Radical Prostatectomy Surgical Margin Status: Grace Hospital Experience 2001-2005 with Identification of a Potentially Significant Subclass

by

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A Practicum submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfilment of the requirements of the degree of

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Department of Pathology

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II. LIST OF ABBREVIATIONS

+SM	Positive surgical margins
RP	Radical prostatectomies
IP	Intraprostatic
EP	Extraprostatic
SM	Surgical margins
-SM	Negative surgical margins
-EPE	Negative extraprostatic extension
+EPE	Positive extraprostatic extension
+IP	Positive intraprostatic
+EP	Positive extraprostatic
EPE	Extraprostatic extension
PSA	Prostate specific antigen
T	Primary tumor
N	Metastasis to nearby lymph nodes

M	Distant metastasis
ACT	α-1-anti-chymotrypsin
AMG	α-2-macroglobulin
ECE+	Exracapsular extension negative
ECE-	Extracapsular extension positive
SM+	Surgical margin positive
SM-	Surgical margin negative
GH	Grace Hospital
LA	Left anterior
RA	Right anterior
LP	Left posterior
RP	Right posterior

III. ABSTRACT

Purpose: The significance of positive surgical margins (+SM) is uncertain, in radical prostatectomies (RP), largely due to lack of clarity in defining margin location (intraprostatic (IP) or extraprostatic (EP)). In this study, we have documented margin status in a large series of RP with specific attention to particular subgroups.

Materials and Methods: From October 2001 to December 2005, 467 RP were performed at the Grace Hospital. Pathology reports for all of these cases were retrieved and reviewed. Gleason Grade and pathologic stage were documented. Five subclasses of surgical margin (SM) status were documented. These included negative surgical margins (-SM) and negative extraprostatic extension (-EPE), +SM and –EPE, -SM and positive EPE (+EPE), and +SM and +EPE. The last group was specifically examined for the presence of positive IP (+IP) margins, positive EP (+EP) margins, or both.

Results: 60% of our cohort demonstrated the presence of +SM. However, of this group only 4% were +EP margins. Of patients with both +SM and +EPE, only one quarter (26%) had true +EP margins. 10% of the total cohort demonstrated EPE with +IP margins only.

Conclusions: Patients with +SM and extraprostatic extension (EPE) are considered to represent a high-risk group, adjuvant radiation therapy is often offered. The majority of patients in our institution do not have positive EP (+EP) margins and should be assessed separately in considering adjuvant therapy.

IV. INTRODUCTION

Prostate cancer is now the most frequently diagnosed cancer in North American men and the sixth most common cancer in the world (6, 15, 23). Despite its relatively low mortality rate on an individual basis, it is the second leading cause of death among carcinomas in men (23).

The incidence of prostate cancer rises significantly with age (23). Out of all patients with the diagnosis of prostate cancer, 75% are in the 60 to 80 years age range. In the past, most of these cases (70-90%) are incidental findings at the time of autopsy or if the prostate was removed for another medical reason such as prostatic hyperplasia (6). However, this statistic has changed markedly in the world since the advent of prostate specific antigen (PSA) screening (vide infra). Statistics from autopsy studies show that less than 10% of men among 40 to 50 years of age have prostate cancer and up to one-half older than 80 years of age have the disease (6).

The highest rates of prostate cancer are reported in the United States and the Scandinavian countries, with the lowest frequencies in Mexico, Greece, and Japan (6, 23). One explanation for this outcome is the high prostate cancer rate in African American men. They display a rate twice as high (70%) as that of American White men (23). Ethnic differences in incidence suggest that genetics play a role in the development of prostate cancer. Some studies have found that a diet high in animal fat may increase the risk for developing prostate cancer, while a diet high in fruits and vegetables (especially tomato-based products) may decrease the risk (26). Furthermore, migration and changes in rates with time also show that environment and lifestyle are also

important factors. Unfortunately, the environmental risk factors for the development of prostate cancer are not well understood (23).

Of all primary prostatic tumors, 98% are adenocarcinomas. Adenocarcinomas are composed of small glands that are back-to-back, with little or no intervening stroma. Cytologic features of adenocarcinoma include enlarged round, hyperchromatic nuclei that have a single prominent nucleolus. Mitotic figures suggest carcinoma. Less differentiated carcinomas have fused glands called cribriform glands, as well as solid nests or sheets of tumor cells, and many tumors have two or more of these patterns (6). Prostatic adenocarcinomas almost always arise in the periphral outer zone of the prostate and are often multifocal and usually bilateral (10).

Prostatic adenocarcinomas are usually graded according to the Gleason grading system based on the pattern of growth. There are five grades based upon the architectural patterns. Adenocarcinomas of the prostate are given two grades based on the most common and second most common architectural patterns. These two grades are added to get a final grade of 2 –10 (6, 7, 8). The stage is determined by the size and location of the cancer, whether it has invaded through the prostatic capsule or into the seminal vesicles, and whether it has metastasized. The internationally accepted staging system the (TNM system) describes the extent of the primary tumor (T), the absence or presence of metastasis to nearby lymph nodes (N), and the absence or presence of distant metastasis (M). Patients are placed in pathologic stage groupings based on TNM data. These stage groupings are used by clinicians to determine therapy and prognosis (6). TNM staging parameters are shown below. They can be determined either clinically (through the use of imaging studies) or pathologically (through examination of surgical specimens).

T - PRIMARY TUMOR	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histological finding in 5% or less of tissue resected
T1b	Tumor incidental histological finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than half of one lobe, but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends beyond the prostate
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicles
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

**Adopted from WHO 2004*

N – REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

* *Adopted from WHO 2004*

M – DISTANT METASTISIS	
MX	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other sites

**Adopted from WHO 2004*

The grade and the stage correlate well with each other and with the prognosis. The prognosis of prostatic adenocarcinoma varies widely with tumor stage and grade. Cancers with a Gleason score of six or less are generally low grade and not aggressive. Cancers with a Gleason score seven are of a moderate aggressive cancer and a score of 8-10 have a high mortality rate (> 70%) (7,23). Advanced prostatic adenocarcinomas typically cause urinary tract obstruction, metastasize to regional lymph nodes and to bones. Metastases to the lungs and liver are seen in a minority of cases.

In many cases prostate cancer has no symptoms in its early stages. Before PSA screening, the disease was usually discovered during a routine physical examination. As the disease develops, certain symptoms are more likely to appear. These symptoms include: weak or interrupted flow of urine, frequent urination (especially at night), difficulty in starting to urinate, inability to urinate, pain or burning sensation during urination, blood in the urine, continuous pain in the lower back, hips, or thighs and painful ejaculation (26). The majority of prostate cancers form in the peripheral zone, therefore transition zone enlargement causing bladder outlet obstruction is usually indicative of hyperplasia as opposed to carcinoma (23).

Before the serum PSA test became common the first step in diagnosing prostate cancer was usually a digital rectal examination. In a digital rectal examination, a doctor will place a gloved, lubricated finger into the patient's rectum and feel for any firm areas or nodules in the prostate. However, many patients with palpable prostatic masses were found to have high stage invasive prostate cancer. The situation has changed radically with introduction of wide spread use of PSA screening in North America (6).

PSA is a protein produced by prostatic epithelial cells and secreted into the prostatic ductal system. It is present in serum, predominantly in a complex with either α-1-anti-chymotrypsin (ACT) or α-2-macroglobulin (AMG), with only a small "free" component. Total PSA rises with age. Most men less than 50 years old have PSA values less than 2.5ng/ml., by age 80 the 95% cut off level is 6.5ng/ml (6).

PSA has been utilized as a screening test for cancer because most men with cancer have a high PSA. Generally a PSA level of above 4.0ng/ml will merit consideration of further investigations (including biopsy) to rule out prostate cancer. At levels greater than 10 ng/ml, most patients will have prostate cancer (6). However, PSA screening is neither sensitive nor specific for prostate cancer particularly if the arbitrary cut off is not adjusted for age (vide supra).

Many men with increased PSA do not have prostate cancer. Furthermore, a significant minority of prostate cancer occurs in men with PSA lower than 4.0ng/ml. This may be preferentially true in patients with high-grade cancer that secretes decreased PSA (6).

Various manipulations of PSA data have been utilized in order to increase the sensitivity and specificity of the test including free PSA to total PSA ratio, PSA density and PSA velocity/doubling time. Other markers are also being investigated to predict the presence of prostate cancer, but none are in wide use presently.

Once the decision to biopsy has been reached, the standard protocol is similar whether a palpable prostate lesion is present or not. Multiple prostate biopsies are performed trans-rectally using a "biopty" gun with transrectal ultrasonic localization (TRUS) (6). The current standard of practice is to perform "Double Sextant" biopsies as

well as bilateral transition zone biopsies. This usually results in 14 needle cores. However, up to 60 prostate biopsies may be performed. The use of 18 gauge biopsy needles and local anesthetic allows this procedure to be performed without general anesthetic and with minimal morbidity.

Once prostate cancer has been confirmed by biopsy, additional tests are carried out to stage the tumor particularly a bone scan to rule out metastasis to the skeleton (26).

A number of treatments are available for localized prostate cancer. The treatment chosen depends on the patient's age and general health, the stage of the tumor, the presence of other illnesses, and other factors. The two most common forms of treatment for curable prostate cancer are surgery and radiation (26).

Surgery involves the removal of the entire prostate gland and seminal vesicles. In addition, pelvic lymph nodes near the prostate are generally removed to see if nodal spread has occurred.

Radiotherapy is also used with curative intent with prostate adenocarcinoma. Radiation can be delivered either from an external source (external beam radiotherapy) or through the placement of radioactive needles into the prostate itself (Brachytherapy) (26).

For more advanced cases of prostate cancer, hormone therapy may be necessary. Prostate cells need the male hormone testosterone to grow. Therefore, one way to stop the growth of prostate cells is to reduce the amount of testosterone in the body. One solution to accomplish this is to surgically remove the patient's testicles (orchiectomy). The testicles are the organs that produce testosterone. Another means to achieve the same goal is to administer antagonists of pituitary luteinizing hormone releasing

hormone. Inhibition of luteinizing hormone release decreases testosterone production and results in pharmacological castration (23).

Traditional chemotherapy with cytotoxic agents may be used if the cancer has metastasized, particularly if the metastasis are not responding to hormone therapy. However, this therapy is usually ineffective (6).

A final form of treatment is no treatment at all. Prostate cancers sometimes develop very slowly and it may take years for it to become a serious threat to the patient's life. That fact is considered in treating older men. In many cases, the man is likely to die of other causes before prostate cancer becomes a serious concern. The patient receives regular checkups and if no major changes are found, no treatment is offered. If the tumor becomes significantly larger, one of the above forms of treatment may be used (11, 26).

The major aim of PSA screening and extensive biopsy protocols is to detect prostate adenocarcinoma at an early curable stage. Nonetheless, most men (80%) diagnosed with prostate cancer will not die of prostate cancer. Aggressive therapy will inevitably result in over treatment of many individuals (6).

Radical prostatectomy has very low mortality in experienced hand but significant morbidities including incontinence and impotence. External beam radiation has a lower incidence of these side affects (although they are not absent), with the addition of radiation proctitis and cystitis, which can be debilitating. Brachytherapy has the lowest incidence of side affects but does not have the established cure rate of radical prostatectomy (10).

With the advent of PSA screening and the development of surgical technique to preserve potentency (nerve sparing) radical prostatectomy has become a very common

treatment for prostate cancer. In healthy patients under the age of 70, radical prostatectomy is the gold standard for cure (10). It has the additive advantage of allowing detailed assessment of pathological parameters and tumor stage, which can allow an accurate estimation of patient prognosis when combined with other clinical factors in a well established patient nonogram (6,16).

When assessing a radical prostatectomy specimen grossly and microscopically, the crucial parameters are Gleason score, T status (EPE), and SM. Generally, the presence of EPE and + SM in a given case merit consideration of adjuvant (additional) therapy, classically external beam radiation or androgen ablation. This is an evolving change in practice as in the past; surgeons have not consulted radiation or medical Oncologists in the absence of a biochemical PSA recurrence.

The aim of this study is to undertake a literature review of the significance of marginal status (both IP and EP) on biochemical PSA recurrence and overall survival. Furthermore, we intend to compare a large volume local prostatectomy experience to literature norms in a wide variety of pathological parameters. Finally, we will attempt to prove a hypothesis that the majority of + SM in our patients with pT3 disease are actually IP margins and that this group should be considered separately in the analysis of pT3 margin positive adenocarcinoma.

IV.1 Literature Review

The significance of margin status after radical prostatectomy and the potential role of adjuvant radiation therapy have been examined in many studies. The definition of a +SM has varied among Pathologists. In a study performed by Zeitman *et al* (29), a +SM is defined as tumor within 1mm of the painted surgical margin. On the other hand, Epstein (7) believes that if the tumor is not at the inked surface then this should be considered a clear margin. At present, a surgical margin is considered positive when the tumor is at the inked margin and should be designated as negative even if there is only a fraction of a millimeter of uninvolved tissue between the tumor and the inked margin (7,28). The incidence of +SM has changed considerably over the past few years. Epstein (7) found that in earlier studies from 1982-1988 41% of RP have positive surgical margins, which decreased to 16% between 1994-1995. In 1999, they found the incidence of positive margins for all patients operated on by one surgeon to be 5.8% (7). A study performed by Swindle *et al* found +SM rate of 12.9%. In his literature review he noted a range of 6%-41% with a decrease in more recent series (24). The overall incidence of positive surgical margins in a 3-year trial done by Watson *et al* was 34% (28). The literature revealed a +SM range of 16%-47%. The apex was involved in 40% of the positive cases. The apex is reported as a +SM in 7%-62% of RP (28). Pettus *et al* states, "that the apex is the most common location of positive surgical margins with apical margins consisting of as many as 64% of all positive margins in some series" (19). Between 18%-58% of positive margins have been reported as posterolateral while attempting the nerve-sparing technique (28). A study by Epstein *et al* where the authors followed up 507 men who had a RP over a span of 3.9 years showed 41% had +SM. The

common sites of positive margins were apical (22%), posterior (17%), and posterolateral (14%) (9). They concluded that radical prostatectomy was an excellent source of treatment as only 8% of patients exhibited local reoccurrence (9). According to Karakiewicz *et al*, occurrence of a positive surgical margin has been reported to range from 10%-48% (14). Given the high incidence rate of +SM, intraoperative frozen section examination of marginal tissue is performed in some institutions, however, as a determined Tsuboi *et al* (27), the technique is not sensitive enough to significantly reduce the +SM rate.

Several studies indicate that +SM are significantly linked with risk of biochemical progression (19). In a study conducted by Pettus *et al*, of the 498 men tested, 400 had -SM, 28 had apex only positive margins, 13 had multiple positive margins, and 57 had nonapical isolated positive margins. Biochemical recurrence rates were 9.3%, 21.4%, 30.8 %, and 26.3%, respectively (19). It was concluded that a +SM suggests increased risk for biochemical recurrence (19). According to Pinto *et al* (20), 10%-26% of patients will ultimately develop clinical biochemical recurrences even if the tumors are pathologically organ confined. Most of the patients will experience biochemical progression expressed as an elevation in PSA (20). Of the 350 patients tested by Pinto *et al* (20), 67 had biochemical failure (19.1%), while 283 were disease free.

Many of the fore mentioned studies are flawed by failure to distinguish between IP and EP positive margins. Epstein's work in particular with Walsh (the surgeon who originated nerve sparing RP) did not refer to IP dissections. Rather, all +SM were assumed to be EP in nature. Fields in which tumor extended to the inked edge of an IP margin were "equivocal" due to prostatic "disruption"(9). Nonetheless, it became clear

when RP were widely performed at multiple institutions that the majority of positive margins are IP in nature.

Given the commonness of IP margins, an important question to address is whether IP positive margins are a negative prognostic indicator in otherwise organ-confined disease. These patients are staged as pT2+, as EPE cannot be excluded adjacent to areas of IP dissection, but have no evidence of EPE elsewhere. Barocas *et al*, state that there is no statistical difference in the likelihood of disease progression between patients with positive IP margins and those with negative margin organ-confined disease. However, the follow up in this study was very short (3 years) (2). A large-scale study by Blute *et al* (including Dr. David Bostwick) examined a large series of 2932 patients with organ-confined disease (T2). Of this group, 27% of patients had +SM (IP by definition) and they found that surgical margin status was an independent predictor of biochemical recurrence in a multivariate analysis controlling for a Gleason grade and preoperative PSA. The patients of this study with +SM had a biochemical recurrence rate of 25% versus 14% for individuals with negative margins (3). However, this study demonstrated no increase in clinical progression or death

Radical prostatectomy is currently the gold standard for the treatment of prostate adenocarcinoma. Until recently, postoperative radiation therapy was not offered until the patient suffered a PSA biochemical recurrence. The majority of patients, even in pathological high-risk groups do not suffer a biochemical recurrence. However, the role of adjuvant therapy (postoperative radiation therapy in high-risk patients) is an active area of research. The goal of Teh *et al* was to assess the impact of elective postoperative radiation therapy on PSA recurrence. In patients with +SM, their results demonstrated

that the 5 and 10 year biochemical cure rates were 90.9% and 90.9% for the elective postoperative radiotherapy group, 66.4% and 54.5% for the observation group, respectively. Median time to biochemical failure was longer in the elective postoperative radiotherapy group (88.6 months) compared to the observation group (45.5 months) (25). In this study, patients with both T2 and T3 disease were included, but the majority of patients (68%) had T3 disease. However, the nature of the positive margins was not specified. On the other hand, according to a study performed by Han *et al* (13), immediate radiation therapy did not have a major impact on survival for men with Gleason score 7 disease with +SM. Between 1982-1997, 112 men with Gleason score 7 disease and positive surgical margins that did not undergo immediate radiation therapy or hormonal therapy were studied. The median follow-up was 8 years (1-16) and 45 men were followed 10 years or more. The results showed that 5 and 10-year post-prostatectomy biochemical, local, and distant recurrence rates were 40% and 52%, 6% and 6%, 7% and 16%, respectively. For 20 men who received radiation therapy for isolated PSA elevation actuarial 5-year post-radiation biochemical recurrence-free rate was 34%. This lack of control suggested that most PSA recurrences in this group related to subclinical metastases as opposed to local disease.

The largest multi-institutional study on +SM status was carried out by a group led out of Memorial Sloan Kettering Cancer Center, with Dr. Kattan as one of the senior authors (14). This study is unique in its volume (5831 consecutive radical prostatectomy patients from 8 institutions). This group received no adjuvant therapy prior to PSA biochemical recurrence. Multiple pathological parameters were integrated into the database. From the point of margin status, four specific groups were analyzed: surgical

margin negative and extracapsular extension negative (SM- and ECE-), SM positive (SM+) and ECE negative (ECE-), SM- and ECE+, and SM+ and ECE+. In this study, the SM+ and ECE- group was that of organ-confined disease with positive IP margins. The biochemical cure rate of this group (61% at 10 years) was substantially lower than that of margin negative organ-confined disease (81% at 10 years). Furthermore, this study showed that the worst prognostic group was SM+ and ECE+ (10 year biochemical cure rate 25%). However, death rates were not examined in this study. Furthermore, even this large study failed to address the main hypothesis of the current study, mainly that a significant proportion of this poor prognostic group will be composed of +EPE patients with positive IP margins only, in an era where adjuvant radiation therapy is increasingly common in this subgroup. Pathological clarification of this subgroup is required.

IV. 2 Hypothesis and Objectives

The objective of this study is two fold. First, we plan to compare histological grade, pathologic stage, and margin status with the relevant literature. We hypothesize that our Gleason score distributions are similar to that of the recent literature and our margin positivity rate is higher than literature averages (an impression gained through personal observation of the practicum pathologist).

The second component of the hypothesis relates to the group of "Extraprostatic Extension positive and Margin positive" prostatectomy specimens. We hypothesize that the most of this group represent cases in which surgical margins are IP only. Although EPE is present (T3 disease) we hypothesize that most of these cases will have clear margins at those sites. +SM/+EPE tumors are considered a uniform group with a poor prognosis in the literature and these patients are often offered adjuvant radiation therapy. However, if a large proportion of this group demonstrates IP margins only, this subgroup should be separated out and assessed separately in ongoing trials of radiation therapy.

V. MATERIALS AND METHODS

The study population consists of 467 prostatectomies from one community hospital, accrued sequentially between 2001-2005. The prostatectomies were all processed in a standard fashion as follows: Prostatic bases and apices were amputated and sectioned in the sagittal plane. As of 2005, the apex was coned in a radial fashion. The bilateral seminal vesicles were submitted in their entirety. If no tumor was grossly visible, 4-5 histological sections were submitted per quadrant. Grossly identifiable tumors were submitted in their entirety. This protocol resulted in approximately 75% submission of the entire specimen on average. The organ was painted with India (black) ink on its exterior surface prior to sectioning. A single experienced Pathologists' Assistant grossed the vast majority of radical prostatectomy specimens. Gross tumor could be identified in approximately 75% of RP. Four urological surgeons performed the surgeries. One surgeon performed approximately 60% of the total procedures.

Each specimen was signed out by one of two experienced Pathologists using similar diagnostic criteria. EPE was defined as tumor identified in the periprostatic fat (whether or not associated with nerves). A +SM was defined by the presence of malignant glands at black ink, and a +IP margin was defined as malignant glands at black ink within the prostate (unassociated with fatty infiltration). A +EP margin was defined as malignant glands at an EP margin. Lymph nodes from pelvic dissections were submitted in their entirety. As a rule perinodal fatty tissue was not submitted. Gleason scoring was assigned following current standard of practice.

The following data elements were entered into an Excel database for each radical prostatectomy specimen:

-Tissue number

-Surgeon

-Pathologist

-Gleason score

-Dominant tumor size

-Dominant tumor location

-+/- EPE

-Site of EPE

-+/- SM

-Site of +SM

-Nature of margins (IP, EPE)

-Lymph nodes (+/-)

-Seminal vesicles (+/-)

VI. RESULTS

VI. 1 Gleason Score Distribution (Table 1)

Within our study population, Gleason score was split into 3 groups, as per current practice. Tumors with a score 6 and below were considered to be low-grade, and tumors with Gleason score 8-10 were considered high-grade. Gleason scores of 7 were a separate category of intermediate grade tumors. No attempt was made to separate Gleason score 7 tumors into 3+4=7 and 4+3=7. 34% of tumors were Gleason score 6 or below, and of these, only 1% were score 5 and none were score 4 (data not shown). As a rule, Grace Hospital (GH) pathologists do not assign a pattern 2 designation to radical prostatectomy specimens. 56% of tumors were Gleason score 7 and 9% were score 8-10.

VI. 2 Pathological Stage Distribution (Table 2)

Tumors were organ-confined (limited to the prostate) in 81% of cases. In 19% of cases established EPE was present. No attempt was made to quantify the degree of EPE (focal versus extensive). 7.5% of patients demonstrated positive seminal vesicle invasion, and 2.6% demonstrated the presence of positive lymph nodes.

VI. 3 Surgical Margin Status (Table 3)

40% of the total specimens demonstrated the presence of –SM (IP or EP). 60% demonstrated the presence of +SM (IP or EP). 56% of the specimens demonstrated +IP margins and 4% demonstrated +EP margins. Of all cases with +SM, only 6.5% demonstrated +EP margins.

VI. 4 Sites of +SM, EPE and +EP Margins (Tables 4&5)

Detailed site-specific analysis of SM (IP and EP) is presented in Table 4. Of interest is the fact that 45% of cases demonstrated a positive apical margin. This represents three quarters of margin positive cases. 18% of cases had positive apical margins only. It is important to note that apical margins were IP by definition in all cases. Prostatic basal positive margins were rare (6% of total cases). The majority of prostatic basal margins were IP in nature (73%). The presence or absence of invasion into the bladder neck was not consistently identified independently of margin status throughout the cohort and was therefore not included in the presented data. +EP margins at the prostatic base were seen in 1.7% of total cases.

Anterior margins were also commonly positive. The left anterior (LA) margin was positive in 12% and right anterior (RA) margin in 11% of cases. Left or right anterior margins were involved in 19% of cases. Anterior margins were only very rarely diagnosed as EP in nature (2 cases in entire cohort).

The majority of EPE was identified involving the posterior and posterolateral prostate. 17% of the cases demonstrated left posterior (LP) +SM and 14% demonstrated right posterior (RP) +SM. 8.6% of cases demonstrated EPE in the LP lobe versus 6.6% in RP lobe. 14% demonstrated EPE in the right or left posterior lobe. Please note that the posterior lobe as defined in this study included the posterior and posterolateral prostate. Despite the presence of EPE posterior and posterolaterally, the great majority of +SM even in these areas were IP in nature. A +EP margin was identified in the LP lobe in 2.6% and RP lobe in 1.1% of cases. 85% of LP +SM were IP and 92% of RP +SM were IP in nature.

VI. 5 Correlation of marginal/stage status (Tables 6&7)

In table 6, the entire cohort was split into 4 subgroups based on margin status and presence or absence of EPE. 35% of cases demonstrated –SM and no evidence of EPE. 46% of patients demonstrated the presence of +SM in the absence of EPE. By definition all +SM in this group are IP in nature. The third group demonstrated +EPE with -SM. This was a small group making up 4.3% of the cohort. The fourth group included patients with +SM and +EPE. This group makes up 15% of the cohort. The +SM, +EPE group has been further subdivided in order to investigate the central hypothesis of this thesis. Within this group (table 7), the great majority of cases demonstrated +IP margins only (74%). Only 3.9% of the 467 patients demonstrated a +EP margin.

VII. DISCUSSION

This thesis has reviewed the GH radical prostatectomy experience from 2001-2005, particularly in relation to SM status. However, prior to focusing on the major hypothesis, it is worthwhile to review the Gleason grading and pathological stage data and compare it to the literature.

Of particular interest in our cohort is the relatively low percent of Gleason score 6and below radical prostatectomy cases. Overall, 34% of cases were Gleason score 6 or lower. Of this group only 4 were Gleason score 5 and were lower. As a convention, Gleason pattern 2 is rarely included in radial prostatectomy scores. Additionally, Gleason score 4 diagnoses are never rendered. 56% of our cases were Gleason score 7 and 8.6% were Gleason score 8-10. Several large institutional series in the literature assign a higher percentage of Gleason score 6 tumors and a lower percentage of Gleason score 7 tumors. In a Johns Hopkins review in 2001 (12), consisting of 2494 patients, 62% of cases were Gleason score 6 or less and only 31% were 7. In a recent multi-institutional review from the United Kingdom radical prostatectomy database (4), 34% of cases were Gleason score 7. However, a Canadian Community Hospital needle biopsy study undertaken by Sirgiley (1) diagnosed a score 7 in 42% of cases. Furthermore, pooled data from four large centers (1994-2000) demonstrated a Gleason score 7 rate of 47% (1). In addition, a recent (2005) study by Montironi *et al*, demonstrated a Gleason score 6 or lower in 26% of cases (18), a figure lower than our data. In general, Gleason pattern 4 has been diagnosed more aggressively in the past decade than in the past (personal observation of the practicum Pathologist). Furthermore, GH Pathologists include any percent of pattern 4 in the formal Gleason grade in radical prostatectomy

specimens. Some urologic Pathologists do not include this component in the formal score if it makes up less than 5% of the total tumor area. In a recent Gleason score conference (8), no consensus could be reached on this issue, but either approach is considered acceptable. Our percentage of high-grade carcinoma (9%) is well within literature parameters.

In examining the GH stage data, the most pertinent figure is a pT3 rate of 19%. Once again, this is somewhat lower than T3 rates found as in our literature review. In the Johns Hopkins experience (12), 50% of the study population demonstrated pT3 stage or higher. Foster *et al* (10), in their reference text quote figures of between 23% and 52% in various series. The previously cited United Kingdom study (4) demonstrated a pT3 or higher rate of 43%. There are several potential reasons for a lower pT3 rate in our series. Firstly, we do not completely submit the prostate in our cases (see Materials and Methods). Although there is controversy in this area some authors believe that partial sampling is not as sensitive as complete sampling (4,10). However, our sampling is near complete in most cases and the specimens processed in a standard fashion. Furthermore, a high-rate of +SM would appear to rule against inadequate sampling. A second possibility is that a lower pT3 rate represents the result of stage migration. Stage migration relates to the hypothesis that presently diagnosed prostate adenocarcinoma in the era of PSA screening are of lower stage then those detected in earlier series. This is a hypothesis that we can not definitely address in our series for two reasons. First, we do not know what proportion of our cohort was detected by PSA screening. Second, tumor volumes were not systematically evaluated in the cohort. A third possibility relates to our criteria for defining EPE. In our institution anteriorly located +SM are almost never

diagnosed as EP. This is because there is no periprostatic tissue in this area in which to diagnose such extension. Foster *et al* (10) states that EPE can be diagnosed in this area if tumor extends beyond "the normal contour" of the prostate. This is a criterion that in experience of GH Pathologists can be rarely applied. Epstein on the other hand defines all positive anterior margins as EP (17) because "the surgeon transects this region as far anteriorally away from the prostate as possible". This is a rationale for the diagnosis of EPE with which GH Pathologists respectfully disagree. In the detailed study by Bostwick's group published in 1999 (5), positive anterior SM was common (15%). As they noted EPE in only 5% of anterior margins, it is clear that most of their positive anterior margins were considered IP. Nonetheless, if the present study utilized Epstein's criteria pT3 status would shift to 36%, a figure in range with current literature.

GH data in relation to seminal vesicle positivity (7.5%) is in line with recent literature (5,12). We have a relatively low lymph node positivity rate (2.6%). This may relate to the fact that approximately 60% of our slated RP include frozen section examination of pelvic lymph nodes. If macro metastatic disease is found (lymph node tumor greater than 0.2 cm in diameter) the procedure is aborted. In the remainder of our slated RP, frozen sections are only performed if the surgeon feels that the lymph nodes are palpably abnormal.

Our final point of discussion relates to the incidence and nature of margins in this cohort, and the identification of a significant subclass which should be separately evaluated with clinical trials. Percentage of SM positivity in the pathological literature ranges between 1.3% and 71% (7). However, many large institutional studies fall within the range of 30% (3,5,21). As such, the GH institutional rate is relatively high for the

literature, particularly given in a trend towards lower +SM rates in the recent literature (4). This raises the concern that our patient population might suffer a poor clinical outcome post-radical prostatectomy in terms of biochemical recurrences, systemic metastasis, or death. Given our analysis of the literature and the nature of the prostatic margins in this cohort, we do not believe that this is the case. Rather we are concerned, given the increased tendency to recommend radiation therapy for +SM and +EPE (25) that a proportion of our cohort may be over treated with adjuvant radiation therapy.

It is important to note that greater than 90% of our +SM were IP in nature. In patients with organ-confined +SM (46%of our population), the prognostic significance of margin status is very controversial. The two largest studies addressing this issue are those of Blute *et al* (3), from Mayo and Karakiewicz *et al* (14), a large multiple-institutional study. In the Blute *et al* study, organ-confined adenocarcinoma with +SM demonstrated a statistically significant increase in biochemical recurrence (25% versus 14%) in comparison with -SM cases at 5 years (3). However, no difference in clinical progression or cancer specific death rates was noted. In the multi-institutional study published by Karakiewicz *et al* in 2005, the cohort was of 5831 patients. In this study, the biochemical progression rate for organ-confined disease at 10 years was 38% for +SM versus 19% for -SM. However, their study did not provide clinical recurrence, metastatic disease, or death rates. Although it seems clear that +IP margins in this context result in higher biochemical recurrence rates, it is not clear that they are of significant clinical impact. It seems reasonable that these patients should not be offered routine postoperative radiation therapy at this time.

On the other, the literature appears clear that patients with +SM and +EPE are at a high risk of a poor clinical outcome (7,10,14). The Karakiewicz *et al* study found that patients with +SM and +EPE had a biochemical recurrence rate of 75% at 10 years. Adjuvant therapy would appear reasonable in these patients if PSA recurrence is felt to represent locoregional disease. However, in the GH Pathologists opinion, this group of patients has not been critically analyzed in the literature. In an earlier article (22), in which the Ohori group assessed the significance of +SM, it is clear that their group of patients with +SM and +EPE was restricted to patients with +EP margins. In this group of 478 patients, 16% had +SM as defined by current criteria and11% demonstrated +SM at the site of EPE (+EP margins). The remaining 5% demonstrated +SM in the absence of EPE (-EP margins). None of this patient group demonstrated EPE with +IP margins only. In the GH cohort, 15% of the total cohort is within the high-risk group of +SM and +EPE. However, GH Pathologists routinely document the nature of +SM in their pathology reports. Therefore, we have been able to document +EP margins in 3.9% of the total cohort (26% of the high-risk group). The remaining three quarters of patients in this high-risk group demonstrate EPE with -SM at those sites and +IP only. In total, 11% of the entire cohort is within this stage/margin group. It is not at all clear from the current literature that these patients would benefit from adjuvant radiation therapy, as this group has never been separately analyzed. Although EPE (pT3) is a significant risk factor for clinical progression (7,10) it is unclear if this remains significant in the absence of +EP margins. In the Johns Hopkins study (12), Gleason score 6 tumors with EPE and -EP margins had a prognosis equivalent to organ-confined disease. In the previously

quoted Bostwick study (5), EPE was not a negative prognostic indicator if SM were negative.

The issue of inter-surgeon variability has not been addressed in this study. However, the highest volume surgeons in the group demonstrated similar margin positivity rates (63% and 57%).

VIII. CONCLUSION

A large volume single institution community hospital cohort of radical prostatectomy specimens has been examined in terms of Gleason grade distribution, stage, and SM status. Our Gleason grade spectrum is slanted towards Gleason score 7, in comparison with the older literature but is consistent with recent Gleason score trends. Our stage distribution is in the low end of the literature spectrum, a finding that might be explained by stage migration but is more likely due to conceptual differences in the definition of anterior SM status. Finally and most importantly, we have confirmed that most of our patient cohort with EPE and +SM (74% of this high-risk group) demonstrate +IP margins only. Only 3.9% of the entire cohort demonstrate +EP margins. Patients with EPE and +IP margins only should be classified separately by Pathologists and analyzed as a distinct group in clinical trails prior to offering these patients adjuvant radiation therapy.

IX. TABLES

IX.1 Gleason Score Distribution

Year	% Gleason Score 6	% Gleason Score 7	% Gleason Score 8-10
2001	46.7%	46.7%	4.4%
2002	32.2%	56.4%	8.7%
2003	37.8%	49.6%	11.8%
2004	36.5%	55.4%	6.8%
2005	21.3%	70.0%	7.5%
Total	33.8%	55.9%	8.6%

IX.2 Pathological Stage Distribution

Year	% EPE	% Positive Lymph Nodes	% Positive Seminal Vesicles
2001	20.0%	0.0%	0.0%
2002	25.5%	1.3%	6.0%
2003	14.3%	4.2%	5.9%
2004	14.9%	2.7%	9.5%
2005	16.3%	3.8%	15.0%
Total	18.8%	2.6%	7.5%

IX.3 SM Status

Year	% +SM	% -SM	% +IP Margins	% +EP Margins
2001	60.0%	40.0%	55.6%	4.4%
2002	59.1%	40.9%	54.4%	4.7%
2003	66.4%	33.6%	63.9%	2.5%
2004	56.8%	43.2%	54.4%	2.7%
2005	57.5%	42.5%	52.5%	5.0%
Total	60.4%	39.6%	56.5%	3.9%

IX.4 Sites of +SM/EPE/+EP Margins

Year	Site	%+SM	%EPE	% +EP Margins
2001	LP	22.2%	13.3%	4.4%
	LA	17.8%	4.4%	0.0%
	RP	13.3%	2.2%	0.0%
	RA	13.3%	2.2%	0.0%
	Apex	44.4%	0.0%	0.0%
	Base	11.1%	22.0%	0.0%
2002	LP	15.4%	8.1%	2.0%
	LA	10.1%	2.0%	0.7%
	RP	14.1%	12.8%	2.0%
	RA	10.1%	1.3%	0.0%
	Apex	40.9%	0.0%	0.0%
	Base	7.4%	10.7%	0.7%
2003	LP	20.2%	8.4%	2.5%
	LA	13.4%	0.0%	0.0%
	RP	12.6%	2.5%	0.0%
	RA	14.3%	0.0%	0.0%
	Apex	50.4%	0.0%	0.0%
	Base	5.0%	5.9%	0.8%
2004	LP	13.5%	8.1%	1.4%
	LA	10.8%	1.4%	0.0%
	RP	20.2%	5.4%	1.4%
	RA	10.8%	0.0%	0.0%
	Apex	47.3%	0.0%	0.0%
	Base	4.1%	12.2%	2.7%
2005	LP	15.0%	7.5%	3.8%
	LA	10.0%	2.5%	1.3%
	RP	8.8%	5.0%	1.3%
	RA	8.8%	2.5%	1.3%
	Apex	40.0%	0.0%	0.0%
	Base	6.3%	12.5%	5.0%
Total	LP	16.9%	8.6%	2.6%
	LA	11.8%	1.7%	0.4%
	RP	13.7%	6.6%	1.1%
	RA	11.3%	1.1%	0.0%
	Apex	44.5%	0.0%	0.0%
	Base	6.4%	9.2%	1.7%

IX.5 Apex Only +SM

Year	% +SM
2001	17.8%
2002	14.8%
2003	21.0%
2004	17.6%
2005	22.5%
Total	18.4%

IX.6 Marginal/Stage Status

Year	%-SM & -EPE	%+SM & -EPE	%-SM & +EPE	%+SM & +EPE
2001	33.3%	46.7%	6.7%	13.3%
2002	34.2%	39.6%	6.0%	20.1%
2003	31.9%	53.8%	2.5%	11.8%
2004	37.8%	47.3%	5.4%	9.5%
2005	41.3%	42.5%	1.3%	15.0%
Total	35.3%	45.6%	4.3%	14.8%

IX.7 Subclassification of +SM/+EPE

Year	% +SM & +EPE	% -EP Margins	% + EP Margins
2001	13.3%	8.9%	4.4%
2002	20.1%	15.4%	4.7%
2003	11.8%	9.2%	2.6%
2004	9.5%	6.8%	2.7%
2005	15.0%	10.0%	5.0%
Total	14.8%	10.9%	3.9%

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