The Significance of Margin Involvement in Radical Prostatectomy Specimens for Presumed Localized Adenocarcinoma of Prostate in Relation to PSA (Biochemical) Failure Rate

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Abstract

Background: There is no clear cut way of predicting which patients would develop PSA failure after radical prostatectomy for localised prostate cancer.

Aims: To investigate the hypothesis that pursuant to radical prostatectomy for localised prostate cancer, surgical margin involvement and non-involvement influence the PSA failure and non failure rate.

Patients Materials and Methods: The Clinical records, laboratory results including histology reports, serum PSA levels, all radiological investigations and reports of our initial 50 consecutive patients who underwent radical prostatectomy were reviewed and outcome of the prostatectomy was recorded with regard to PSA failure or non failure as well as surgical margin involvement or non involvement by tumour.

Analysis of outcome was done to ascertain the proportion of patients who developed PSA failure and non failure in both patients whose tumours involved the surgical margin and those without margin involvement. Statistical analyses were done using sure start to check if there is any significant difference in the outcome of both tumour groups.

Results: 5 patients out of 7 whose tumours were assessed to have involved the margin (71.42%) had PSA failure. 6 patients out of 43 whose tumours did not involve muscle (13.95%) developed PSA. The difference in outcome was statistically significant.

Conclusions: Prostate cancers that involve the surgical margin at radical prostatectomy have a higher chance of developing PSA failure and should be treated with adjuvant therapy.

Keywords: Adenocarcinoma, Prostate, Surgical margin, Involvement, Non involvement, PSA, Failure, Non failure, Analysis.

Introduction

Some studies have reported that the PSA failure rate following radical prostatectomy for localised prostate cancer are influenced by the margin status of the tumour. Other studies have not confirmed the aforementioned observation. It would be useful if the PSA failure rate in every unit that performs radical prostatectomy is known. It would also be useful if the parameters affecting the PSA failure rate of each, unit is known so that these parameters affecting the outcome following radical prostatectomy could be discussed with the patient using local experience to guide the patient and figure out which group of patients would need adjuvant therapy.

This study was undertaken to investigate our local experience in order to ascertain whether or not our surgical margin involvement in our experience would a determining factor that would influence PSA (biochemical) failure rate after radical prostatectomy for localized prostate cancer.

Patients, Materials and Methods

The case notes, automated letter system, histology results, the laboratory results of first consecutive 50 patients who underwent radical prostatectomy for localised prostate cancer at North Manchester General Hospital were reviewed in order to document the following.

(a) Whether or not there was surgical involvement or non involvement; in the case of tumours close to the surgical margin the results the distance from the surgical margin was recorded.

(b) The patient outcome during follow-up was recorded as PSA failure and non failure over the follow-up period. PSA failure after radical prostatectomy was defined as a value of 0.2 ng/ml, (0.2ug/L) and one subsequent rise.

(c) The results of all the patients were recorded individually by the audit department and summarized as: margin involvement / non involvement by tumour, and in the case where the tumour is close to the margin it is recorded as within 1 or 2 mm of margin; PSA failure / non failure over the follow-up period as well as time of PSA failure; the percentage of patients...
with PSA failure and non failure were worked out in relation to tumour margin involvement or non involvement.

(d) Statistical analyses of outcome (PSA failure / non failure) in relation to margin status of tumour was carried out independently by the statistician in charge of statistical work for the Trust using sure start and computing a number of analyses including: Nominal Independence, Anova, Linear Trend, Nominal Association, and Ordinal.

Results

50 patients underwent Radical prostatectomy for localized prostate cancer. They had a follow-up ranging from 4 months to 7 years with a mean follow-up of 28.7 months. The average age range of the patients was 62 years; 1 patient was aged >70 years; 14 patients were aged between 66 and 70 years; 15 patients were aged between 61 and 65 years; 13 were aged between 56 and 60 years; 6 were aged between 50 and 55 years; 1 was less than 50 years old. During the period of follow-up 11 patients (22%) developed PSA failure and one of these patients died of his prostate cancer but the remaining 10 patients were free of clinical disease and they were either referred for adjuvant therapy or have been receiving adjuvant therapy. The only patient who died of his prostate cancer was initially treated with radical radiotherapy prior to his radical prostatectomy however, he developed PSA (Biochemical) failure and he then opted to undergo radical prostatectomy. He also continued to be on hormonal treatment but died. With regard to the ten patients who developed PSA failure the outcomes were as follows:

* One patient developed PSA failure by the 6th post operative period with PSA values of 0.681 ug/L, [ng/ml], and 1.95 ug/L, [ng/ml. He was referred to the Oncologist and has been treated by radical radiotherapy and he is also receiving hormonal therapy.

* One patient developed PSA failure at 4 months with serum PSA of 0.22 ug/L. He was referred to the oncologist and he had undergone radical radiotherapy and is receiving hormonal treatment as well. His last serum PSA was < 0.050 at the time of the study.

* One patient developed PSA failure at 33 months and has received radical radiotherapy as well as he is on hormonal treatment. His last 3 serum PSAs were

* One patient developed PSA failure at 4 months post operatively and was referred to the oncologist following which he received radical radiotherapy. His last serum PSA was >0.050 ug/L.

* One patient developed PSA failure 7 years post operatively and had just been referred to the oncologist.

* One patient developed PSA failure 4 years post operatively and had just been referred to the oncologist.

* One patient developed PSA failure 3 years post operatively and was referred to the oncologist following which he received radical radiotherapy. His last 3 serum PSA levels have been:

* One patient developed PSA failure 8 months post operatively; he was referred to the oncologist and he received radical radiotherapy; his last 2 serum PSA levels were

* One patient developed PSA failure 2 months post operatively; he was referred to the oncologist and he received radical radiotherapy and is also on hormonal treatment. His last 3 serum PSA levels were

* One patient developed PSA failure 2 years post operatively; he was referred to the oncologist and he received radical radiotherapy. His last serum PSA was

Out of 6 patients with margin involvement 4 (66.67%) had PSA failure and, 2 did not develop PSA failure. One patient whose tumour was within 1 mm from the surgical margin had PSA failure. One patient whose tumour was within 2 mm of the surgical margin did not develop PSA failure. Out of 42 patients whose tumours did not involve the surgical margin 6 (14.3%) had PSA failure (see table 1). Out of 7 patients whose tumours were within 1 mm off the surgical margin or involved the surgical margin 5 (71.42%) developed PSA failure. Out of 43 patients whose tumours did not involve the surgical margin or the tumour was at least 2mm from the surgical margin, 6 (13.95%) developed PSA failure (see table 2).

Various statistical analyses done using sure start including: Nominal Independence, Anova, linear Trend, Nominal Associate, and Ordinal showed that the difference in outcome of PSA failure and Non failure between the two groups (tumours with margin involvement or within 1 mm from the surgical margin, and tumours which did not involve the surgical margin or at least 2 mm from the surgical margin) was statistically significant as shown in the ensuing statistical analysis data:

Discussion

Kaussik and associates [1] reported on 842 patients who underwent radical prostatectomy for localized prostate cancer. They reported that a total of 354 patients (42%) had ? 1 positive surgical margins
whereas 488 patients (58%) demonstrated no margin involvement. The sites of margin positivity were as follows: apex (n=163), base (n=47), posterior prostate (n=227), and anterior prostate (n=11). A total of 111 patients had ≥2 positive margins. The 5-year survival free of clinical recurrence and / or biochemical failure (post operative PSA level > 0.2 ng/ml) for patients with no positive surgical margin was 76% and was 65% for patients with 1 positive surgical margin (p=0.0001). There was no significant difference in biochemical disease progression between patients with 1 versus those with ≥2 surgical margins (65% vs 62%). Multivariate analysis revealed that positive surgical margins were a significant predictor (P=0.0017) of clinical disease recurrence and biochemical failure (relative risk, 1.55; 95% confidence interval, 1.18-2.04) after controlling for preoperative serum PSA, Gleason score and DNA ploidy. They made the ensuing conclusions: In the current study positive surgical margins were found to be a significant predictor of disease recurrence in patients with pT3a/b N0 prostate carcinoma, a finding that is independent of PSA, Gleason score, and DNA ploidy. The benefit of adjuvant therapy in optimizing recurrence-free survival remains to be tested.

Pierorazio and associates [3] in another long-term study reported that patients with extra-prostatic extension had 39% failure and 11% death rate by 12 years.

Paulson [4] found “Margin status” to be an independent predictor of recurrence. In an early study in perineal prostatectomy patients [4], for patients with positive margins the 5 year biochemical recurrence was 58%, which resulted in a cancer death rate of 40% at 13.5 years. Patients with positive margins had double the overall death rate (60%) as those with organ or specimen confined disease (30%). A number of other studies [5, 6, 7, 8, 9, 10, 11], have shown that margin positive disease has a 19 – 64% 5 – year survival / biochemical failure free survival; and a 10 year failure free survival of 26% to 61% [7, 12, 13].

Kupelian and associates [14] reported that if patients have other high risk factors (i.e. PSA>20 ng/ml; and Gleason score > 7) the 5 year recurrence free survival is very low (15%).

Some studies however, have found margin status irrelevant. In the first of two studies conducted by the same authors Quinn and associates [15] with a mean follow-up of 41 months, found on multivariate analysis, lymph node positivity, pathologic stage (i.e. extra-prostatic-extension), seminal vesicle involvement and Gleason score were an prognostic at exclusion of margins or capsular invasion. In the second study [16] with a mean follow-up of 55 months, PSA was the only significant factor on multivariate analysis.

The results of this study confirm that the involvement or non involvement of surgical margin by the tumours influence the PSA failure rate in that, tumours with surgical margin involvement or within 1 mm of the surgical margin were more commonly associated with PSA failure in comparison with tumours that did not involve the surgical margin or were at least 2 mm from the surgical margin. Another point of clinical importance is with the knowledge that tumours that involve the surgical margin or lie within 1 mm from the surgical margin are more likely to be associated with PSA failure such tumours are the tumours which should be treated with adjuvant therapy as an attempt to reduce PSA failure. On the other hand patients whose tumours do not involve the surgical margin or lie at least 2 mm from the surgical margin should not receive adjuvant therapy in view of the low PSA failure rate.

References

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Author

The study was designed by Mr Anthony K-G Venyo who adopted and modified the North West Regional Prostate Cancer Audit proforma to include follow-up data on all patients with particular emphasis on tumour margin involvement and non involvement and who discussed the audit project with Drs Sarang Shah and Shahid Imran, Mr Douglas Barnes as well as the Audit Department of North Manchester General Hospital. Mr Anthony Kodzo-Grey Venyo explained in detail to Drs Sarang Shah and Sharid Imran the Gleason Grading / Scoring System, as well as the Staging of Prostate Cancer to Drs Sarang Shah and Shahid Imran. All the Radical prostatectomies were performed by Mr D G Barnes and Mr Anthony Kodzo-Grey Venyo assisted at some of the operations as well as reviewed some of the patients post-operatively. Mr Anthony Kodzo-Grey Venyo supervised Drs Sarang shah and Dr Shahid Imran to collect and enter all the data. Mr Anthony Kodzo-Grey Venyo cross checked all the clinical entry.
laboratory results, radiology results, the PSA levels, Gleason Scores, clinical staging and patient outcome as the subsequent PSA levels entered by both Drs Shah and Imran and all three were in agreement regarding the entries of every patient. The raw data was given to the audit Department for entry into a spread sheet format and analysis of Data without knowledge of all the clinicians. Ruth Gordon did all the analyses and entry of the results with the exception of the statistical analyses. Mr Douglas Barnes reviewed all the patients at initial and subsequent follow-ups and Mr Anthony Kodzo-Grey Venyo also reviewed some of the patients at some stage in the follow-up of some of the patients. Mr Anthony kodzo-Grey Venyo wrote the manuscript which was then read by all authors. Dr Sarah Cotterill explained to Mr Anthony Kodzo-Grey Venyo the appropriate statistical analyses pertinent to our data based upon the numbers involved. Dr Sarah Cotterill did all the statistical analyses in the presence of Mr Anthony Kodzo-Grey Venyo and cross checking that all the results were correctly entered for the statistical analyses.
Illustrations

Illustration 1

Statistical analysis data:

Statistical analyses of outcome (PSA failure / non failure) based upon Margin Status of tumours (tumours with margin involvement / within 1 mm of margin versus tumours without margin involvement (at least 2 mm from margin)

Contingency table analysis

Observed 2 5 7
Expected 5.46 1.54
% of row 28.57% 71.43%
% of col 5.13% 45.45% 14%

Observed 37 6 43
Expected 33.54 9.46
% of row 86.05% 13.95%
% of col 94.87% 54.55% 86%

Total 39 11 50
% of n 78% 22%

TOTAL number of cells = 4

Warning: 1 out of 4 cells have EXPECTATION < 5
NOMINAL INDEPENDENCE
Chi-square = 11.588799 DF = 1  P = 0.0007
G-square = 9.560851 DF = 1  P = 0.002
Fisher-Freeman-Halton exact  P = 0.0036

ANOVA
Chi-square for equality of mean column scores = 11.357023
DF = 1  P = 0.0008

LINEAR TREND
Sample correlation (r) = -0.481431
Chi-square for linear trend (M²) = 11.357023
DF = 1  P = 0.0008

NOMINAL ASSOCIATION
Phi = 0.481431
Pearson's contingency = 0.433779
Cramér's V = -0.481431 (signed)
ORDINAL

Goodman-Kruskal gamma = -0.878173

Approximate test of gamma = 0: SE = 0.108155 P < 0.0001 95% CI = -1.090152 to -0.666194

Approximate test of independence: SE = 0.375486 P = 0.0193 95% CI = -1.614112 to -0.142233

Kendall tau-b = -0.481431

Approximate test of tau-b = 0: SE = 0.155503 P = 0.002 95% CI = -0.786211 to -0.176652

Approximate test of independence: SE = 0.205849 P = 0.0193 95% CI = -0.884888 to -0.077975
## Illustration 2

### Table 1

Margin or Non Margin Involvement and PSA (Biochemical) Failure after radical prostatectomy for presumed localized prostate cancer

<table>
<thead>
<tr>
<th>Margin status</th>
<th>PSA Non Failure</th>
<th>PSA Failure</th>
<th>Total</th>
<th>Percentage Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>66.7%</td>
</tr>
<tr>
<td>Within 1 mm of margin</td>
<td></td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Within 2 mm of margin</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>Margin not involved</td>
<td>36</td>
<td>6</td>
<td>42</td>
<td>14.3%</td>
</tr>
</tbody>
</table>
## Illustration 3

### Table 2

Margin involvement and non-involvement by tumor and PSA (Biochemical) failure after Radical prostatectomy for presumed localized adenocarcinoma of prostate

<table>
<thead>
<tr>
<th>Margin status</th>
<th>PSA Non Failure</th>
<th>PSA Failure</th>
<th>Total</th>
<th>Percentage with PSA Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin involved or within 1 mm of margin</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>71.42%</td>
</tr>
<tr>
<td>Margin not involved or at least 2 mm from margin</td>
<td>37</td>
<td>6</td>
<td>43</td>
<td>13.95%</td>
</tr>
</tbody>
</table>
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