyroidism; 4) the
extent to which hormone synthesis is inhibited which is, in turn, a function of the amount and timing of doses of the drug. If large stores of hormone are present in multinodular goiters, or have been induced by prior treatment with stable iodine, response to antithyroid therapy may be delayed for several weeks or months. Conversely, in Graves' disease without considerable thyroid enlargement, the rapid rate of secretion may exhaust the small supplies of hormone so quickly that distinct improvement may be noted within 3 or 4 days.

Propylthiouracil (PTU) decreases peripheral effectiveness of thyroxine (T₄) in the rat and there is some evidence that it does so in hyperthyroid humans (Furth et al, 1966). This effect can almost certainly be attributed to significant inhibition in the rate of conversion of T₄ to triiodothyronine (T₃) (Saberi et al, 1975). However, carbimazole and methimazole do not share this property, and yet these agents seem to improve symptoms as rapidly as PTU. Therefore, the role of extrathyroidal actions of PTU in the therapeutic response is not clear. In any case, with commonly used doses of several thionamide drugs,
the average time to the first definite improvement is 8 days, and the basal metabolic rate (BMR) falls as an exponential function of time, decline each day by 3% of the previous day's BMR. The average time to reach an euthyroid state is 6.5 weeks, but this is quite variable, depending particularly on the height of the BMR initially.

Many physicians employ antithyroid drugs without other treatment for some or most patients with hyperthyroidism. In this form of treatment, the initial dose is continued until the patient is euthyroid or actually beginning to be hypothyroid. The plan should be continuous treatment for a year or more. If symptoms or signs of hyperthyroidism reappear during the course of therapy, a larger dose may be given for a few months before reduction in dose is attempted. The aim throughout the maintenance period is to keep the patient euthyroid. The patient should be examined biweekly for the first 6 weeks, monthly for the next 3 months and less often thereafter.

Occasionally, β-adrenergic blockade such as propranolol is used for the treatment of hyperthyroidism (Geffner & Hershman, 1992). β-
blockers do not alter thyroid gland secretion. The principle mechanism of action of β-blockers in hyperthyroidism is to antagonize β-receptor-mediated effects of catecholamines. Therefore, β-blockers are effective only in treating hypermetabolic symptoms. They are often used as adjuvant therapy to antithyroid medication, surgery or radioactive iodine treatment. In addition, bile acid sequestrants have been reported as useful for rapidly correcting hyperthyroidism. It has not been considered routinely as a drug for hyperthyroidism treatment (Shakir et al., 1993).

2. Permanent Remission After Medication

The aim of treatment is to achieve permanent remission of hyperthyroidism after treatment is discontinued. With a regular course of treatment, approximately one-half of unselected patients remain well indefinitely, according to a large number of studies published in the 1950s and 1960s (Hershmman et al, 1966). However, the remission rate in the United States declined significantly in the late 1960s and in the 1970s (Wartofsky, 1973), although it remained constant in Scotland.
(Alexander et al, 1970). It has been postulated that this difference is due to an adverse effect of high dietary iodine intake in the United States (Wartofsky, 1973).

Some authors have investigated characteristics related to permanent remission. Some evidence suggests that the prognosis for ultimate remission is better if it is the patient's first episode of hyperthyroidism and if symptoms are less than 1 year's duration (Werner, 1978). Neither age, sex, severity of disease, nor presence of complications makes any significant difference in the outlook for permanent remission (Werner, 1978). Whereas the initial characteristics of the illness afford little useful prognostic information, predictability improves during the course of treatment. If the thyroid decreases in size during treatment, then the probability of subsequent permanent remission increases (Solomon et al, 1953). Similarly, if one finds that the thyroidal uptake of $^{131}$I can be suppressed by the concurrent administration of thyroid hormone and antithyroid drug, this is an excellent prognostic sign (Alexander, 1970).
3. Treatment Plan

Although, there have been many suggested modifications of the basic plan of antithyroid drug treatment, none has appeared to alter the incidence of permanent remission. For example, if thyroid hormone is administered alone with a thionamide drug, it should be introduced only after the patient has become euthyroid. This modification affords only the advantage of preventing hypothyroidism.

Treatment is usually commenced with methimazole or carbimazole in a divided dose of 20 - 40 mg a day or propylthiouracil at 300 - 600 mg a day. The dosage is generally reduced by at least half when a clinical and biochemical response occurs after two to six weeks. Apart from their effect to inhibit thyroid hormone synthesis, an immunosuppressive effect has also been shown, suggesting that the use of these agents may favor a remission of immunoglobulin-mediated hyperthyroidism (Burman and Bake, 1985). It is customary to divide the daily dose of antithyroid drug into three or four doses, but once-a-day dosage is also recommended. Once a response to
antithyroid drugs has been obtained, the drug treatment should continue for six months to two years, followed by observation to see if the remission is sustained.

4. Toxic Reaction of Antithyroid Drugs

Important side effects of antithyroid drugs include gastrointestinal intolerance, fever, rash, urticaria, arthralgia, toxic hepatitis and vasculitis with a lupus-like syndrome (Cooper, 1984), effects that usually abate when the drug is stopped. Fetal aplasia cutis has been reported with methimazole during pregnancy, but not with propylthiouracil. The most important side effect of these drugs is agranulocytosis, a granulocyte count is usually below 400/\text{mm}^3 (normal /\text{mm}^3) and in fact may be near zero (Cooper et al, 1983). Agranulocytosis often presents as acute malaise, fever and sore throat, usually after 2 to 4 weeks of therapy, and more commonly in older patients. It is crucial that all patients given antithyroid drugs be warned of this side effect. If this complication is recognized promptly and the drug stopped, there is usually improvement in the leukocyte count after several days. Whether
agranulocytosis is a dose-dependent side effect is uncertain. One study has suggested a dose-dependent effect with methimazole, but not with propylthiouracil (Cooper et al., 1983). Toxic reactions to antithyroid drugs may be classified as sensitivity reactions of serum sickness and agranulocytosis. The antithyroid agents have the potential of inducing hypothyroidism if given in excessive quantities over prolonged periods. These results can be reversed either by reducing the dosage of the antithyroid drug or by administering supplemental thyroid hormone.

Treatment of Hyperthyroidism by Surgery

1. Subtotal Thyroidectomy

Prior to the advent of radioactive iodine, subtotal thyroidectomy was accepted as the treatment of choice for thyrotoxicosis. The operative procedure is almost always performed under endotracheal anesthesia and generally planned to remove most of the gland tissue and leave a remnant of 3 to 6 gm of the gland (Schwartz et al., 1982). By this procedure, both the hyperthyroidism and the goiter are eliminated.
Precise knowledge of the surgical anatomy of the thyroid is crucial to the surgeon performing thyroid surgery. The recurrent laryngeal nerve, the external motor branch of the superior laryngeal nerve and the parathyroid glands exist in such intimate proximity to the usual thyroidectomy dissection. Advantages of surgery include: 1). Cure of hyperthyroidism is rapid, subtotal thyroidectomy provides rapid correction of the thyrotoxicotic state in about 95% of patients. 2). Patient compliance is required for a shorter period of time than it is in prolonged antithyroid drug treatment. Disadvantages of surgery include: 1). The patient must be hospitalized. The patient's usual stay in the hospital is 4 to 5 days. Full recovery and resumption of work follows 6 weeks after the operation. 2). Surgical and anesthetic risks are incurred. The mortality rate of the operation was reported as 0.15%. 3). Surgical complications may occur, some of these are permanent and severe (Werner, 1978).
2. Mortality and Complications of Surgical Treatment

a. Mortality rate of the operation

In large clinics throughout the world, mortality for thyroid surgery generally has ranged between 1:100 and 1:500 patient (Beahrs and Sakulsky, 1968). Mortality tends to be much lower in highly experienced hospitals. Mortality has been decreased under subtotal thyroidectomy (Sawyers et al., 1972). This applies to both toxic diffuse and nodular goiters. In the surgical experience at the Columbia Presbyterian Medical Center, there were no deaths in 3776 patients with hyperthyroidism operated upon between 1931 and 1975.

b. Postoperative hypothyroidism

Hypothyroidism is the most common long-term complication following surgery. Subtotal thyroidectomy removes most of the thyroid gland. If the remainder of the gland fails to maintain an adequate plasma level of hormone, hypothyroidism will occur. The early incidence of postoperative hypothyroidism in adults is under 15 percent, it may rise slightly with time to about 20 percent
(Ingbar and Woeber, 1974; Toft et al., 1978). If hypothyroidism becomes permanent, supplementary thyroid should be given in low dosage to maintain normal function.

c. Thyroid storm

Thyroid storm occurs in patients with preexisting thyrotoxicosis who either have not been treated at all or have been treated incompletely. It usually occurs in patients with Graves' disease but may be related to toxic multinodular goiter. In the past, before adequate preparation with antithyroid drugs, surgical treatment was the most common precipitating factor. Presently thyrotoxic crisis is a rare complication of surgical treatment.

When thyroid storm is related to surgical treatment, the manifestation may develop during the operative procedure or in the recovery room. The patient becomes markedly hyperthermic with profuse sweating and tachycardia. Nausea, vomiting, and abdominal pain are common. Initial tremor and restlessness may progress to delirium with eventual coma.

The mortality rate for this complication is
approximately 10 percent. Treatment is directed at inhibiting the production of thyroid hormone and antagonizing effects of hormone.

d. Wound hemorrhage

The commonest complication of thyroid surgery is bleeding. This is a problem of the early postoperative period, i.e., within the first few hours. It has been reported in 0.3 to 1 percent of consecutive thyroidectomies. Hemorrhage in the neck is a significant problem, since small amounts of blood may obstruct the airway and result in respiratory death. The complication is usually caused by bleeding from branches of the inferior thyroid or superior thyroid artery.

The patients are rarely in shock. The initial manifestation is swelling of the neck and bulging of the wound, which demands immediate attention. If untreated, respiratory obstruction due to compression eventually ensues. Treatment consists of opening the incision, evacuating the clot, and securing the bleeding vessel. This constitutes an emergency procedure and frequently should be performed at the patient's bedside. Sometimes, temporary tracheotomy must be performed.
e. Recurrent laryngeal nerve injury

The recurrent laryngeal nerve lies adjacent to the posteromedial aspect of the thyroid near the small groove between the lateral aspects of the trachea and esophagus. This nerve contains the motor fibers innervating the abductor muscles of the true vocal cords. If conduction through the nerve is blocked by operative division or trauma, immediate hoarseness is apparent.

Damage to the recurrent laryngeal nerve may be unilateral or bilateral and may be temporary or permanent. In a series of 1,011 thyroidectomies there were 28 examples of vocal cord paralysis, three of which proved to be permanent (Toft et al., 1978). The incidence of recurrent nerve injury in another series of 1,000 patients was 0.2 percent (Gould et al., 1965). Colcock and King (1962) evaluating 1,246 thyroid operations, noted one bilateral recurrent laryngeal nerve paralysis. Some authors reported (Heimann and Martinson, 1975) 0.4 percent for permanent vocal cord paralysis.

Loss of function of the recurrent laryngeal nerve may result from excessive trauma to the
nerve during exposure, inclusion of the nerve in a ligature, or an inadvertent sectioning of the nerve. If the injury is related to dissection and the nerve is intact, function should return usually within 3 months, and invariably within 9 months.

The incidence of this complication can be markedly reduced by identifying the nerve or nerves routinely during thyroidectomy.

f. Postthyroidectomy hypoparathyroidism

Parathyroid glands are 3-6 in number, and located on the posterior portion of the thyroid. Parathyroid secrets hormone that regulates calcium and phosphorus metabolism. Parathyroid hormone helps to maintain plasma calcium level by increasing intestine absorption of calcium and decreasing the excretion of the calcium in the urine.

Overt manifestations of hypoparathyroidism following thyroidectomy is usually a temporary syndrome related to dissection in the region of the parathyroid glands. It is necessary to leave only one gland in situ with an adequate blood supply to avoid the complication. Postoperative
permanent hypoparathyroidism occurred in 0.6 percent of the 1,000 thyroidectomies reviewed by Gould et al. (1965). Other authors report a 0.3 percent to 0.8 percent incidence for permanent hypoparathyroidism (Perzik, 1976).

Postthyroidectomy hypoparathyroidism may be due to the inadvertent removal of the parathyroid glands but more frequently is caused by damage to the blood supply. Damage of the parathyroid end arteries can causes infarction of the gland. The anastomotic arterial network is so extensive that if proximal arteries are injured, there is sufficient collateralization.

The clinical manifestations usually occur within the second 24 hours after the operation and almost invariably within the first week. The initial symptoms are circumoral numbness, tingling, and intense anxiety. As the disease progresses, muscle cramps and frank tetany develop. Prolonged hypoparathyroidism may cause cataracts, convulsive episodes, and psychoses. Serum calcium is reduced and serum phosphorus is increased. The treatment of hypoparathyroidism should be initiated promptly. Replacement of
calcium and vitamin D is the most effective treatment. Parathyroid hormone and dihydrotachysteriol should be reserved for the exceptional case when usual measures fail. Parathyroid transplantation have been used by some authors. Clinical improvement was noted despite histologic evidence of graft rejection (Watkins et al., 1962).

Radiation Therapy

1. Method of Treatment

The introduction of radioactive iodine for the treatment of hyperthyroidism was a historic event in medicine (Hamilton and Lawrence, 1942; Hertz and Robert, 1942; Hertz and Robert, 1946).

The aim of $^{131}$I administration is the production of radiation thyroiditis. In the optimal case, there is just enough damage to the gland to reduce thyroid function to normal without causing hypothyroidism. Radioiodine produces damage by two mechanisms, acute radiation thyroiditis and chronic gradual thyroid atrophy. The eventual result of radiation to the thyroid is progressive atrophy associated with an
obliterative endoarteritis and interstitial fibrosis that occurs over a period of years. These changes are similar to those in any irradiated tissue. In thyroid glands, examined after radioactive iodine administration, there is marked irregularity in nuclear size and shape, suggesting genetic damage despite continued survival of cells. There is also a variable degree of lymphocytic infiltration. These factors are considered to be responsible for the progressive loss of thyroid function seen in patients after $^{131}$I treatment and are also considered to account for the rising incidence of hypothyroidism with time.

A single dose of iodine 131 ($^{131}$I) causes a decrease in function and size of the thyroid gland over a period of 6 to 12 weeks. About 75 percent of patients with Graves' disease are made euthyroid by a single dose; those who are still thyrotoxic after 12 weeks are given a second dose. Additional doses can be given if needed. Eventually, almost all patients are cured in this way.
2. Complications of Radiation Treatment

a. Hypothyroidism after radioactive treatment

Hypothyroidism is the chief complication of radioiodine therapy. Reported incidence within one year after treatment varies between 7 and 22 percent, averaging about 10 percent. In one series this complication was induced with as little as 2690 rad and a dose of $^{131}\text{I}$ as low as 2 mCi. Subsequent onset of hypothyroidism has been reported at a rate of 2 to 4 percent a year, totaling with early incidence 15 to 70 percent of patients (Werner, 1978). In this same experience, patients treated for toxic recurrent goiter or given multiple doses of $^{131}\text{I}$ developed the highest incidence.

The clinical picture of induced hypothyroidism may be somewhat atypical. The suggestion has been made that these patients continue to secrete $\text{T}_3$ but not $\text{T}_4$. This may create a pseudohypothyroidism according to the low thyroxine concentration in serum.

The problem of mechanisms responsible for late onset of hypothyroidism has been discussed. The probable explanation is that the thyroid cell
nucleus is sterilized by the radiation dose with subsequent loss of the cell's ability to mitose.

b. Exacerbation of hyperthyroidism

A transient outpouring of thyroid hormones may follow $^{131}$I therapy (Riggs, 1948). The increase usually occurs within the initial 2 weeks after administration and lasts a similar length of time. As a rule there is no clinical exacerbation of the hyperthyroidism, but severe and even lethal responses have occurred (Lamberg, 1959). One such fatality has been described in the literature following a 5 mCi dose of $^{131}$I (Nelson et al., 1952) and another, also following a 5 mCi dose has been reported to the author. In both instances symptoms began several days after ingesting of the isotope and progressed to thyroid storm. Death ensued early in the second week of the reaction.

Apart from storm-like reaction, increased severity of hyperthyroidism may precipitate cardiac arrhythmia or induce heart failure in the patient with borderline compensation; or preexisting heart failure may become exaggerated.

This complication can be prevented by pretreatment with thionamides.
c. Radiation thyroiditis

The acute inflammatory reaction known as radiation thyroiditis may produce, in rare instances, severe pain, swelling, erythema, and fever. This condition generally lasts only a few days and can be treated with anti-inflammatory agents.

d. Hypoparathyroidism

This rare complication has been reported after $^{131}$I therapy from small as well as large dosage (Eipe et al, 1968; Fulop, 1971; Orme McI'E and Conally, 1971). It is of interest that low-dose external radiation in youth may have induced adenoma formation by the parathyroid gland.

e. Acute leukemia

The Thyrotoxicosis Follow-up Project of Radiation Health Section of the National Institutes of Health has summarized the experience of the United States in the treatment of hyperthyroidism with $^{131}$I and the resulting incidence of leukemia (Saenger et al., 1968), but there was no definite evidence of an increased incidence being observed.

The later survey included 119,000 patient-
years following $^{131}$I therapy. Acute leukemia developed in eight patients per 100,000 patient-years, which, with three instances of chronic leukemia, made an adjusted total incidence of 13/100,000 years, allowing for years of follow-up. This is approximately half again the expected incidence of 8.5/100,000 patient-years. However, approximately the same incidence were observed in the surgical patients followed for a total of 114,000 patient-years. Thus there appears to be a predisposition to leukemia on the part of hyperthyroid patients to explain the finding, but no increased prevalence due to radiation effect.

f. Thyroid cancer

No increased prevalence of thyroid cancer has been observed in data from the large series of patients of the Thyrotoxicosis Follow-up Project who had been given $^{131}$I therapeutically (Dobyns et al., 1974). Indeed some authors believed that there probably is a lower number of cancers than expected from spontaneous incidence. This appears to be due to the same sterilization of thyroid cell nuclei that has followed radiation exposure in excess of 1600 rad (Maxon, 1976).
g. Genetic risk

The average dose of radiation to the ovary during treatment of hyperthyroidism with radioactive iodine has been estimated to be roughly equivalent to the dose received during a barium enema, and therefore, to be an acceptable risk to woman in the reproductive age. Some studies have shown that much larger doses of gonadal irradiation do not cause infertility or an increased incidence of congenital anomalies in first-generation offspring, but it is too early to exclude the possibility of more subtle genetic damage that might become manifest only in the second or subsequent generations. Therefore radioactive iodine as treatment of hyperthyroidism in children and women of reproductive age is still avoided (Bech et al., 1979; Beierwaltes, 1978; Halnan, 1983).

Purposes of the Study

All three current treatments for hyperthyroidism are remarkably effective. However, it is often difficult for patients with the disease and their physicians to choose among
these treatment options (Franklyn, 1992; Landenson, 1991). Although in general, most American practitioners favor radio-iodine for most of their patients because of the ability to deliver effective single-shot therapy, some practitioners do like to offer a trial of antithyroid drugs. Hypothyroidism requiring lifelong hormonal replacement therapy develops in the majority of patients with surgery or radioactive iodine. Antithyroid drug treatment is occasionally complicated by troublesome hypersensitivity reactions and, very rarely, by the life-threatening side effects of agranulocytosis and hepatitis. Thyroid surgery is an effective management but occasionally complicated by injury to adjacent structures in the neck. However, even in the recent year, the number of surgeries has declined dramatically, some surgeons still believe that surgical treatment is the first choice for hyperthyroidism caused by Grave disease (Falk, 1990).

It is difficult for patients with hyperthyroidism and their physicians to choose among the treatments, not only because of the
differences in efficacy, but also because of concern about the demonstrated and conceivable side effects associated with each type of therapy.

The three treatment strategies, their respective trade-offs, and outcome preferences were modeled using SMLTREE, a microcomputer program for clinical decision analysis.
Decision Analysis
for Treatment of hyperthyroidism

Method

In this study three treatment strategies for hyperthyroidism are compared: 1) medication, 2) surgery, and 3) radiation (see Figure 1). The potential treatment outcomes and the utilities of each strategy are compared quantitatively using decision analysis. The strategy with the highest expected value is the preferred treatment.

![Decision Tree](image)

Figure 1. Decision tree for treatment of hyperthyroidism. Diamond-shaped nodes at the far right represent the subtrees for each respective treatment detailed in Figures 2, 3, and 4.
1. Medication

The subtree for initial treatment of hyperthyroidism by drug treatment is shown in Figure 2. Toxic reaction to medication is the primary complication. Complications are divided into three categories: major, minor, and none. Major toxicity is mainly agranulocytosis. Minor toxicity is mainly skin reaction (Werner, 1978). Patients who tolerate morbidity associated with minor toxicity and those without side-effects (i.e., no toxicity) may have their hyperthyroidism either respond (i.e., cure) or not respond (i.e., no cure) to medication.

Patients not cured by an initial period of medication would ordinarily choose to either continue medication, or opt for surgery or radiation. To make the utility assessment more accurate and the comparison of the three treatments more clear, in this study, the decision tree is terminated after the first period of medication treatment.
Figure 2. Subtree $\mathcal{M}$: medication for hyperthyroidism.

2. Surgical treatment

The subtree for surgical treatment of hyperthyroidism is shown in Figure 3. Surgery subjects the patient to a chance of operative death. If the patient survives, surgery may (i.e., cure) or may not (i.e., no cure) be successful in
treat hyperthyroidism. Surgery may also entail additional complications. Surgery may or may not result in vocal cord paralysis, hypothyroidism, or hypoparathyroidism. This study considers only long-term disabilities and ignores short-term complications such as wound bleeding or thyroid storm. All complications will be treated as independent events in the analysis.

Figures 3 and 4 are the subtree of surgical treatment. An assumption of independent events of the complications is made.
Figure 3. Subtree for surgical treatment. Diamond-shaped node Comp represents the subtree at the bottom of the figure. A represents subtree for complication.
Figure 4. Subtree of Surgical Treatment
3. Radiation treatment

Almost all patients will be cured after three or less doses of $^{131}$I radiation treatment. For this analysis, the baseline cure rate of radiation ($^{131}$I) treatment is 100% (Werner, 1978). The subtree for radiation treatment of hyperthyroidism is shown in Figure 5. Although radiation treatment assures cure of hyperthyroidism, the treatment may result in some complications. In the present study, hypothyroidism and progression of ophthalmopathy are considered. Short-term exacerbation of hyperthyroid hormones and radiation thyroiditis may follow $^{131}$I therapy (Riggs, 1948). Acute leukemia and thyroid cancer have been reported following $^{131}$I treatment, these conditions are not complications of radiation therapy but manifestation of preexisting disease.
Figure 5. Subtree radiation ($^{131}$I) treatment for hyperthyroidism.

**Probabilities of The Events**

1. Probability of events: medical treatment

   The aim of treatment by antithyroid drug is to achieve permanent remission of hyperthyroidism after treatment is discontinued. According to a large number of studies published, approximately one-half of the unselected patients remained well indefinitely (Werner, 1978). The rate of toxicity
of antithyroid drug is slightly different with the dosage and type of drug chosen. The baseline probabilities used in the present analysis are shown in Table I.

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major toxicity</td>
<td>0.003</td>
</tr>
<tr>
<td>Die</td>
<td>0.001</td>
</tr>
<tr>
<td>Survive</td>
<td>0.999</td>
</tr>
<tr>
<td>Minor toxicity</td>
<td>0.040</td>
</tr>
<tr>
<td>No cure</td>
<td>0.450</td>
</tr>
<tr>
<td>Cure</td>
<td>0.550</td>
</tr>
<tr>
<td>No Toxicity</td>
<td>0.957</td>
</tr>
<tr>
<td>No cure</td>
<td>0.550</td>
</tr>
<tr>
<td>Cure</td>
<td>0.450</td>
</tr>
</tbody>
</table>


2. Probability of events: surgical treatment

The advantage of surgery is its rapid cure of hyperthyroidism. The disadvantages include hospitalization, risk associated with anesthesia, and surgical complications (Table II). The mortality rate of surgery is about 0.15% (Ingbar, 1987). The only recent study to follow patients
for a long duration (i.e., 30 years of follow-up) was one by Sugrue et al (1983). The probabilities reported by Sugrue were chosen as baseline values for the present analysis. Table II shows the probabilities of the events following surgical treatment.

3. Probability of events: radiation treatment

A single dose of $^{131}$I can cause a decrease in function and size of the thyroid gland. About 75% of the patients suffering Graves' disease are made euthyroid by a single dose, and those who are still thyrotoxic after 12 weeks are given a second dose. Eventually, almost all patients are cured. However, hypothyroidism occurs in about 47% of the patients and about 2% of patients have progression of ophthalmopathy (Table III).
Table II. The Probabilities for the Events Resulting from Surgical Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical mortality</td>
<td>0.0015*</td>
</tr>
<tr>
<td>No cure (hyperthyroidism relapse)</td>
<td>0.158*</td>
</tr>
<tr>
<td>Cure</td>
<td>0.842</td>
</tr>
</tbody>
</table>

**Complications**

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocal cord paralysis</td>
<td>0.033</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.208</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>0.030</td>
</tr>
</tbody>
</table>

*Werne Ingber et al., 1978.*
**Sugrue et al., 1983.*

Note: The study by Sugrue et al. (1983) is the only study of surgery outcomes to follow patients over a long duration (30 years).

Table III. The Probabilities for the Events Resulting from 131I Treatment*

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>0.47</td>
</tr>
<tr>
<td>Progression of ophthalmopathy</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Werner, 1987; Wilson & Foster, 1992.*
Utility Values for the Outcomes of Treatments

From the decision tree we can see that there are totally 27 outcomes following treatments for hyperthyroidism. To perform utility analysis, we need utility values for the corresponding outcomes. This brings us to a central question: whose preferences ought to be the basis for clinical decisions? In other words, who is the appropriate judge of utilities? It would seem desirable for physicians to assess the probabilities of events and for patients to assess their own utilities, because it is the patient who is facing the gambles on life and health. Boyd et al. recently (1990) examined the sources of variations in the utilities assigned to health states, and emphasized the importance of patient utilities in clinical decision making and the need to gain greater understanding of the factors that influence the utilities assigned by patient to health states. However, there are some disadvantages in the use of patient assessment of utilities. The utility values given by patients may be influenced by patient's education and cultural background. More importantly, the same
patient with the same disease but in a different stage of the disease may assign a different utility value for the same outcome. On the other hand, utility values assigned by physicians are more stable and consistent.

In this study, physician assessment of utility value was applied. Two surgeons and an internist who are proficient in treating hyperthyroidism were involved in the assessment of the utility values. Direct scaling methods to determine the utilities was used. This method is easy to understand, and easy to use. First, assign value 1.00 to "cure without complications and value 0.00 to "death of the patient" (no matter what kinds of treatments, these two outcomes' values are fixed). All other outcomes are given utilities between 0 to 1. Tables IV to VI show the utility values of outcomes assigned by the three physicians.
Table IV. Utility Values of the Outcomes for Medication

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Utility value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure without complication</td>
<td>1.00</td>
</tr>
<tr>
<td>Cure with minor toxicity of drug</td>
<td>1.00</td>
</tr>
<tr>
<td>No cure and no toxicity of drug</td>
<td>0.80</td>
</tr>
<tr>
<td>No cure and minor toxicity of drug</td>
<td>0.80</td>
</tr>
<tr>
<td>Major toxicity and alive</td>
<td>0.70</td>
</tr>
<tr>
<td>Die from major toxicity of the drug</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table V. Utility Values of the Outcomes for Radiation Treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Utility value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure without complications</td>
<td>1.00</td>
</tr>
<tr>
<td>Cure and progression of ophthalmopathy after $^{131}$I treatment</td>
<td>0.80</td>
</tr>
<tr>
<td>Cure and hypothyroidism after $^{131}$I treatment</td>
<td>0.80</td>
</tr>
<tr>
<td>Cure and hypothyroidism and progression of ophthalmophathy after $^{131}$I treatment</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Table VI. Utility Values of the Outcomes for Surgical Treatment

<table>
<thead>
<tr>
<th>No Cure</th>
<th>Vocal Cord Paralysis</th>
<th>Outcomes</th>
<th>Hypoparathyroidism</th>
<th>Hypoparathyroidism</th>
<th>Utility Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0.30</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>0.35</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>0.40</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.45</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0.55</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>0.60</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.65</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0.55</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>0.60</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>0.65</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0.70</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>0.75</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>0.80</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Die 0.00

+: Present, -: Absent
Results

Expected Values of the Treatments

The technique of folding back is used to evaluate the expected utility of each treatment for hyperthyroidism. The technique involves summation and multiplication of terminal node utilities and path probabilities to obtain a quantitative value for each strategy. The strategy with the maximum value is considered the favored treatment.

Table VII represents the expected values of the three different treatments. As we have already discussed before, expected value is the weighted average of the possible values.

Table VII. Expected Values of the Treatments

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Expected Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>0.87106</td>
</tr>
<tr>
<td>Medication</td>
<td>0.88943</td>
</tr>
<tr>
<td>I-131</td>
<td>0.90560</td>
</tr>
</tbody>
</table>
Table VII shows that the highest expected value is that of $^{131}$I treatment, the second is that of antithyroid drug, and the third is that of surgical treatment. According to the decision analysis role, the higher the expected value, the more preferable the treatment. Based on the above expected value, the most preferable therapy for hyperthyroidism is $^{131}$I.

**Sensitivity Analysis and Threshold Analysis**

Sensitivity analysis provides the most important results of the analysis. Sensitivity analysis allows us to perform successive evaluations of any variable in the decision tree, to determine the effect of varying parameters. A successive series of sensitivity analyses are performed to assess the affect of variation in the value of the probabilities and utilities changes. A threshold analysis is conducted to determine the exact value of the parameter where the decision changes from one treatment to an alternative treatment.

The results of the sensitivity analysis in this study show that change of the values of some
variables can change the decision. These variables are sensitive for decision making. For example, the value of utility of "cure with hypothyroidism after radiation treatment" was assigned 0.80, and the decision for choosing the treatment based on this value was $^{131}$I. If we changed this value to 0.60 or below, then, drug treatment has a higher expected value. On the other hand, there are some insensitive variables, which do not change the decision when their values are changed. Table VIII has the list of sensitive variables. All other variables not listed are insensitive variables.

Threshold probability is the probability where the expected values of the two treatments are equal. The software used in this study called SMLTREE can access threshold probability analysis. Table IX shows the results of threshold analysis between drug and $^{131}$I treatments. Table X shows the results of threshold analysis between $^{131}$I and surgical treatments.

Two way and three way threshold probability analysis have been performed. Most of the surgical complications that are not sensitive in
one way analysis become sensitive in two way analysis. The probability of vocal cord paralysis following surgery, for example, was insensitive in one way analysis, but become sensitive using two way analysis. The literature reported probability is 0.033 for vocal cord paralysis following surgical treatment, and 0.208 for hypothyroidism following surgical treatment. In comparison of surgical treatment with $^{131}$I treatment, in one way analysis of threshold probability, decrease in the probability of vocal cord paralysis, regardless of the magnitude, does not change the expected value of surgical treatment and $^{131}$I will always have higher expected value than surgery. In the two way analysis of threshold probability, on the other hand, when the probability of hypothyroidism decreases to 0.05, the threshold probability of vocal cord paralysis will become 0.017, which means that below this value (0.017), surgery will have higher expected value than $^{131}$I.
Table VIII. List of Sensitive Variables

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of No progress of ophthalmopathy with hypothyroidism after radiation therapy</td>
</tr>
<tr>
<td>Utility of No progress of ophthalmopathy with no hypothyroidism after radiation therapy</td>
</tr>
<tr>
<td>Probability of No cure after surgery</td>
</tr>
<tr>
<td>Probability of Hypothyroidism after $^{131}$I treatment</td>
</tr>
<tr>
<td>Probability of Hypothyroidism after surgery</td>
</tr>
<tr>
<td>Probability of Major toxicity of drug</td>
</tr>
<tr>
<td>Probability of Progress of ophthalmopathy after medication therapy</td>
</tr>
</tbody>
</table>
Table IX. Threshold Analysis for $^{131}$I and Medication**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Assigned value*</th>
<th>Threshold value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of hypothyroidism after $^{131}$I treatment</td>
<td>0.47</td>
<td>0.55</td>
</tr>
<tr>
<td>Probability of progression of ophthalmopathy</td>
<td>0.02</td>
<td>0.174</td>
</tr>
<tr>
<td>Utility of hypothyroidism after $^{131}$I treatment</td>
<td>0.80</td>
<td>0.76</td>
</tr>
<tr>
<td>Utility of no complication</td>
<td>1.00</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*At this value, $^{131}$I is more preferable.

**Beyond this value, drug becomes more preferable.

***No threshold value found for variables in Medication branch.
Table X. Threshold Analysis for $^{131}$I and Surgery***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Assigned value*</th>
<th>Threshold value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of hypothyroidism after $^{131}$I treatment</td>
<td>0.47</td>
<td>0.7016</td>
</tr>
<tr>
<td>Probability of progression of ophthalmopathy after $^{131}$I</td>
<td>0.02</td>
<td>0.4947</td>
</tr>
<tr>
<td>Utility of hypothyroidism after $^{131}$I treatment</td>
<td>0.80</td>
<td>0.7013</td>
</tr>
<tr>
<td>Utility of cure without complication after $^{131}$I</td>
<td>1.00</td>
<td>0.9120</td>
</tr>
</tbody>
</table>

*At this value, $^{131}$I is more preferable.

**Beyond this value, drug becomes more preferable

***No threshold value found for variables in Surgical treatment branch
Cost-effectiveness analysis

Utility measure is one of the hardest aspects of decision analysis, sometimes, however, it is not enough when every aspect of the decision analysis is considered. SMLTREE program has a simple mechanism for including 2 separate utility scales in the tree. Also it can perform special calculations when the utilities are costs and effectiveness. Cost can be in terms of dollars, effectiveness can be in terms of quality of live. Marginal-cost and marginal-effectiveness can be calculated by taking the value of the more expensive strategy and subtracting from them the values of the next cheaper strategy. When the marginal-effectiveness is positive, a marginal-CE ratio is calculated to give the added cost for each unit of effectiveness that the more expensive strategy provides. When the marginal-effectiveness is negative, more money buys less, so, that strategy is not worth considering. In our cost-effectiveness analysis, we estimate that the cost for surgery is $6,000, for $^{131}$I is $4,000, and for drug treatment is $3,000. Table XI shows the cost-effectiveness analysis results.
Table XI. Results of Cost-Effectiveness Analysis*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>Eff'ness&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CE Ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Marg-Cost&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Marg-Eff&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>6,000</td>
<td>0.8711</td>
<td>6,982</td>
<td></td>
<td></td>
</tr>
<tr>
<td>131&lt;sub&gt;I&lt;/sub&gt;</td>
<td>4,000</td>
<td>0.9056</td>
<td>4,416</td>
<td>2,000</td>
<td>-0.0345</td>
</tr>
<tr>
<td>Drug</td>
<td>3,000</td>
<td>0.8894</td>
<td>3,373</td>
<td>1,000</td>
<td>+0.0162</td>
</tr>
</tbody>
</table>

<sup>a</sup>Eff'ness: Effectiveness.
<sup>b</sup>CE Ratio: Cost/Effectiveness ratio.
<sup>c</sup>Marg-Cost: Marginal-Cost.
<sup>d</sup>Marg-Eff: Marginal-Effectiveness.

Cost 1000 = $61,728 (per 1 unit)

*Modified from computer print-out.
Discussion

Hyperthyroidism is a common disease. There are three available treatments for this disease recently. Because of the high incidence of late hypothyroidism following $^{131}$I therapy, the risk from surgery, and the low remission rate and prolonged interval of treatment with antithyroid drugs, choice of treatment becomes more difficult. Disagreement over the indications for use of the various therapeutic modalities to treat hyperthyroidism has been existed for long time (Kinser et al., 1989; Stockigt and Topliss, 1936; Falk, 1990). This study considered the choice among the three therapies in patients with hyperthyroidism. The result of utility analysis shows that radiation therapy is the most preferable choice overall. However, the expected value of the three therapies are quite close. The analysis indicates that the importance for each variable in making decisions is unequal. Some variables affect the decision and are sensitive parameters. Therefore, they are important variables. While some variables are insensitive and thus are unimportant variables. For example,
when comparing the radiation therapy and drug therapy, the probability for the outcome of hypothyroidism after $^{131}$I treatment, the utility values for the outcomes of hypothyroidism after radiation therapy are sensitive parameters. When the surgery and radiation treatments are compared, the utility value for the outcome of hypothyroidism after radiation therapy is the most sensitive parameter. On the other hand, some variables do not even affect the decision no matter what value they have, and thus are insensitive parameters. Table VIII shows the list of sensitive variables. These variables are important for decision making. Other variables not listed on the table are not sensitive and not important for decision making. However, some variables which are not sensitive when considered alone (in one way analysis) become sensitive when using two way analysis. The probability of the complication of surgery are examples of these variables, which are sensitive when two way sensitivity analysis is applied.

In our analysis, we used 0.0015 for the mortality rate of the surgery. This is the average
rate from a large number of literature reports. It is interesting to know that there is no threshold value for this parameter. We consult the computer output of the sensitivity analysis and see that even when the mortality rate of surgery reduced to 0.00, there is still no change in making decision for treatment. In other words, this parameter is not sensitive. The reason probably is that the mortality rate for subtotal thyroidectomy is already very low, so there is no room for it to increase the expected value to the level at which the decision will be changed.

Utility value reflects the degree of patient's preference among possible outcomes from different treatments of the disease. This value can affect the expected value of the treatment outcomes, by which the decision is finally affected. From sensitivity analysis, the change of utility value affects the expected value. Here are some important examples.

1). Utility value of hypothyroidism after $^{131}$I treatment: After $^{131}$I treatment for hyperthyroidism, some patients may suffer from hypothyroidism. This is because too much thyroid
tissue is destroyed, and the remaining thyroid tissue can not fulfill the task of maintaining thyroid hormone at normal levels. In those cases, exogenous thyroid hormone should be given. The hypothyroidism can be temporary or permanent. Some patients take this complication very seriously, others do not care very much about it because they prefer hypothyroidism rather than hyperthyroidism with which drug therapy usually is not effective. In our analysis, the assigned value for uhypo.T was 0.8. The analysis result indicates that this is a very sensitive parameter since the threshold value is 0.76, only 0.04 away from the assigned value. If the utility value is given below 0.76, then drug therapy will be more preferable than $^{131}\text{I}$ treatment.

2) Utility value of hypothyroidism after $^{131}\text{I}$ treatment (u hypoT. I) is also sensitive for the choice of treatment between surgery and $^{131}\text{I}$. The threshold is 0.70, a value close to the assigned value of 0.8. If we give a utility value lower than 0.70, surgical treatment will become more preferable than $^{131}\text{I}$ treatment. These threshold analyses results show the importance of utility
analysis for making decisions. Care should be taken in assessment of utility value because the results of threshold analysis indicated that the threshold value for some utilities were very close to the utilities assigned in this study. The more consistent the utility assessment is, the more adequate the study will be. Further study is recommended for assessing patient utilities.

Cost-Effectiveness analysis

From Table XI we can see, if we are just concerned about one scale -- effectiveness, $^{131}$I is the most preferable choice. When we are concerned about the cost only, drug treatment is the cheapest one. When, however, we are concerned about both cost and effectiveness, the situation becomes complicated. Surgery, with its most expensive cost and lowest expected value, is not the choice for treatment in our study. The expected value of $^{131}$I treatment is 0.9056 which is 0.016 higher than that of drug treatment. The price for 0.016 increase of the expected value from drug treatment to $^{131}$I treatment is $1,000. In other words, we have to pay $1,000 to get 0.016
increase of the expected value or $6,250 to get 0.1 increase in utility score:
\[ 1,000 + 0.016 + 10 = 6,250. \]
To get 100% change in utility score (i.e., from 0 to 1), $62,500 is needed. In the present study, utility 0 represents death, utility 1 represents healthy life. If we suppose the average age of patients with hyperthyroidism is 40 years and the life span for a normal person is 80 years, $1,562 cost per year of life saved (without discounting):
\[ (1000+0.016)+(80-40)=1562 \]
We have to balance the money we spend and the utility we get when we compare two different treatments.

**Generalization of the study**

The decision for choosing treatment among surgical, medical, and radiation therapies is difficult for many patients with hyperthyroidism. It may depend upon the personal characteristics of the patient such as age, sex, and marriage status; the severity of the patient's disease; the patient's desire; and sometimes the physician's desire. The patient's desire depends upon the
patient's knowledge of the probabilities of the possible outcomes for the available treatments, understanding about the detail of the outcomes, and the patient's preference among the possible outcomes. So the physician should fully inform the patient about the prognosis of each treatment. Clinical decision analysis combines this information and gives us a numerical expression of the patient's preference. The result of clinical decision analysis is not the only source for the support of the decision for both the patient and physician, but it plays a significant role in helping them to make final decisions. In our study, the expected value of radiation therapy is the highest one, so that radiation therapy is probably the most preferable choice.

At this point, a very interesting question may be raised: can this decision model be applied to all patients with hyperthyroidism? Our answer to this question is: yes. The reason is that all the treatment methods we used in the present study are the main methods available to date for treating hyperthyroidism. The probabilities for the possible outcomes of each treatment in the
study are based on objective data base, which are represented not only for specific patients but also for the whole population.

In conclusion, generalization of the study results should be applied with great care. The model can be used with little risk of bias for patients with hyperthyroidism. In addition, clinical judgment, and patient's understanding of the disease and outcomes are very important.

**Limitation of the study**

To perform the utility analysis, it is necessary to create a model. In our study, we constructed a tree-like structure called a decision tree as a model. To question the model is legitimate in regard to the issue of validity. Certainly the decision tree upon which our analysis is based is simplified. The outcomes for the complications of each therapy, in the real situation, are more complex than we have presented in the trees.

In the present study, each of the three therapies is treated as a single treatment used alone. In practice, however, they may be used as a
combination for severe cases. Antithyroid drug by itself can be used to treat hyperthyroidism, it also can be used on patients sometimes as a complement therapy for the main therapy of surgical or radiation therapy. Some physician used to give antithyroid drug before or after operation or $^{131}$I in order to control the symptoms. When surgical or radiation therapy is used as a major treatment, comparing the consequences result from the operation or $^{131}$I to that from the complement use of antithyroid drug, the latter is considerably minor because of the low dosage and short period of using these drugs. Therefore, in our study, we ignored the reactions (including complications and beneficial reactions) of the drug as a complement therapy in patients undergoing surgical or radiation therapies due to the insignificant risk for affecting the decision.

A model is a simplification of the real world, for the purpose of description and analysis, or sometimes because of limitations of the available information. Whenever it is possible, we have to make the model to reflect the real world as closely and precisely as we can.
Utility value reflects preference of the decision. In this study utility values were assigned by three physicians. Although assessment of utility value by physician has some advantages, possible biases may exist. Physician may have different attitude towards some outcomes in comparison with patient. Additionally, physician with different specialty may have different opinion.

In further study, assessment of utility values by a large number of physicians involving different specialties could be used in order to minimize biases.

What can a physician learn from the study

The decision analysis can support a physician and a patient with hyperthyroidism in choosing the best treatment. What else can we learn from this study? After carefully studying the results of sensitivity analysis, it is interesting to find that this study gave us some important information for better quality in further medical practice.

Physicians, especially those who are treating patients with hyperthyroidism, such as
endocrinologist, general surgeon, or radiologist, will discover some crucial information to improve their treatment skills. As we discussed earlier, there existed some very sensitive parameters for making the decision. It is these particular parameters that provide important guide for improving medical services. Physicians should pay great attention to these parameters in order to make the treatment more acceptable by patients with hyperthyroidism. For example, if a surgeon could reduce greatly the recurrent rate of hyperthyroidism after subtotal thyroidectomy, or decrease the complications of hypothyroidism, hypoparathyroidism and vocal cord paralysis, the quality of the operation will be increased. Reducing the post-hypothyroidism rate of \( ^{131}I \) treatment is very crucial for a radiologist to improve the treatment quality. For physicians of internal medicine or endocrinologists, it is important to increase the cure rate of hyperthyroidism by antithyroid drugs.

In conclusion, the utility analysis is not only a guide for choosing a therapy but also a guide for improving the treatment of the disease.
REFERENCES


Chapter II.
The Choice of Treatment for Gallbladder Cancer

Introduction

Epidemiology and Clinical Features

Gallbladder cancer is an uncommon neoplasm. This disease was found in only 46 of 13,034 autopsies (0.33%) in one series (Illingworth, 1935). It was reported that it accounts for under 1% of all deaths from cancer in Great Britain (Cooke et al., 1953). In the Cancer Registry of the Doubs region in France it ranks sixth in all gastrointestinal malignancies and comprises nearly 2% of these lesions (Schraub et al., 1978-1985). Cancer of the gallbladder occurs more often in women especially in women older than 60 years. Peak incidence is in the 70-75 year-old group (Donaldson & Busutill, 1975). Gall stones co-exist in 90% of cases and chronic cholecystitis is frequently present. However, the great majority of patients with gallstones never develop cancer. Carcinogenic properties of gallstone or bile seems unlikely (Cooke et al., 1953). It has been noted that since 1968 the total deaths and total crude mortality for
gallbladder cancer has fallen in the United States, but
the number of cholecystectomies has risen (Tompkins,
1982). This, while it may indicate that an increased
removal of the gallbladder lowers the risk of dying from
gallbladder cancer, may be a coincidental observation
(Tompkins, 1982).

There are some racial and ethnic differences in the
incidence of gallbladder cancer. The highest incidence of
cancer of the gallbladder occurs in American Indians,
Americans of Mexican origin, Alaskan natives, northeastern
Europeans, Israelis, and Japanese immigrants to the United
States. The frequency of this cancer in Alaskan natives
is about the same as that for the Indians of New Mexico
(Boss et al., 1982) which has been estimated to be more
than six times that of the non-Indian population.
American Indian women are twice as likely to develop the
cancer than are Spanish American women, who are almost ten
times as likely to develop the cancer than are non-Spanish
American whites (Diehl, 1980). The lowest rates are
reported for black Americans, black Rhodesians, Indians in
India, and Spaniards in Spain (Diehl, 1980).

The symptoms of carcinoma of the gallbladder are not
specific. Progressive loss of weight, deterioration of
health and persistent right upper quadrant pain are common
symptoms. The clinical presentation differs depending on stage of the disease, but there is no distinct pattern because the presenting symptoms and their duration are dependent on the site of the lesion, its extent, and the presence or absence of pre-existing biliary symptoms. Malignancy in patients with pre-existing biliary symptoms generally produces a noticeable change in symptoms.

Neither the physical finding nor the laboratory features are specific. A right upper quadrant mass may be apparent and is usually tender. The presence of a palpable gallbladder represents advanced disease. Jaundice may be early and sudden due to obstruction by tumor arising in the neck of the gallbladder or lymphatic involvement at the hilum of the liver. The jaundice is accompanied by pain in the majority of patients, which may be of use in distinguishing this disease from a periampullary carcinoma.

Histologically, 75-90% of these lesions are well-differentiated, mucin-secreting adenocarcinomas, 5% are squamous and approximately 10% are anaplastic. DNA ploidy studies have not shown a histological pattern associated with outcome (Donohoe et al., 1990). The mode of spread of carcinoma of the gallbladder is mainly by the lymphatic along the cystic duct and the common bile duct, or by
direct extension into the liver. The common hepatic duct is frequently involved by direct extension (Shimada et al., 1988). Tumors close to the fundus of the gallbladder may involve the duct to the anteroinferior segment of the liver early as a result of direct liver invasion.

Diagnosis and Staging

Because of the non-specific clinical presentation, preoperative diagnosis is uncommon. Many patients may have a history of biliary disease of more than one year's duration, but 50% will have no such story. The majority of patients are diagnosed either as an incidental finding at elective biliary surgery or during laparotomy for suspected cholangiocarcinoma at the confluence of the duct. Preoperative diagnostic rate is less than 10% (Piehler & Crichlow, 1978). A minority of patients have early carcinomas as incidental findings at cholecystectomy. Selective involvement of ducts and vessels in the anteroinferior part of the right lobe of the liver on cholangiography/angiography, particularly in the presence of obstructive jaundice, should arouse suspicion of gallbladder cancer. CT scanning may also suggest the diagnosis. A calcified gallbladder seen on X-ray may indicate carcinoma (Polk, 1966). Occasionally,
endoscopic retrograde cholangiopancreatography reveals an irregular filling defect within the gallbladder, or obstruction of the common hepatic duct close to the hilus and a failure of the gallbladder to fill.

About 20 years ago, Nevin described a staging system for gallbladder cancer according to the depth of invasion and spread (Nevin et al., 1976). Five stages are used from stage I to stage V. Table I shows the Nevin's staging system.

Later, a similar staging system was described by American Joint Commission on Cancer Staging System (AJCC system) (American Joint Committee on Cancer, 1988). Detailed method is shown in Table II.
Table I
Nevin Staging System for Gallbladder Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Depth of Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intramucosal only</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of mucosa and muscularis</td>
</tr>
<tr>
<td>III</td>
<td>Transmural invasion</td>
</tr>
<tr>
<td>IV</td>
<td>Transmural invasion and cystic duct</td>
</tr>
<tr>
<td></td>
<td>lymph-node metastasis</td>
</tr>
<tr>
<td>V</td>
<td>Metastasis, involvement of liver by direct</td>
</tr>
<tr>
<td></td>
<td>extension or metastases, or metastases to any</td>
</tr>
<tr>
<td></td>
<td>other organ</td>
</tr>
</tbody>
</table>
Table II

American Joint Commission on Cancer

Staging System for Gallbladder Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Depth of Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>In-situ carcinoma</td>
</tr>
<tr>
<td>I</td>
<td>Involvement of mucosa or muscularis</td>
</tr>
<tr>
<td>II</td>
<td>Transmural invasion</td>
</tr>
<tr>
<td>III</td>
<td>Transmural invasion and lymphatic invasion, or invasion of the liver&lt;br&gt;&lt;2 cm from the gallbladder fossa</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of two or more adjacent organs, invasion of the liver &gt;2 cm from the gallbladder fossa, or distant metastasis</td>
</tr>
</tbody>
</table>
Treatment and Prognosis

Surgical resection of the tumor and involved tissue is the main method for the treatment of gallbladder cancer. The results of exisional treatment are in general poor, but when cholecystectomy is carried out for cancer which has only microscopically involved the gallbladder, the results are better. Bergdahl studied 32 patients in whom the gallbladder had been removed for presumed benign disease, but who had been discovered to have a gallbladder cancer on microscopy. Eleven of these cases had cancer confined to the mucosa and submucosa. In 21 cases, the carcinoma involved the entire gallbladder wall. Five-year survival rate in the group of patients with only mucosal and submucosal involvement was 63.6% (Bergdahl, 1980). Bergdahl recommends that a wedge resection of approximately 5 cm of normal liver tissue and dissection of the regional lymph nodes be carried out. Surgeons argue the extent of surgical resection necessary for patients with gallbladder cancer. Although some recent reports do not support radical surgery for extensive disease, extirpative surgical procedures for gallbladder cancer continue to be performed (Gall et al., 1991; Nakamura et al., 1989; Ogura et al., 1991; Tashiro et al., 1982). These reports, however, do not demonstrate a
statistically significant increase in survival rates despite the increasing morbidity and mortality rates due to radical surgery.

There is little evidence that adjunctive chemotherapy or radiotherapy, or combinations of these modalities produces marked improvement, although some have reported a modest prolongation of survival after such treatment (Perpetuo et al., 1978; Silk et al., 1989; Treadwell & Hardin, 1976).

Purposes of the Study

Although gallbladder cancer is a rare disease, it is, however, the most frequent malignancy of the biliary tract and the sixth in all gastrointestinal malignancies (Schraub et al., 1978-1985). Decision of choosing between the surgical procedures is still quite difficult because of the existence of the controversy regarding the effectiveness of the treatments. Furthermore, the study of gallbladder cancer is clouded by the fact that there are two staging systems presently in use as described above. The purposes of this study were to assess the relationship the Nevin staging system and the AJCC staging system, with the survival of the patients with gallbladder cancers seen at the Massachusetts General Hospital between
1960 to 1989; and to assess the effects of the five different surgical procedures on the survival of these patients.
Methods

Design and Subjects

This was a hospital-based retrospective observational cohort study. More specifically, the subjects were from patients who were diagnosed and treated for gallbladder cancer seen at the Massachusetts General Hospital (MGH), Boston between 1960-1989.

The eligible study subjects included: (1) all the patients who died and were diagnosed with gallbladder cancers; and (2) all survivors who were diagnosed gallbladder cancers seen but no longer and/or still followed by the general surgeons of the MGH. There were 121 patients included in the study.

Records of 121 patients with the diagnosis of gallbladder cancer treated at the Massachusetts General Hospital during the years of 1960 - 1989 have been reviewed. Histologic documentation of the presence of gallbladder cancer was obtained in 101 patients. The records of 16 of the 101 patients were excluded as being inadequate for assessment because of either inadequate follow-up data or incomplete information concerning the type of surgery or the extent of disease. There were totally 85 remaining study subjects in the analyses.
Data Collection and Variables

Data on the 85 patients were gathered from patient's charts, from death certificates, and from pathology reports.

Table III shows the data abstraction form. As presented in Table III, the variables assessed included age and sex of the patients, chief complaint, preoperative diagnosis, surgical procedures (simple cholecystectomy; cholecystectomy + biliary or intestinal bypass; cholecystectomy + hepatic wedge resection; exploratory laparotomy, biopsy, and biliary or intestinal bypass; and exploratory laparotomy and biopsy), pathology of the cancer (adenocarcinoma, squamous carcinoma, carcinoma in situ, and anaplastic), grade of adenocarcinoma (well-differentiated, mod-differentiated, and poorly-differentiated), stage of the cancer (Nevin and AJCC systems, respectively), postoperative chemotherapy and radiation therapy, and decades treated (1960-1970, 1971-1980, and 1981-1989). Information on the race of the patients was not completed in most of the patient charts, therefore, race was not included in the statistical analysis.
Table III. Data Abstraction Form
(Gallbladder cancer study)

<table>
<thead>
<tr>
<th>Name</th>
<th>Patient Unit Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Sex</td>
</tr>
<tr>
<td>Chief Complaint</td>
<td></td>
</tr>
<tr>
<td>Pre-Op Dx</td>
<td></td>
</tr>
<tr>
<td>Surgical Procedure</td>
<td></td>
</tr>
<tr>
<td>Surgical Date</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Grade of Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Stage of the Cancer:</td>
<td></td>
</tr>
<tr>
<td>Nevin</td>
<td>AJCC</td>
</tr>
<tr>
<td>Post-Op Chemo</td>
<td></td>
</tr>
<tr>
<td>Post-Op XRT</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Cause of Death</td>
</tr>
<tr>
<td>Death Date</td>
<td></td>
</tr>
<tr>
<td>Last Contact Date</td>
<td></td>
</tr>
<tr>
<td>Remark</td>
<td></td>
</tr>
</tbody>
</table>
Statistical Analysis

Descriptive frequencies were calculated for all the variables. Univariate cumulative survival rates were estimated using the Kaplan-Meier survival function. Survival data were examined for individual variable effects using the log-rank test. The Cox's proportional hazard model were used to assess the multivariate survival analysis. The method of backward stepwise regression were employed to select the most statistically and clinically appropriate model.
Results

Characteristics of the Study Population

Among the 85 study subjects, patient's age ranged from 41 years old to 98 years old, averaging 71.7 years old. The average ages were 72.2 years old with a standard deviation of 10.51 for females and 69.6 with a standard deviation of 10.76 for males. The sex ratio was 4:1 with female dominant (Table IV). About half of the cohort had abdominal pain (Table V). Thirty-five percent presented themselves with evidence of jaundice. Eleven percent reported systemic symptoms such as nausea, vomiting, weight loss, and fatigue (Table VI).

Preoperative diagnosis of gallbladder carcinoma was made in only 10% of the patients (Table VI). The most common preoperative diagnosis was acute cholecystitis (17% of the patients), cholelithiasis (15% of the patients), common duct obstruction (10% of the patients), cholangiocarcinoma (9% of the patients), chronic cholecystitis (9% of the patients), and pancreatic carcinoma (2% of the patients).

Table VII summarizes the surgical procedures. Five different surgical procedures were performed in this group of patients. Of the 85 patients in this study, 30 patients
underwent cholecystectomy (procedure A), 13 underwent cholecystectomy plus biliary or intestinal bypass (procedure B), 6 underwent cholecystectomy plus hepatic wedge resection (procedure C), 12 underwent exploratory laparotomy, biopsy, and biliary or intestinal bypass (procedure D), and 24 underwent exploratory laparotomy and biopsy. No extended radical procedures such as extended right hepatectomy, lymphadenectomy or pancreatoduodenectomy were performed.

Cholelithiasis was documented in 72 patients (85%), 3 patients (4%) had calcified gallbladder or a porcelain gallbladder. Pathology analysis was done from tissue samples removed during surgical procedures (Table VIII). Most of the patients had adenocarcinoma (79 patients, 95%). Other cell types included squamous carcinoma (4%), carcinoma in situ (2%), and anaplastic neoplasm (1%). In the adenocarcinoma group, 2% were well-differentiated, 43% were moderately differentiated, and 55% were poorly differentiated (Table IX).

No patient received preoperative radiation therapy or adjuvant chemotherapy. Nine patients received postoperative radiation therapy, and 10 patients received postoperative chemotherapy.

According to Nevin staging system, there were 2 stage
I patients, 1 stage II patient, 11 stage III patients, 22 stage IV patients, and 49 stage V patients. While in AJCC staging system, the frequencies of the patients in the different stages were 2 stage I, 1 stage II, 38 stage III and 44 stage IV.

Univariate Analyses with Kaplan-Meier Survival Function

While performing univariate analysis using Kaplan-Meier survival function, for the variable of "chief complaint of the patients", the survival rates for patients with abdominal pain, jaundice and systemic symptoms were very similar. The one-year survival rates were 20% (P=0.4) for abdominal pain, 18% (P=0.28) for jaundice, and 28% (P=0.25), respectively. Therefore, these variables were not included in the multivariate analysis. For the variable of "preoperative diagnosis", there were 9 categories and the number of patients in each category was too small to be analyzed. For histology of the gallbladder cancer, adenocarcinoma was compared against other types of cancer. The result of the analysis was very similar. For grade of adenocarcinoma, mod-differentiated cancers were compared with poorly differentiated cancers. Surprisingly, the survival rate of the patients with these two different grades of cancers
were also similar (the one-year survival rates were 19% for mod-differentiated and 15% for poorly differentiated, \( p=0.24 \)). These insignificant, both statistically and clinically, variables (i.e. chief complaint, preoperative diagnosis, histology of the cancer, and grade of the cancer) were not included in the multivariate analysis.

Tables X, XI and XII show the univariate analyses of the variables that were the major interests of this study.

Table X (Nevin) and XI (AJCC) were survival rates for patients with different stage gallbladder cancers. Patients with stages I and II (either Nevin or AJCC system) had a 100% survival at 1 year and 3 years after the surgery. The mean survivals for I and II were 82.8 months and 102.1 months, respectively, in both Nevin and AJCC systems. The 1-year and 3-year survival rates were 45% and 9%, respectively, with mean survival of 16.3 months in Nevin stage III. The 1-year and 3-year survival rates were 5% and 0%, respectively, with mean survival of 4.0 months for Nevin stage IV. And the 1-year and 3-year survival rates were 10% and 0%, respectively with mean survival of 5.3 months in Nevin stage V.

Table XII presents the results of crude mortality and mean survival length (Kaplan-Meier survival analysis for the entire study period). The mean length of survival
was longer for female patients (17 months) than that for male patients (5 months). But this did not reach a statistical significance. Survival rates were similar between patients with and without chemotherapy, and between patients with and without radiation therapy. Gallbladder cancer patients treated during 1960 to 1970 had shorter mean survival (9 months) than those treated during 1971 to 1980 (mean survival 15 months), and during 1981 to 1989 (mean survival 12 months).

Figures 1-5 and Table XIII show survival curves as defined by the type of operation and by the stage of disease in the Nevin system, and in AJCC system by Kaplan-Meier survival function. There was no difference in terms of survival among the different surgical procedures.

Multivariate Analyses with Cox's Model

Survival rates were analyzed by Cox's Proportional Hazards regression model and the results of these analyses are presented in Figures 6-8 and Table XIV. The results of the analysis was adjusted for both the Nevin and the AJCC staging systems (Figures 6 and 7) and therefore there were two Cox's models in this study. Backward stepwise regression was used to select the final model. The criterion P values were 0.2 for both removal and
reentering. The variables included in the initial models were age, sex, decade, stage (Nevin or AJCC), chemotherapy, radiation therapy and surgical procedures. The final models contained variables of stage, chemotherapy and surgical procedures. There were only 6 patients underwent surgical procedure C (cholecystectomy plus hepatic wedge resection), therefore, the analyses were repeated without procedure C (Table XV). From clinical point of view, the surgical procedures A, B, D, and E were similar except procedure C, comparison of other procedures with procedure C was also assessed (Table XVI).

For surgical procedures (Figure 6 and Table XIV), the reference procedure in both of the Cox's models was cholecystectomy. The only statistically significant finding was a decreased survival rate in patients who underwent solely exploratory laparotomy and biopsy (relative risk 1.9 with a 95% confidence interval of 1.03 to 3.49) in the model containing the variable of AJCC stage system. There was no difference in survival rate in comparisons of patients who underwent simple cholecystectomy or of those who had a cholecystectomy with hepatic resection. There was a trend towards an increased survival rate in patients who underwent cholecystectomy and either biliary or intestinal bypass. The results of
analyses without surgical procedure C (Table XV) were similar with the above findings. The comparison of other procedures (A, B, D, and E) with procedure C (Table XVI), the relative risks were 1.68 for procedure C with a P value of 0.24 when adjusted for Nevin staging system, and 1.92 for procedure C with a P value of 0.15 when adjusted for AJCC staging system.

The relative risk for patients with postoperative chemotherapy was 0.32 with a 95% confidence interval of 0.14 - 0.75 in the model containing Nevin's staging system, and 0.38 with a 95% confidence interval of 0.17 - 0.82 in the model containing AJCC staging system.

Only stages III, IV and V in Nevin system, and stages IV and V in AJCC system were entered into the multivariate Cox's model. The number of patients with stages I and II in both staging systems was too small to be analyzed. Even when stages I and II were combined. The reference stage was III in Nevin system and IV in AJCC system. The results were presented in Figure 8. In the model containing Nevin's staging system, patients with stage IV and V cancers had a significantly much poor outcome in terms of survival compared to those with stage III cancers. The relative risks were 4.0 with a 95% confidence interval of 1.54 - 10.48 for patients with
stage IV cancers, and 3.1 with a 95% confidence interval of 1.40 - 6.84 for patients with stage V cancers.

In the model containing AJCC staging system, the relative risk was 1.2 for patients with stage IV cancers as compared to those with stage III cancers. However, this finding did not reach a statistical significance.
<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>63</td>
<td>74.1%</td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>25.9%</td>
</tr>
</tbody>
</table>

**Age (years)**

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Range</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>71.7 ± 10.71</td>
<td>41 - 98</td>
<td>72.2 ± 10.51</td>
<td>69.6 ± 10.76</td>
</tr>
</tbody>
</table>

(mean ± S.D.)
Table V
Chief Complaint of the Patients

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Jaundice</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Systemic</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Other*</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

*Other included nausea, vomiting, and diarrhea.
Table VI
Preoperative Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cholecystitis</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Abdominal carcinoma</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Cholelithia</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Common bile duct obstruct</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Chronic cholecystitis</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>85</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

*Other included pancreatitis, bowel obstruction, etc.
Table VII
Operative Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Code</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystectomy</td>
<td>A</td>
<td>30</td>
</tr>
<tr>
<td>Cholecystectomy + Biliary or</td>
<td>B</td>
<td>13</td>
</tr>
<tr>
<td>Intestinal Bypass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy + Hepatic</td>
<td>C</td>
<td>6</td>
</tr>
<tr>
<td>Wedge Resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory Laparotomy, Biopsy</td>
<td>D</td>
<td>12</td>
</tr>
<tr>
<td>and Biliary or Intestinal Bypass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory Laparotomy &amp; Biopsy</td>
<td>E</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>85</td>
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Table VIII
Pathology of the Cancer

<table>
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<tr>
<th>Pathology Diagnosis</th>
<th>Frequency</th>
<th>%</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>79</td>
<td>93</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Carcinoma in situ</td>
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<tr>
<td>Anaplastic</td>
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<td>1</td>
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<td><strong>Total</strong></td>
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Table IX
Grade of Adenocarcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Frequency</th>
<th>%</th>
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<tr>
<td>Well-differentiated</td>
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<tr>
<td>Mod-differentiated</td>
<td>37</td>
<td>43</td>
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<td>Poorly-differentiated</td>
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<tr>
<td>Total</td>
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<td>100</td>
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**Table X**

*Survival with Nevin Staging*

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Mean Survival (months)</th>
<th>% 1 yr Survival</th>
<th>% 3 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>82.8*</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>102.1**</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>16.3</td>
<td>45</td>
<td>9</td>
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<tr>
<td>IV</td>
<td>22</td>
<td>4.0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>49</td>
<td>5.3</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

*One patient died from a myocardial infarction after 138 months.*

*One patient was well after 49 months.*

**One patient died from a myocardial infarction after 96 months.*
<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Mean Survival (months)</th>
<th>% 1 yr Survival</th>
<th>% 3 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>82.8*</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>102.1**</td>
<td>100</td>
<td>100</td>
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<tr>
<td>III</td>
<td>38</td>
<td>7.3</td>
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<td>2.7</td>
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<td>IV</td>
<td>44</td>
<td>4.8</td>
<td>13.6</td>
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</tbody>
</table>

*One patient died from a myocardial infarction after 138 months.
One patient was well after 49 months.

**One patient died from a myocardial infarction after 96 months.
### Table XII

**Kaplan-Meier Survival Function**

**Crude Mortality and Mean Survival Length (month)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>%</th>
<th>Mean Dying</th>
<th>Mean Survival</th>
<th>P</th>
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<tr>
<td>Sex:</td>
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<td>17</td>
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<td>Female</td>
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<td>89</td>
<td>17</td>
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<td>Chemotherapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>90</td>
<td>11</td>
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<td>0.16</td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>92</td>
<td>15</td>
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<td>Radiation therapy</td>
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<td>100</td>
<td>10</td>
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<td>0.26</td>
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<tr>
<td>No</td>
<td>73</td>
<td>90</td>
<td>15</td>
<td></td>
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<td>Decade</td>
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<td></td>
</tr>
<tr>
<td>1960-1970</td>
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<td>96</td>
<td>9</td>
<td></td>
<td>0.34</td>
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<td>15</td>
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<td>1981-1989</td>
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<td>Nevin Stage</td>
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<tr>
<td>I&amp;II</td>
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<td>0</td>
<td>120</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>82</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>22</td>
<td>94</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage V</td>
<td>49</td>
<td>98</td>
<td>5</td>
<td></td>
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<td>AJCC Stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I&amp;II</td>
<td>3</td>
<td>0</td>
<td>120</td>
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<td>0.02</td>
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<tr>
<td>III</td>
<td>38</td>
<td>92</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>Stage IV</td>
<td>44</td>
<td>98</td>
<td>6</td>
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</table>
Table XIII
Mean Survival Length (Month)
(Kaplan-Meier Method)

<table>
<thead>
<tr>
<th>Type of Surgery*</th>
<th>Nevin Stage</th>
<th>AJCC Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>III IV V</td>
<td>III IV</td>
</tr>
<tr>
<td>A</td>
<td>15 7 7 11 7</td>
<td>7</td>
</tr>
<tr>
<td>B</td>
<td>9 6 14 6</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3 6 3 10</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>14 3 6 5 6</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>4 4 4 4 4</td>
<td></td>
</tr>
</tbody>
</table>

Surgery A: Cholecystectomy
Surgery B: Cholecystectomy + Biliary or Intestinal Bypass
Surgery C: Cholecystectomy + Hepatic Wedge Resection
Surgery D: Exploratory Laparotomy, Biopsy and  
           Biliary or Intestinal Bypass
Surgery E: Exploratory Laparotomy & Biopsy
Table XIV
Results of Multivariate Cox's Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff.</th>
<th>P-Value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: with Nevin Staging System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td>1.00*</td>
</tr>
<tr>
<td>IV</td>
<td>1.3892</td>
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<td>4.01</td>
</tr>
<tr>
<td>V</td>
<td>1.1312</td>
<td>0.005</td>
<td>3.10</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.00*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
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<td>C</td>
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<td>0.252</td>
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<td>D</td>
<td>-0.0236</td>
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<td>0.98</td>
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<td>E</td>
<td>0.3019</td>
<td>0.363</td>
<td>1.35</td>
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*Reference group.
Table XIV
Results of Multivariate Cox's Model
(cont.)

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<th>Relative Risk</th>
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<tbody>
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<tr>
<td>Stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
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<td>1.23</td>
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<td>1.00*</td>
</tr>
<tr>
<td>A</td>
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<td>-0.3441</td>
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*Reference group.
Table XV

Results of Multivariate Cox's Model

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<th>P-Value</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
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<td>3.94</td>
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<td>V</td>
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<td>0.005</td>
<td>3.10</td>
</tr>
<tr>
<td>Surgery A</td>
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</tr>
<tr>
<td>B</td>
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<td>0.55</td>
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<td>D</td>
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<td>1.31</td>
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Table XV
Results of Multivariate Cox's Model
(cont.)

<table>
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<th>Variable</th>
<th>Coeff.</th>
<th>P-Value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2: with AJCC Staging System without Surgery C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>1.00*</td>
<td></td>
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<td>Stage IV</td>
<td>0.2500</td>
<td>0.322</td>
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<td>Surgery A</td>
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<td>Surgery B</td>
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<td>Surgery D</td>
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<td>Surgery E</td>
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*Reference group.
Table XVI
Results of Multivariate Cox's Model

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<th>P-Value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: with Nevin Staging System and Comparison of other Surgeries with Surgery C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
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<td>IV</td>
<td>1.4763</td>
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<td>Surgery A,B,D,&amp;E</td>
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*Reference group.
Table XVI

Results of Multivariate Cox's Model
(cont.)

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<th>P-Value</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Model 2: with AJCC Staging System and Comparison of other Surgeries with Surgery C</td>
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<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>III</td>
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<td></td>
<td>1.00*</td>
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<td>1.22</td>
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<tr>
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<td>1.00*</td>
</tr>
<tr>
<td>C</td>
<td>0.6510</td>
<td>0.15</td>
<td>1.92</td>
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<td>1.00*</td>
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<td>Yes</td>
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<td>0.03</td>
<td>0.43</td>
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</table>

*Reference group.
Survival Curve
(AJCC stage 3)

Cumulative Survival (%)

Follow Up Interval (month)

Surgery A: Cholecystectomy (n=15)
Surgery B: Cholecystectomy + Biliary or Intestinal Bypass (n=4)
Surgery C: Cholecystectomy + Hepatic Wedge Resection (n=4)
Surgery D: Exploratory Laparotomy, Biopsy and Biliary or Intestinal Bypass (n=7)
Surgery E: Exploratory Laparotomy & Biopsy (n=10)

Figure 1
Survival Curve
(AJCC stage 4)

Cumulative Survival (%)

Follow Up Interval (month)

Surgery A: Cholecystectomy (n=12)
Surgery B: Cholecystectomy + Biliary or Intestinal Bypass (n=9)
Surgery C: Cholecystectomy + Hepatic Wedge Resection (n=2)
Surgery D: Exploratory Laparotomy, Biopsy and Biliary or Intestinal Bypass (n=5)
Surgery E: Exploratory Laparotomy & Biopsy (n=14)

Figure 2
Survival Curve
(Nevin stage 3)

Cumulative Survival (%)

Follow Up Interval (months)

- Surgery A
- Surgery D

Surgery A: Cholecystectomy (n=9)
Surgery D: Exploratory Laparotomy, Biopsy and Biliary or Intestinal Bypass (n=2)

Figure 3
Survival Curve
(Nevin stage 4)

Cumulative Survival (%)

Follow Up Interval (month)

- Surgery A
- Surgery B
- Surgery C
- Surgery D
- Surgery E

Surgery A: Cholecystectomy (n=4)
Surgery B: Cholecystectomy + Biliary or
     Intestinal Bypass (n=2)
Surgery C: Cholecystectomy + Hepatic Wedge Resection (n=1)
Surgery D: Exploratory Laparotomy, Biopsy and
     Biliary or Intestinal Bypass (n=4)
Surgery E: Exploratory Laparotomy & Biopsy (n=8)

Figure 4
Survival Curve
(Nevin stage 5)

Cumulative Survival (%)

Follow Up Interval (month)

Surgery A: Cholecystectomy (n=14)
Surgery B: Cholecystectomy + Biliary or Intestinal Bypass (n=11)
Surgery C: Cholecystectomy + Hepatic Wedge Resection (n=5)
Surgery D: Exploratory Laparotomy, Biopsy and Biliary or Intestinal Bypass (n=6)
Surgery E: Exploratory Laparotomy & Biopsy (n=16)

Figure 5
Relative Risk by Surgery

Surgery A: Cholecystectomy
Surgery B: Cholecystectomy + Biliary or Intestinal Bypass
Surgery C: Cholecystectomy + Hepatic Wedge Resection
Surgery D: Exploratory Laparotomy, Biopsy and Biliary or Intestinal Bypass
Surgery E: Exploratory Laparotomy & Biopsy

Figure 6
Relative Risk by Chemotherapy

Figure 7
Relative Risk by Stage

![Graph showing relative risk by stage with stages III, IV, and V represented. The graph indicates a significant difference (*P < 0.005) between Nevin and AJCC stages.]

Figure 8.
Discussion

Gallbladder cancer has been reported to be a rare disease. Only 121 patient records were found during the years of 1960-1989 at the Massachusetts General Hospital, Boston. It was reported that females have higher incidence of gallbladder cancer than that of males, most patients were older than 50 years old (de Aretxabala et al., 1992). In the present study, the average age was 71.9 years and older than some previous reports. Female patients were four times more frequent than male patients in this study.

Although no study confirms the causative effect of gallstone in cancer formation, there is a well-established association between cancer of the gallbladder and gallstones, which are reported presenting in at least 70% of patients, a figure far greater than that found in the age-matched general population (Diehl, 1983). A parallel exists between the epidemiology of cancer of the gallbladder and gallstones. In both conditions there is a higher incidence in females, and increasing incidence with age, and variation among ethnic groups. Cancer of the gallbladder associated with cholelithiasis is found in about 0-5% of autopsies, whereas this figure ranges from
about 1-2% in patients undergoing cholecystectomy. There is no predilection for development of carcinoma in a gallbladder containing single or multiple stones. But there may be some relationship to the size of a stone, as it has been suggested that the risk for developing carcinoma in a patient with a 3 cm gallstone is ten times that for one with a stone less than 1 cm (Diehl, 1983). In this study, although the size and the number of gallstone are not recorded, there seems to be a relationship between gallbladder cancer and gallstones. Seventy-two patients (85%) in this study has been found to have gallstone. This result is in agreement with that of the previous studies and suggests the need for further study of the relationship between gallstone and gallbladder cancer.

In addition to gallstones, there are some other pathological conditions of the gallbladder presumably associated with the development of carcinoma of the gallbladder. These conditions include cholecystoenteric fistula, porcelain gallbladder and adenoma (Kozaka et al., 1982). Cancer of the gallbladder is also reported more frequent in the presence of congenital biliary dilation (Kozaka et al., 1982). In the present study, these conditions were not observed.
Most gallbladder carcinomas are adenocarcinoma. It was reported that adenocarcinoma comprises 82% of cases and may be cirrhotic, papillary, or mucin-producing. Undifferentiated carcinoma occurs in 7% and squamous cell occurs in 3%. The latter is believed to arise from pluripotential cells in the basal layers of the epithelium. Mixed carcinoma, or adeno-akanthoma, comprises 1%. Unusual tumors include lymphosarcoma, rhabdomyosarcoma, reticulum cell sarcoma, fibrosarcoma, melanoma, carcinoid, and carcinosarcoma (Strauch, 1960). In this study, only 4 types of cancer were found. Adenocarcinoma comprised 93% of the cases. This rate is higher than some previous studies. No unusual tumors such as sarcomas were identified in this study.

Preoperative diagnosis of gallbladder cancer is very difficult because the symptoms of carcinoma of the gallbladder are not specific. It was reported that pain occurs in 66%, weight loss in 59%, jaundice in 51%, anorexia in 40%, and right upper quadrant mass in 40% of patients (Solan & Jackson, 1971; Tanga & Ewing, 1970). In the present study, abdominal pain (50% of the patients) and jaundice (35% of the patients) were the two major symptoms. The clinical presentation differs depending on the stage of the disease. However, there is no distinct
pattern because the presenting symptoms and their duration are dependent on the site of the lesion, its extent, and the presence or absence of pre-existing biliary symptoms. Most patients came to the hospital because of the symptoms that were not directly related to the gallbladder cancer. In this study, 10% of the patients were diagnosed preoperatively. Some reports have much lower rate of correct preoperative diagnosis. In one recent study, no one was diagnosed preoperatively (Bosset et al., 1989). Although the correct preoperative diagnosis is made infrequently, certain combinations of signs and symptoms should arouse suspicion. These include an elderly female with biliary complaints presenting with a change in frequency or severity of pain, right upper quadrant mass or hepatomegaly, and constitutional symptoms of malignant disease.

Carcinoma of the gallbladder usually is associated with a poor prognosis. It was reported that about 88% of the patients died within a year of diagnosis and only 4% were alive after 5 years in a review of nearly 6,000 patients (Piehler & Crichlow, 1978). In our study, the one-year survival rate was 16% which is higher than previous reports. Recently, surgeons argue the extent of surgical resection indicated for patients with gallbladder
cancer. Aggressive surgery for cancer of the gallbladder is reported to improve survival. Isolated instances of extended survival following radical surgical resection were reported as early as the 1930's (Booher & Pack, 1949; Finsterer, 1932). Carcinoma of the gallbladder spreads by several routes: lymphatic, vascular, intraperitoneal seeding, neural, intraductal and direct extension. All four major types of tumors (adenocarcinoma, undifferentiated, squamous, and mixed) appear to spread in a similar manner. In 1963, a clinicopathologic study defined the modes of spread of gallbladder carcinoma (Fahim et al., 1962). The incidence of spread was: hepatic 34%, neural 24%, venous 13%, and intraductal 4%. Nonetheless, some surgeons extend radical resection to include possible metastatic sites because a few reports have described long-term survival in patients with disseminated disease who have undergone extended resection (Donohoe et al., 1990; Tsunoda et al., 1987), although operative morbidity and mortality rates are increased with extended resection (Ogura et al., 1991). In patients studied here, no difference existed in terms of survival rates between patients undergoing simple cholecystectomy and those undergoing cholecystectomy with hepatic wedge resection.
The extent of radical resection ranged from cholecystectomy with hepatic wedge resection to cholecystectomy, lymphadenectomy, extended right hepatectomy and pancreatoduodenectomy. Survival rates of patients undergoing radical resection frequently represent a subset of patients who are considered appropriate for resection. The majority have Nevin stage I, II, or III disease. Patients with gallbladder cancer with Nevin stage I or II disease have a 64% 5-year survival rate and a 44% 10-year survival rate after simple cholecystectomy. Patients with Nevin stage III disease have a 30% 1-year survival rate (Bergdahl, 1980). Overall 5-year survival rates for patients with gallbladder carcinoma are less than 5%. Operative morbidity rates in extended surgical resection reach 54%, and operative mortality rates are as high as 5.4% (Bergdahl, 1980; Jones, 1990). Some other papers reported that direct comparisons between radical procedures and simple cholecystectomy did not disclose a statistically significant difference in survival rate among patients with Nevin stage I, II, or III disease. Although the number of our patients was small, there was no difference between patients with Nevin stage IV or V disease in comparisons of surgery by cholecystectomy alone and of cholecystectomy with hepatic wedge resection. The
findings reported by the Mayo Clinic indicated that there were no differences in survival with hepatic wedge resection in the treatment of patients with Nevin stage I, II, or III disease (Donohoe et al., 1990). There are, however, isolated reports of patients with Nevin stage IV or V disease who have undergone curative resection and have achieved extended long survival. Statistical evidence fails to support any value of radical liver surgery for the relief or cure of gallbladder cancer, except occasionally to permit removal of a gallbladder for palliation.

Although the effectiveness of chemotherapy and radiation therapy in gallbladder carcinoma is generally poor (Jones, 1990), some reports state that adjuvant postoperative external irradiation have positive results. In a recent study, seven patients received postoperative external-beam irradiation (XRT) after apparent complete removal of gallbladder carcinoma (Bosset et al., 1989). The minimum follow-up was 5 months and the maximum was 58 months in the study. Five of the seven patients were alive with no evidence of disease after 5, 9, 11, 31 and 58 months, respectively. ¹⁹²Iridium wire in combination with external beam radiation and chemotherapy are reported effective in providing a good remission, if not cure
(Jones, 1990). In our study, patients with postoperative chemotherapy had statistically better survival than those without chemotherapy (figure 7). Radiation therapy postoperatively did not show any effect on patient survival.

Care must be taken when generalizing the results of this study because there exist several unavoidable limitations. Readers should keep in mind that this is only a preliminary study and furthur study is necessary. First and most importantly, the five surgical procedures were not randomly performed on the study subjects. In another words, this is not a clinical trial. A clinical trial is the most definitive tool for evaluation of the applicability of clinical research. Selection of the surgical procedures by the surgeons and the patients may introduce a bias to the study results. Second, there was low statistical power due to the relatively small number of patients in this study. Especially when the number of subpopulations increases, this problem becomes more serious. In this study, there were only 6 patients who underwent cholecystectomy plus hepatic wedge resection. Third, data abstracted from patient records may be prone to information bias. Information in patients’ records may be recorded by different nurses, residents and physicians.
Incorrect information is not an uncommon phenomenon. Fourth, this study was based on surgeries performed between 1960 to 1989. During this long period of time, the diagnosis criteria for gallbladder cancer may change and the precision of the microscope used by the pathologist for diagnosis of the cancer may improved. Misclassification bias may be generated from these changes. A clinical trial should be conducted in the future to obtain definitive comparison of the study procedures.

In conclusion, at this hospital, radical surgery for gallbladder cancer does not extend survival as compared with the results of simple or palliative surgical procedures. This finding supports the therapy plan as simple cholecystectomy with postoperative chemotherapy for patients with Nevin stage I, II or III disease and cholecystectomy with an accompanying bypass procedure when possible, for more extended disease.
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Chapter III.
Open Cholecystectomy versus
Laparoscopic Cholecystectomy
For Gallstone Disease

Introduction

Epidemiology of the disease

Gallstone disease is a major health problem in the United States and in most western countries. Approximately 15 to 20% of adults in the United States have gallstones (McSherry et al., 1985). The incidence of cholelithiasis in the United States is reported to be 10% in the general population (Bennion & Crundy, 1978; Brett & Baher, 1976), and it increases steadily with age.

Types of the gallstones

Approximately 10% of stones are cholesterol stones, 15% are pigment stones, and the remaining 75% are mixed stones (Holzbach, 1989). Most of the mixed stones consist mainly of cholesterol.

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Other constituents include calcium salts, bilirubin and trace amount of fatty acid, phospholipid, bile acid and glycoproteins. Crystallography confirms that the cholesterol is in monohydrate and anhydrous forms and is the major constituent, with calcium carbonate and phosphate, palmitate and amorphous materials also identified (Cowei et al., 1973; Sutor & Wooley, 1971). The nature of the nucleus of the stone is uncertain, pigment, glycoprotein and amorphous material have all been suggested.

The formation of gallstones is complex. All gallstones form as a result of biliary solids precipitating out of solution. Cholesterol stones are large, smooth, and multiple. The solubility of cholesterol in bile depends on the concentration of bile salts, lecithin, and cholesterol. Lecithin and cholesterol are insoluble in aqueous solution, but dissolve in bile salt-lecithin micelles. Failure by the liver to maintain a micellar liquid can be caused by an increase in the concentration of bile salts or lecithin; either can result in cholesterol stone formation. Conversely, increasing the biliary concentration of lecithin and bile salts should hinder cholesterol stone formation. This theory has been
investigated in the treatment of patients with cholesterol stones and prophylactically in patients with a predisposition to stone formation. Pure pigment stones are smooth and are green or black in color; they are associated with hemolytic disorders such as sickle cell anemia or spherocytosis. Calcium bilirubinate stones are associated with infection or inflammation of the biliary tree. Infection results in an increase in biliary calcium as well as an increase in β-glucuronidase (which convert conjugated bilirubin to the unconjugated form). The calcium binds to the unconjugated bilirubin and precipitates to form calcium bilirubinate stones. Normal bile contains glucaro-1,4-cactone, which inhibits the conversion of conjugated to unconjugated bilirubin and thus deters calcium bilirubinate stone formation. In the western world, most stones (70%) are made up of all three elements (cholesterol, bilirubin, and calcium) with cholesterol as the major component. The gallbladder is important in providing nuclei for stone formation and acting as a reservoir allowing growth of the stone. Infection in the gallbladder provides nuclei for stones and alters the chemical composition of the bile favoring precipitation.
Although gallstones, both cholesterol and pigment types are reported in children (Forester, 1950; Hay, 1966). There is a steady increase in gallstone prevalence with advancing year. The presentation is usually in the 50s and 60s (Torvik & Hoivik, 1960).

Cholesterol-rich gallstones are more common in women than in men. This is supported by autopsy findings (Torvik & Hoivik, 1960) and clinical experience (Holland & Heaton, 1972). This female predominance is particularly so before the age of 50 (Bouchier, 1971). The incidence is higher in multiparous than nulliparous women. Surveys of patients on long-term oral contraceptives have shown a two-fold increased incidence of gallstone over controls (Boston Collaborative Drug Surveillance Program, 1973). A further study of post-menopausal women taking estrogen-containing drugs has shown a highly significant increase in gall-bladder disease (Boston Collaborative Drug Surveillance Program, 1974). These findings are presumably related to the mildly cholestatic effect of estrogens with reduction of hepatic bile-acid secretion and the production of more lithogenic bile (Persemlidis et al., 1973). Obesity seems to be more common among gallstone sufferers than
in the general population. The reason for that is not clear. A high calorie diet and obesity have been associated with more cholesterol in bile (Sarles et al., 1971). The high concentration of cholesterol in bile increases the incidence of gallstone formation. The prevalence of the gallstone disease differs geographically (Heaton, 1973). The population with the highest known prevalence is American Indians. This seems to be related to supersaturation of the bile with cholesterol with consequent reduction of the circulating bile-salt pool (Thistle & Schoenfield, 1971; Vlahcevic et al., 1972). Gallstones are very frequent in the United States, United Kingdom, France, Germany, and Sweden. They are uncommon in oriental counties and if present tend to be associated with infestations of the biliary tract with parasites such as clonorchis sinensis or ascaris lumbricoides. Africans are largely free of cholelithiasis. Disease or factors which reduce the bile-acid pool increase the risk of gallstone formation. Ileal resection breaks the enterohepatic circulation of bile salts and reduces the total bile-salt pool. It is associated with a high incidence of gallstones (Beaton & Read, 1969). Patients on long-term cholestyramine therapy, who lose
bile acids with the feces, have a reduced bile-acid pool and an increased incidence of gallstones. Cholesterol-lowering diets seems to be associated with gallstones. In a study from the Veterans Administration in Los Angeles, autopsied men who ate a diet high in unsaturated fat and plant sterol, and low in saturated fat and cholesterol, had a 34% incidence of gallstones compared with 14% incidence of gallstones in control subjects (Sturdevant et al., 1973). There is a strong association of cirrhosis of the liver with gallstone (Nicholas et al., 1972). In one study, 30% of patients with cirrhosis had gallstones (Bouchier, 1969). Although the bile-acid excretion is reduced in cirrhosis, the gallstones are usually pigment stones. Several reports (Messing et al., 1983; Roslyn et al., 1983) documented an increased incidence of gallstones among both children and adults maintained on long-term TPN. Messing (Messing et al., 1983) using ultrasound found sludge formation in the gallbladder of 50% of patients after 4-6 weeks of therapy and gallstone formation in 6 of 14 patients who developed gallbladder sludge. Gallbladder stasis caused by long-term TPN use also results in pigment sludge and stone formation (Doty et al., 1984, 1985; Pitt et al., 1983a,b; Roslyn
et al., 1983). Cholescintigraphic and ultrasound studies in animal models and human beings suggest that a key pathogenic mechanism for the origin of biliary sludge and stone formation is prolonged stasis in the gallbladder.

The clinical findings of gallstones are different. The patients may have a variety of symptoms such as mild right upper quadrant abdominal or right scapular pain following a fatty meal or severe, crampy abdominal pain with nausea, vomiting, and other systemic symptoms. Normally, stones in the gallbladder are symptomless (silent gallstones) unless they migrate into the neck of the gallbladder or into the cystic or common bile ducts. Migration of the stones to the neck of the gallbladder or cystic duct cause obstruction of the cystic duct resulting in chemical irritation of the gallbladder mucosa by the retained bile, and this is succeeded by bacterial invasion. According to the severity of the changes, acute or chronic cholecystitis results. Acute cholecystitis may gradually subside or progress to acute gangrene and perforation of the gallbladder or to empyema. If it subsides spontaneously, chronic inflammatory changes persist with subsequent acute exacerbations.
**Diagnosis of gallstone**

Physical examination may reveal tenderness or guarding in the right upper quadrant or a mass in that area. An elevated temperature suggests infection of the gallbladder. Only about 10% of gallstones are radio-opaque, compared with 90% of renal calculi. Visualization is due to the calcium content of the stone. Thus pure cholesterol or bilirubin gallstones are non-opaque, whereas mixed stones may or may not have sufficient calcium to be rendered visible. Abdominal ultrasound is the best method of demonstrating biliary calculi. The technique identifies abnormalities with a 95% to 98% accuracy. The procedure requires the ingestion of iopanoic acid tablets on the evening before the study. Real-time ultrasonography has a 90% to 93% accuracy in identifying calculi, but is limited in detecting large stones. CT scanning is expensive, but delineates dilated ducts as well as retroperitoneal lymphadenopathy and lesions of the pancreatic head, the liver or the stomach. Percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) are useful in the evaluation of the jaundiced patients. Intravenous
cholangiography was performed in the past for gallstone disease but is no longer used. Laboratory study might help to evaluate gallstone patients. Elevation of amylase levels suggests an associated pancreatitis secondary to spasm of the sphincter of Oddi or passage of common bile duct stones. An elevated white blood cell count suggests infection.

Gallstones traversing the common bile duct may pass unevenfully into the duodenum, or remain clinically silent in the duct, but usually result in partial obstruction of the common bile duct with intermittent obstructive jaundice. Infection behind the obstruction is common, with consequent cholangitis, and may ascend to the liver, giving rise to abscesses.

Treatment of gallstone

Treatment for gallstones can be classified as either nonsurgical or surgical. Nonsurgical treatments include oral dissolution therapy, lithotripsy and cholecystolitholysis. In 1936 the American Surgeon Rewbridge described the successful dissolution of gallbladder stones by oral administration of bile acids in two of five patients (Rewbridge, 1936). Since then two agents have been established as effective for
gallstone dissolution when taken orally: Chenodiol (chenodeoxycholic acid; Chenix) and Ursodiol (ursodeoxycholic acid; Actigall). The total bile-salt pool is reduced in patients harboring gallstones. Attempts at expansion and increasing the bile-salt concentration in the bile might therefore be of use in dissolving gallstones. Chenodeoxycholic acid causes the fasting duodenal bile to become unsaturated. Cholesterol crystals disappear and chenodeoxycholic acid becomes the predominant bile acid (Thistle & Hofmann, 1973). Chenodeoxycholic acid pool increases 2-6 times while the cholic and deoxycholic pools decrease, so that the total of bile-acid pool is raised only 2 times (Danzinger et al., 1973). A major effect may be on decreasing cholesterol output in bile (Northfield & Hofmann, 1973). Chenodeoxycholic acid may have a specific effect on lithogenicity apart from the expansion of the total bile-acid pool. At present, the indications for dissolution therapy are unclear. Patients with mildly symptomatic, small floating stones who are at increased surgical risk or who refuse surgery are the primary candidates for this treatment.

More recent dissolution therapy is the application of topical dissolving agents. The most effective
agent, methyl tert-butyl ether (MTBE), has a high solvent capacity for cholesterol (14g/dl). MTBE causes only very slight tissue damage in man and in dogs when instilled strictly into the gallbladder (Allen et al., 1985), but if MTBE enters the circulation, it may cause hemolysis and pulmonary complications (Soehendra et al., 1990). Although 20 to 30% of patients with symptomatic gallbladder stones may be suitable for MTBE (Leuschner et al., 1991), MTBE-dissolution of gallstone is still under investigation and not an approved treatment in the United States (Allen et al., 1985).

The efficacy of Extracorporeal Shock Wave Lithotripsy (ESWL) has been accepted for the management of renal stones and has most recently been applied to the treatment of gallstones. Although it is not approved by the FDA in the United States, ESWL is available for the treatment of gallstones in other countries. Gallstones, like kidney stones, can be fragmented with this technique. Lithotripsy has two major objectives: first, to facilitate stone dissolution (Sauerbruch, 1984), especially in the case of stones larger than 1 cm in diameter, for which the efficacy of bile acid dissolution therapy is very low; and second, to allow spontaneous passage of fragments
into the intestine (Greiner et al., 1990). Adjuvant bile acids can be used following lithotripsy for dissolution of stone fragments. Complications include biliary colic, cutaneous petechiae, gross hematuria, and pancreatitis.

Because all forms of treatment in which the gallbladder remains in situ share the major drawback of stone recurrence, cholecystectomy remains the main treatment of choice for patients with symptomatic gallstones. As Langenbuch expressed in the 1890s, "The gallbladder should be removed, not because it contains stones, but because it forms them" (Halpert & Langenbuch, 1932). The benefit of cholecystectomy is that cholelithiasis is permanently cured. It is also the best treatment for the majority of patients with complicated cholelithiasis. In elective cases, the mortality of cholecystectomy is under 1% and deaths are usually due to unexpected events such as a myocardial infarct, pulmonary embolism or anesthetic complications (McSherry, 1989). In patients under 50 years of age, elective cholecystectomy has an operative mortality of 0.1% (McSherry, 1989). As the age of the patients increases, the mortality increases. A recent review reported a mortality of 1.1% in patients with an
average age of 72 years (Pigott & Williams, 1988). Complications occur in about 10% of cholecystectomy patients. Usually, the complications are minor, such as atelectasis, wound infection or a transient fever. More serious complications such as bile duct injury are very uncommon (Henry & Carey, 1983). The average length of hospital stay was 3-4 days (Jordan, 1991).

Laparoscopic cholecystectomy originated in South America and France in 1988. In this procedure, the diseased gallbladder is removed by means of instruments introduced through cannulas; vision of the operative field is maintained by use of a high resolution television camera -- monitor system (video laparoscope). General or epidural anesthesia can be used; after bladder and stomach decompression, a pneumoperitoneum is produced by way of periumbilical needle puncture and insufflation of carbon dioxide. A cannula is then inserted in place of the needle to provide and maintain insufflation adequate for surgery. The video laparoscope is inserted through the cannula and, under direct vision, three additional trocars or cannulas are inserted for placement and control of the instruments used to dissect the gallbladder. Intrahepatic cholangiograms may be selectively done.
The cystic duct and cystic artery are identified and clamped; the gallbladder is dissected by means of electro surgical or laser devices. The video laparoscope is then moved to an upper midline abdominal position to allow visualization of gallbladder removal through the periumbilical cannula by means of claw forceps or extractor.

Laparoscopic cholecystectomy has rapidly become a popular method for removing the gallbladder in the United States and abroad. In the last decade, advances in endoscopic equipment have allowed the development of endoscopic surgical treatment for various gynecologic disease (Semmm, 1977). In 1988, Reddick and Olsen (Reddick & Olsen, 1990) began to advocate the utility of laparoscopic removal of the gallbladder. Laparoscopic cholecystectomy is particularly suitable for patients with non-complicated gallstones who are not obese. The technique for laparoscopic cholecystectomy is quite similar to open cholecystectomy, although there are slight differences in performance. The most important advantage of laparoscopic cholecystectomy is minimization of trauma. Postoperative pain is usually reduced, and patients can be discharged earlier, resuming full activity within a
few days (Dubois et al., 1990). Although, some studies reported above findings, relatively few data on the results of the procedure have been published.

**Purposes of the Study**

The effects of different surgical treatments for gallstones are not clear to date. Controversies have existed for the past several years concerning whether laparoscopic cholecystectomy is better than traditional open cholecystectomy for removal of the gallbladder. The limited available data impedes the disclosure of the answer to this question. The purposes of this study were to assess the effect of laparoscopic cholecystectomy as compared to that of open cholecystectomy in terms of the length of hospital stay, surgical complications, and morbidity; and to compare the cost of these two procedures.
Methods

Design and Subjects

This was a hospital-based retrospective cohort study. The subject population of this study was from the patients undergoing elective cholecystectomy seen at the Rose Medical Center from July 1989 to June 1991. During this study period, only elective cases were scheduled for the laparoscopic technique. Therefore, the study population excluded any emergent cases of acute cholecystitis or those patients suspected of having choledocholithiasis in the preoperative period. The only absolute contraindication to laparoscopic cholecystectomy was coagulopathy. All patients were given prophylactic antibiotics.

The study population included two study groups: open and laparoscopic cholecystectomy. There were 100 laparoscopic cholecystectomies performed in the Rose Medical Center during the study period. These 100 cases were selected for the study. The charts of 100 sex-matched control patients who underwent elective open cholecystectomy in the same institute during the same period were retrospectively reviewed. The same
exclusion criteria for the selection of patients with laparoscopic cholecystectomy applied to the selection of patients with open cholecystectomy.

Data Collection and Variables

The patients' information used in this study were obtained from the medical records in the Surgical Department and the Billing Department of the Rose Medical Center. The data abstraction form was shown in Table I (page 155). All data were abstracted by a trained nurse in the Rose Medical Center.

Information regarding the patients' characteristics (such as age, sex, height, and weight), co-morbid conditions (such as cardiovascular, pulmonary, gastrointestinal, renal, endocrine, and neurologic), treatment (such as type of surgery, intraoperative cholangiography, use of surgical drains, etc.), and outcomes (such as the length of hospital stay, and surgical complications) were obtained from the medical records in the Surgical Department of the Rose Medical Center. Information regarding hospital charges were also obtained from the Billing Department of the same institute. Charges included total inpatient charges to the patients, and the cost of
treatment of any complication.

Statistical Analysis

Descriptive frequencies were calculated for all the variables that were gathered in the study. T-test, analysis of covariance and multiple regression were used to compare the length of hospital stay and the hospital charges for the two surgical procedures. Chi-square and logistic regression were performed to evaluate the preoperative morbidity, procedures (such as intraoperative cholangiography and use of surgical drain), and surgical outcome (morbidity) of the two study groups. Fisher's exact test was employed when the number of events was less than 5. For both multiple regression and multiple logistic regression, backward stepwise method was used to select the final model. Cost-effective analysis for the two surgical procedures was also done. All the statistics were preformed using Epi Info version 5 and BMDP PC90.
### Table I. Data Abstraction Form

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<th>Patient Number</th>
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<tr>
<td>Age</td>
<td>Sex</td>
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<tr>
<td>Height (feet)</td>
<td>Weight (lb)</td>
</tr>
<tr>
<td>Co-Morbid Condition</td>
<td>(please specify)</td>
</tr>
</tbody>
</table>

**Treatment:**

- Surgery: open/laparoscopic (circle one)
  - Operative time: _______ minutes
- Intraoperative cholangiography: yes/no (circle)
- Use of surgical drain: yes/no
- Other (specify)______________________________

**Outcome:**

- Length of hospital stay (days)_______
- Complications (specify)______________________

**Charge (total amount of hospital charges in dollars):**

$
Results

Characteristics of the Study Population

The patients undergoing laparoscopic and open cholecystectomy were comparable with regard to age, height, and weight (Table II). The mean age was 46.00 years old (standard deviation was 13.88) with a range of 23 to 79 in the laparoscopic cholecystectomy group and 43.90 years old (standard deviation was 15.00) with a range of 17 to 88 in the open cholecystectomy group. The difference in the mean ages between these two study groups was not statistically significant. Since the two study groups were selected sex-matched, the distribution of sex in the two groups was the same. Of the 100 patients with laparoscopic cholecystectomy and 100 patients with open cholecystectomy, 21 were males and 79 were females. The mean height in laparoscopic cholecystectomy group was 63.9 inches (standard deviation was 11.87) ranged from 57 to 74 inches. While in the open cholecystectomy group, the mean height was 65.9 inches (standard deviation was 22.92) ranged from 57 to 73 inches. The difference between
the mean height did not reach a statistical significance. The mean body weights were very similar between the two study groups. The value of the mean body weight in the group of laparoscopic cholecystectomy was 158.50 pounds (standard deviation was 43.52) ranging from 95 to 267, in the group of open cholecystectomy was 152.00 pounds (standard deviation was 60.45) ranging from 97 to 350.

The patients in the open group had a higher incidence (42 patients as compared to 28 patients in the laparoscopic cholecystectomy group) of preoperative morbid conditions, but this difference did not reach statistical significance (P=0.28) by Chi-square statistics (Table III).

The mean total operative time in the open cholecystectomy group was 72 minutes with a standard error of 2 (ranged from 25 to 165) as compared to 107 minutes with a standard error of 4 (ranged from 45 to 247) in the laparoscopic cholecystectomy group (Table IV). This difference proved to be significant at the P<0.001 level by t-test. Routine intraoperative cholangiography was performed in 93% of the patients in the open group, whereas only 24% of the laparoscopic patients underwent intraoperative cholangiography.
Use of surgical drains was dictated by the attending surgeon's preference. There were significantly (P<0.001) more cases being drained in the open cholecystectomy groups (27%) as compared to that in the laparoscopic cholecystectomy group (4%) demonstrated by Fisher's exact test.

There were 7 complications in the open cholecystectomy group and 3 in the laparoscopic cholecystectomy group (Table V) and this difference was not statistically significant (P<0.40) using Fisher's exact test. One patient in the laparoscopic group underwent reoperation for a common bile duct injury requiring Roux-en-Y choledochojejunostomy. During the study period, the conversion rate of laparoscopic to open cholecystectomy was 6%. No patient died in both of the study groups.
Table II. Patient Characteristics

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<td></td>
<td>Laparoscopic</td>
<td>Open</td>
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<tr>
<td>(n=100)</td>
<td>(n=100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Mean</td>
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</tr>
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<td>S.D.</td>
<td>11.87</td>
<td>22.92</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>57-74</td>
<td>57-73</td>
<td></td>
</tr>
<tr>
<td>Weight (pounds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>158.50</td>
<td>152.00</td>
<td>0.82</td>
</tr>
<tr>
<td>S.D.</td>
<td>43.52</td>
<td>60.45</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>95-267</td>
<td>97-350</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laparoscopic</td>
<td>Open</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>7</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
<td><strong>42</strong></td>
<td></td>
</tr>
<tr>
<td><strong>P Value (Chi-square)</strong></td>
<td><strong>0.28</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table IV. Comparison of Operative Time

<table>
<thead>
<tr>
<th></th>
<th>Operative Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mean ± S.E.)*</td>
</tr>
<tr>
<td>Open</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>107 ± 4</td>
</tr>
</tbody>
</table>

*Difference was significant at the p<0.001 level.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Laparoscopic</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duct Injury</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary Embolus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clostridia Dificile Colitis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ETOH Withdrawal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

P Value (Fisher's Exact Test) 0.39
Inferential Statistical Analysis

Tables VI, VII and figure 1 show the results of post-operative in-patient days (hospital stay) and in-patient charges for the two surgical procedures analyzed by ANCOVA and stepwise multiple regression. In ANCOVA analysis, the independent variable was type of surgery (i.e. laparoscopic or open cholecystectomy), the covariates were patients' age, height, weight, pre-morbid conditions and the use of surgical drains (Table VI). The variables in the final model of the multiple linear regression (Table VII) were surgery and age of the patients for the dependent variable of length of hospital stay. For the dependent variable of hospital charge, the final multivariate linear regression model contained surgery, age and height of the patients (Table VII). Both of the final models of the multivariate linear regression were selected by backward stepwise method.

As shown in Table VI, laparoscopic cholecystectomy had significantly fewer (about 3 days, P<0.002) post-operative in-patient days and significantly less (about $2,000, P<0.001) in-patient charges than open cholecystectomy. These results were controlled by the patient's age, height and weight, pre-morbid conditions
and the use of surgical drains. The covariates of age and height were significant for hospital stay (\(P=0.000\) and \(P=0.001\), respectively), and age, height and weight were significant for cost (\(P=0.000\), \(P=0.000\) and \(P=0.029\), respectively).

The results of backward stepwise multiple regression were comparable to that of ANCOVA (Table VII). The dependent variables for the multiple regression were length of hospital stay and hospital charge. Therefore, there were two final models of multiple regression analyses. The initial models included variables of patients' age, height, weight, pre-morbid conditions, surgical procedure, intraoperative cholangiography, and use of surgical drains. The variables containing in the final model were age of the patients and surgical procedure for the dependent variable of hospital stay, and age and height of the patients and surgical procedure for the dependent variable of cost. For the model with hospital stay as the dependent variable, the coefficients for age was 0.0356 with a 95\% confidence interval of 0.021 to 0.050, and for surgical procedure (code as 0 for open cholecystectomy and 1 for laparoscopic cholecystectomy) was -3.19 with a 95\%
confidence interval of -3.61 to -2.76. For the model with charge as the dependent variable, the coefficients for age was 45 with a 95% confidence interval of 21 to 69, for height was -23 with a 95% confidence interval of -42 to -4.6, and for surgical procedure was -2245 with a 95% confidence interval of -2945 to -1545.

For the outcome of surgical complications, univariate and multivariate logistic regressions were performed. The dependent variable of surgical complications (morbidity) was categorized at two levels as with or without any surgical complication. Each complication was counted as one event. The logistic regression analysis was performed with low power because there were only 10 events (3 in laparoscopic cholecystectomy group and 7 in open cholecystectomy group). Therefore, only results from univariate logistic analysis with independent variable of surgical procedure, the primary interest factor of this study, was reported (Table VIII). In the multivariate logistic analysis, variables entered initially included patients' age, height, weight, pre-morbid conditions, surgical procedure, intraoperative cholangiography, and use of surgical drains. These variables underwent backward stepwise selection with the criteria P value
of 0.20 for removal and reentering. The final model contained patients' age, height and weight, and surgical procedure.

As compared to open cholecystectomy, in the univariate logistic model (Table VIII), the odds ratio for patients with laparoscopic cholecystectomy to develop surgical complications was 0.81 with a 95% confidence interval of 0.29 to 2.09. In the multivariate logistic model, the odds ratios were 0.44 (95% confidence interval 0.087 to 2.20) for patients with laparoscopic cholecystectomy compared to those with open cholecystectomy (Figure 2), 2.05 (95% confidence interval 1.20 to 3.52) for a patients with a ten-year increase in age, and 2.55 (95% confidence interval 0.76 to 8.60) for a patient with a five-inch increase in height.
### Table VI. ANCOVA Results

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Hospital Stay (days)</th>
<th>Charge ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>4.82</td>
<td>8895.98</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>1.64</td>
<td>6471.18</td>
</tr>
<tr>
<td>(p)</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Covariates (p values)**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Height</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>Weight</td>
<td>0.229</td>
<td>0.029</td>
</tr>
<tr>
<td>Pre-Morbid</td>
<td>0.320</td>
<td>0.178</td>
</tr>
<tr>
<td>Drain</td>
<td>0.192</td>
<td>0.085</td>
</tr>
</tbody>
</table>
Table VII. Results of Backward Stepwise Multiple Regression

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Constant</th>
<th>R-sq</th>
<th>F Value</th>
<th>Coeff.</th>
<th>95% C.I. Lower</th>
<th>95% C.I. Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1. Dependent Variable = Hospital Stay</td>
<td>3.1872</td>
<td>0.1825</td>
<td>121.22</td>
<td>-3.185</td>
<td>-3.606</td>
<td>-2.764</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2. Dependent Variable = Cost</td>
<td>8157</td>
<td>0.2578</td>
<td>22.69</td>
<td>-2245</td>
<td>-2945</td>
<td>-1545</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-23</td>
<td>-42</td>
</tr>
</tbody>
</table>
Table VIII. Results of Univariate Logistic Regression

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Constant</th>
<th>Coeff.</th>
<th>Exp(Coeff)</th>
<th>95% C.I.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Dependent Variable = Morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>-4.760</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td></td>
<td></td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>-.210</td>
<td></td>
<td>0.810</td>
<td>0.293</td>
<td>2.09</td>
</tr>
</tbody>
</table>


### Table IX. Results of Multivariate Logistic Regression (Backward Stepwise Selection for the Final Model)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Dependent Variable: Morbidity</th>
<th>Exp(Coef)</th>
<th>95% C.I. Lower</th>
<th>95% C.I. Upper</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Open</td>
<td>1.00 (ref.)</td>
<td>0.0873</td>
<td>2.20</td>
<td>0.3034</td>
</tr>
<tr>
<td></td>
<td>Laparoscopic</td>
<td>0.8257</td>
<td>0.07192</td>
<td>1.13</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>1.07</td>
<td>0.944</td>
<td>1.21</td>
<td>0.1126</td>
</tr>
</tbody>
</table>
Figure 1. ANCOVA results of post-operative in-patient days (hospital stay) and in-patient charges for the two surgical procedures.
Relative Risk by Surgery

Figure 2. Results of multiple logistic regression
Discussion

The high incidence of gallstone disease (10% in the general population annually (Bennion & Crundy, 1978; Brett & Beher, 1976)) makes the expenditure for the care of this disease a significant portion of the health care cost (National Inpatient Profile, 1989). The traditional method of treatment has been total removal of the gallbladder via an open laparotomy. This therapeutic modality has led to a high actual therapy cost and significant loss of productivity due to prolonged periods of convalescence. Several nonoperative modalities have been proposed as alternatives (Allen et al., 1985; Ell et al., 1986; Inui et al., 1988; Sackmann et al., 1988; Ghany et al., 1989), however, the gallbladder remains intact, leading to high rates of recurrence of cholelithiasis and biliary tract symptoms. The newly developed laparoscopic cholecystectomy has shed some light on this problem, and rapidly become widely accepted as the preferred method of gallbladder removal in many centers (Reddick & Olsen, 1989; Dubois et al., 1990; Schirmer et al., 1991). Its safety and efficacy have been reported (Peters et al., 1991). However, the exact
effects of the laparoscopic cholecystectomy on the outcomes of patients with gallstone disease in terms of surgical complications and length of hospital stay as compared to open cholecystectomy have not been clear. The data on cost-effectiveness of laparoscopic cholecystectomy has been scanty. This lack of information on the effects and cost-effectiveness of laparoscopic cholecystectomy led to the conduction of the present study.

The Study Design

This study used a retrospective cohort design. Cohort designs often are used to study relatively frequent occurrences, such as gallstone disease in this study. The major advantage of the retrospective design is the completion of the study in a relatively short period of time and is therefore considerably less expenses. Additionally, the availability and relative completeness of the patient information made the present study feasible.

The best way to determine the effect of a new treatment method as compared to a traditional treatment method is a clinical experiment -- clinical trial. The high cost of clinical trials often prevents them being
the first choice for treatment comparison studies, especially in small institution. In addition, the mortality of open cholecystectomy is very small, under 1% in selective cases (McSherry, 1989) and 1.1% in patients with an average age of 72 years (Pigott & Williams, 1988). Complications occur in about 10% of patients with open cholecystectomy. Since the morbidity and mortality of open cholecystectomy is small, a large sample size would be needed to conduct treatment comparison studies, increasing the cost of such studies. Furthermore, it is almost impossible to perform a randomized clinical trial to compare the two surgical procedures.

The Study Method

During the initial experience with laparoscopic cholecystectomy, only elective, uncomplicated cases were being performed using this technique at the Rose Medical Center. Patients with acute cholecystitis, or those suspected of having choledocholithiasis preoperatively, were treated in the traditional manner by open cholecystectomy. To keep the two groups comparable, these complicated cases were excluded from the open cholecystectomy group.
Autopsy findings (Torvik & Hoivik, 1960) and clinical experience (Holland & Heaton, 1972) indicate that cholesterol-rich gallstones are common in women as compared to men. This phenomenon of female predominance may relate to the mildly cholestatic effect of estrogens with reduction of hepatic bile-acid secretion and the production of more lithogenic bile (Persemlidis et al., 1973). The formation of gallstones may be associated with obesity and high calorie diet (Sarles et al., 1971). Therefore, socioeconomic factors may play a role in the development of gallstones. The sex-matching of the control group (open cholecystectomy) to the study group (laparoscopic cholecystectomy) eliminated the possible confounding effect of gender on the surgical complication and length of hospital stay. The selection of the study subjects within the Rose Medical Center removed, at least in part, the difficult to measure effects of socioeconomic factors because people seeking medical care at the same hospital usually have similar socioeconomic status.

The data abstraction by a trained research nurse from the medical records in the Surgical Department of the Rose Medical Center ensured the quality of medical
information used in this study. As indicated by Kelsey and associates (1986), hospital data are most appropriate for the study of diseases that are traditionally treated in hospitals. Additionally, the relative current years and short duration of the study period (from July 1989 to June 1991) kept the diagnostic variability to its minimum. On the other hand, some of the medical records were incomplete, and the information used in this study may be unstandardized from physician to physician within the Medical Center.

The hospital charges for the surgical procedures included in the study may vary during this 3-year study period, although surgeon's fees in the same hospital should be very similar. The difference in charges for anesthesia between laparoscopic and open cholecystectomy is expected to be similar since the laparoscopic procedure only requires 30 minutes of increased operative time.

In the entire study period, there was no mortality in either of the study groups. Therefore, surgical outcomes of this study were morbidity (postoperative complications) and length of hospital stay. As mentioned above, the morbidity of open cholecystectomy
is very low. In this study, the complication rate was only 3% in laparoscopic cholecystectomy group and 7% in open cholecystectomy group. The small number of events led to the problem of low power in the logistic regression analyses though the analyses were performed to fulfill the main purpose of this study.

Comparison of the Results of the Two Procedures

The results of this study reaffirm the safety of laparoscopic cholecystectomy in comparison to open cholecystectomy. Complications were defined as those requiring active treatment or prolonged hospitalization, as this definition includes all those occurrences which led to increased costs. Seven complications occurred in the open group as compared to three in the laparoscopic group. One patient in the laparoscopic group required reoperation for treatment of a common bile duct injury. There was no mortality in this population during the entire study period.

The operating time was significantly longer for the laparoscopic group (107 versus 72 minutes). This difference in the duration of operation reflects the learning curve of both experienced surgeons and senior residents. With further experience, the mean operating
time for laparoscopic cholecystectomy should decrease to a more comparable level but will probably never equal that of open cholecystectomy. Although the increased time in the operating room certainly led to higher charges, the overall charges to the patient were reduced by 27% in the laparoscopic group. This reduction is largely due to the decrease in the length of hospitalization from a mean of 4.8 to 1.6 days. Although this study did not specifically address the period of convalescence, open cholecystectomy has usually been followed by a 5 to 6 week period of recovery. The experience of this institute has shown that following laparoscopic cholecystectomy, the patient is able to return to work within 1 week. Therefore, it is expected that laparoscopic cholecystectomy will have an even greater economic impact than just the reduced hospital costs.

Limitations and Further Study

The results of this study provided some valuable information comparing laparoscopic cholecystectomy to open cholecystectomy. However, like every retrospective study, there exist limitations.

As mentioned before, the most definitive tool for
evaluation of the applicability of clinical research is clinical trial. The retrospective cohort design of this study provides some important comparative indications, not definitive conclusions.

The two surgical procedures involved in this study were performed by several surgeons with several anesthesiologists of the Rose Medical Center. Therefore, charges may differ from physician to physician, and complication rate of surgery may also vary from physician to physician. The duration of the study lasted for 3 years, and temporal changes in hospital charges may also exist.

The small number of surgical complications in this study indicates the possibility of bias. Results generated from this study may be distorted due to the problem of low statistical power accompanying small number of the events.

A prospective cohort design is needed to more precisely answer the question of whether laparoscopic cholecystectomy is better than traditional open cholecystectomy for removal of the gallbladder. There are two reasons for choosing prospective cohort study for further comparison of these tow surgical procedures. First, clinical trials are difficult, if
not completely impossible, to conduct for reasons aforementioned. Second, a prospective cohort study is the type of observational design that most closely resembles an experiment -- clinical trial. Major limitations with prospective cohort study are its large sample size and high cost. However, the results of this retrospective study indicate that a prospective cohort study is warranted.

**Conclusion**

In conclusion, based on the results of the present study, laparoscopic cholecystectomy tend to achieve cost savings with significantly better outcomes in comparison with traditional open cholecystectomy.
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