Is there a progression of histologic grade from radical prostatectomy to local recurrence in patients with clinically isolated local recurrence following surgery?

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Objective: *To evaluate whether there is any histologic progression from radical prostatectomy (RP) to local recurrence in patients with clinically isolated local recurrence following RP.*

Methods and materials: *A total of 43 patients with clinically isolated, biopsy proven, local recurrence following RP were retrospectively analyzed with respect to the change in Gleason score (GS) from RP to local recurrence. Central pathology review was undertaken for both RP and local recurrence biopsy specimens. The changes in primary and secondary Gleason grade (GG), and any potential correlation between the extent of GS change and other variables were also examined.*

Results: *Median age at the time of local recurrence was 67 years (range: 55-78). Median interval between RP and local recurrence was 3.6 years (range: 0.3-17.7). Eight had a short course (< 3 months) of hormone therapy prior to RP. Initial GS of RP specimens was 5, 6, 7, 8, and 9 in 1, 3, 29, 1, and 9 patients, respectively. At the time of local recurrence, GS was upgraded in 13, unchanged in 23, and downgraded in 7. The extent of GS change was correlated with the interval between RP and local recurrence, but not with pathological T stage or age.*

Conclusion: *There was no statistically significant change in GS from RP to local recurrence, although there was a trend toward a higher GS at the time of local recurrence. The extent of GS change was associated positively with the elapsed time to local recurrence.*

Key Words: histologic grade change, local recurrence, radical prostatectomy, prostate cancer

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Introduction

In prostate cancer, the natural history of cellular dedifferentiation is not known. It remains uncertain as to whether the histologic grade of prostate carcinoma changes with time or remains the same throughout its long natural history. To provide further

TABLE 1. **Patient characteristics at the time of radical proatectomy**

GS	Negative margin (n=15)				Positive margin (n=28)				Total
	T2A	T2B	T3A	T3B	T2A	T2B	T3A	T3B	
5	0	0	0	0	1	0	0	0	1
6	1	0	0	0	0	1	1	0	3
7	0	4	7	0	1	5	8	4	29
8	0	0	1	0	0	0	0	0	1
9	0	0	1	1	0	0	6	1	9
Total	**1**	**4**	**9**	**1**	**2**	**6**	**15**	**5**	**43**

insight into this unresolved question, we have compared the histologic grade of radical prostatectomy specimen with that of local recurrence in patients with clinically isolated, biopsy proven, local recurrence at the prostate bed following radical prostatectomy (RP).

Materials and methods

A total of 48 patients with biopsy proven local recurrence following RP were referred to Toronto Sunnybrook Regional Cancer Centre for consultation between 1994 and 2001. All underwent bone scan and CT scan of abdomen and pelvis at the time of local recurrence and had no evidence of distant metastasis. Clinical evidence of relapse was confined to the prostate bed and local recurrence was confirmed histologically.

Both RP and local recurrence had a histologic diagnosis of adenocarcinoma of the prostate. In five patients, the central pathology review of both RP specimens and biopsy of local recurrence was not possible, as initial RP specimens could not be retrieved from the referring hospitals. In the remaining 43 patients, central review of both materials was undertaken. These 43 patients were the subjects of this study. Two expert genito-urinary pathologists reviewed all materials. To minimize the impact of shifting standards for Gleason grading over time, all materials were re-assessed over a period of 6 months in 2002. The changes in overall Gleason score (GS), primary Gleason grade (GG) and secondary GG from RP to local recurrence were examined. Potential correlation between GS change and other variables, including the interval between RP and local recurrence, was also evaluated.

Median age at the time of histologically confirmed local recurrence was 67 years (range: 55-78). All had RP between 1983 and 1998 (5 between 1983 and 1987, 13 between 1988 and 1992, and 25 between 1993 and 1998). All except one also underwent bilateral pelvic lymphadenectomy. The pathological characteristics of RP specimens are described in Table 1. Thirteen, 24 and 6 patients had PT2, PT3a and PT3b, respectively. Twenty-eight patients had positive surgical resection margins, while 15 did not. The majority of patients (n=29) had GS 7 in RP specimens. Ten patients (23%) had GS 8 or 9. Only 4 (9%) had GS 5 or 6. Pelvic lymph nodes were pathologically negative for metastasis in 42 patients, and grossly benign in the remaining one patient who did not undergo pelvic lymph node dissection. Eight patients had a short course (< 3 months) of hormone therapy prior to RP: 4 with LHRH analogue for 1-3 months, 2 with flutamide for 4-6 weeks, and 2 with cyproterone acetate for 2-8 weeks.

The interval from RP to the biopsy of local recurrence was 0-2, 2-5, 5-10, 10-15, and 15-20 years (range: 0.3-17.7) in 13, 19, 8, 2, and 1 patient, respectively. Median interval was 3.6 years and mean was 4.2 years

All had detectable and rising PSA (> 0.2 ng/ml) at the time of positive prostate bed biopsy. PSA ranged from 0.5 to 23.2 ng/ml. None had hormone therapy prior to the biopsy of local recurrence at the prostate bed.

Calculations were performed using SAS (release 8.2; SAS Institute Inc., Cary, NC). Changes in GS were tested for statistical significance with the Wilcoxon matched pairs signed rank sum test. The relationship of the change in GS with other variables was examined with correlation analysis.

Results

Table 2 summarizes the change of overall GS from the time of RP to local recurrence. There was no change in GS in 23 patients. At the time of local recurrence,

TABLE 2. **Change of overall GS from the time of RP to local recurrence**

GS at RP	GS at local recurrence						Total
	5	**6**	**7**	**8**	**9**	**10**	
5	0	1	0	0	0	0	1
6	0	1	2	0	0	0	3
7	1	1	18	3	6	0	29
8	0	0	1	0	0	0	1
9	0	1	2	1	4	1	9
Total	**1**	**4**	**23**	**4**	**10**	**1**	**43**

GS was upgraded in 13, and downgraded in 7 patients.

Table 3 shows the change of GS in 35 patients who did not have any neoadjuvant hormone therapy prior to RP. In this subgroup, GS was unchanged, upgraded, and downgraded in 20, 11, and 4 patients, respectively.

Another subset analysis was undertaken after excluding the patients with local recurrences within 2 years following RP or with neoadjuvant hormone therapy prior to RP. The reason for excluding those cases with local recurrence within 2 years following RP is that it is very unlikely to have any significant histologic grade change within this short period of time. Any change in histologic grade during this short interval is more likely a reflection of the multi-focal nature of prostate cancer bearing various histologic grades. Twenty-eight patients met the criteria of this subset analysis. In this group, GS was unchanged, upgraded, and downgraded in 13, 11, and 4 patients, respectively.

The changes in primary and secondary Gleason grade for all 43 patients are summarized in Table 4. Primary GG was upgraded in 10, unchanged in 28,

TABLE 3. **Change of overall GS in the subgroup of 35 patients who did not have hormone prior to RP**

GS at RP	GS at local recurrence					Total
	6	**7**	**8**	**9**	**10**	
5	1	0	0	0	0	1
6	1	2	0	0	0	3
7	1	15	2	5	0	23
8	0	1	0	0	0	1
9	1	0	1	4	1	7
Total	**4**	**18**	**3**	**9**	**1**	**35**

TABLE 4. **Change in primary and secondary Gleason Grade from RP to local recurrence**

Primary grade at RP	Primary grade at local recurrence				Secondary grade at RP	Secondary grade at local recurrence			
	2	**3**	**4**	**5**		**2**	**3**	**4**	**5**
2	0	0	0	0	2	0	1	0	0
3	0	17	7	0	3	0	5	5	3
4	1	3	11	3	4	0	4	13	3
5	0	0	1	0	5	0	2	3	4
Total	**1**	**20**	**19**	**3**	**Total**	**0**	**12**	**21**	**10**

and downgraded in 5. Secondary GG was upgraded in 12, unchanged in 22, and downgraded in 9.

Overall there was a trend toward a higher GS at the time of local recurrence; but it was not statistically significant ($p = 0.36$). This trend was more pronounced when restricted to the 35 patients who did not have neoadjuvant hormone therapy prior to RP ($p = 0.08$). Potential correlation between the extent of GS change and the three variables (age at the time of local recurrence, initial pathological stage of RP specimen, interval between RP and local recurrence) was assessed. The extent of GS change was significantly correlated with the interval between RP and local recurrence (Spearman correlation coefficient = 0.43, $p = 0.004$). The longer the interval, the greater the GS upgrade. The extent of GS change was not correlated with initial pathological stage ($r = -0.18$, $p = 0.26$), or age at the time of local recurrence ($r = -0.03$, $p = 0.85$).

Comments

Cellular dedifferentiation is one of the features of cancer progression. This may be reflected at the morphological level. In prostate cancer, it remains unresolved whether the histologic grade progresses over time or remains the same. There has been a suggestion that, in prostate cancer, the tumor may undergo such dedifferentiation within the primary cancer or within metastases.[1-6] However, the recent series of early stage prostate cancer managed with expectant management suggest that there was no consistent histologic upgrade on the follow-up biopsy within the first 2-3 years after the initial diagnosis of malignancy.[7-8] This raises the possibility that dedifferentiation, if it occurs, may take place over a much longer period of time.

In our series, there was a trend that GS at the time of local recurrence was generally higher than that of RP specimen, although histologic upgrade was not consistent in all patients. One plausible explanation for this observation is histologic progression over time by a process of clonal evolution. Tumor cells show various genotypic and/or phenotypic instability, resulting in the emergence of diverse cell lines. Over time, those cells with selective growth advantage overgrow and dominate the tumor. This selective process, which can be linked to clonal evolution, eventually leads to the appearance of more aggressive phenotype. This postulation of histologic progression over time is further suggested by a positive correlation between the extent of histologic grade change and the interval from RP to local recurrence observed in our study. In our cohort, there was a higher likelihood of histologic upgrade when the interval was longer. The lower histologic grade observed at the time of recurrence in some of our patients may be simply related to sampling variability.

The trend toward histologic upgrade at the time of local recurrence was also evident in the two subset analyses excluding the patients with neoadjuvant hormone therapy prior to RP +/- those with local relapse within the first 2 years following RP in our study. Another approach that one can take for the analysis of the change in histologic grade is to limit it to patients with GS 7 or less for their RP specimens. For those with higher GS to begin with (GS 8 or greater), it would be more difficult to demonstrate histologic progression over time because their tumors are poorly differentiated from the onset. When analyzing the subgroup of patients with GS 7 or less initially, the suggestion of histologic progression over time becomes more evident in our study.

One major drawback for the argument of histologic progression in our series is selection bias. It is possible that as only those patients in whom tumor progressed were selected in our series, they were more likely to have experienced cellular dedifferentiation leading to histologic upgrading. Also, patients referred for the management of clinically isolated, biopsy proven, local recurrence represent only a small fraction of patients who had undergone RP and later showed a sign of tumor recurrence with rising PSA. Our study lacks the information on the denominator of the total number of patients with rising PSA following RP that could have undergone the biopsy of the prostate bed during the study period. It is possible that the majority of such patients who did not have the biopsy of prostate bed may have had local recurrence with no change in histologic grade.

There are other limitations in our study that demand cautious approach for the interpretation of our data. One such limitation is that pathological interpretation of histologic grade is subject to the adequacy of biopsy sampling as well as intra- and inter-observer variability. Also, in those patients who had androgen ablation prior to RP, histologic evaluation is more difficult, resulting in inaccurate grading. Another shortcoming is the small sample size of our series. A small sample size is not unexpected, however, since a majority of patients with rising PSA following RP usually receive therapeutic intervention without the biopsy of the prostate bed in routine clinical practice. Nonetheless, our series is, to the best of our knowledge, the first study comparing the histologic grade of RP specimen with that of local recurrence in order to evaluate any histologic

progression over time in prostate cancer.

A few reports have examined the issue of prostate cancer dedifferentiation. Adolfsson analyzed repeat fine needle aspiration biopsy of the prostate in patients managed with watchful observation alone.[6] On repeat biopsy, the modal deoxyribonucleic acid values in the tumor cells changed towards an increased aneuploidy in 17 out of 72 patients, and the cytological differentiation decreased in 18 out of 78 patients. Cumming examined GS change in 34 prostate cancer patients who underwent two transurethral prostatic resections (mean interval between resections: 2.4 years) while being managed with watchful observation alone.[4] There was a trend toward a higher GS on the second resection specimens (GS increased in 23, unchanged in 5 and decreased in 5). The findings of both studies were supportive of the concept of a gradual dedifferentiation of prostate cancer.

Two series, however, suggest no significant histologic progression over a relatively short period of time. Epstein et al. reported the change of histologic grade in 70 men with clinical stage T1c prostate cancer who underwent repeat needle biopsy while being managed with watchful waiting.[7] During a 1.5 to 2 year period following the initial biopsy, there was no clear evidence of histologic progression. Similar finding was observed in our recent study. We evaluated the change of histologic grade in 67 patients with clinical stage T1b-T2B, low to intermediate grade, prostate cancer who were managed with watchful observation and underwent follow-up repeat prostate biopsy.[8] Median interval between the two prostate biopsies was 22 months. On the follow-up biopsy, GS was unchanged in 20 patients (30%), upgraded in 19 (28%), and downgraded in 27 (40%). These two studies suggest that there is no consistent histologic upgrade during a short follow-up in untreated prostate cancer. However, they do not provide an answer for the question as to whether there is dedifferentiation of prostate cancer over much longer periods of time. This raises the possibility that dedifferentiation, if it occurs, may take place over a much longer period of time.

Conclusion

Within the limitations of the study, there was no significant overall change in GS from RP to local recurrence, although there was a trend toward a higher GS at the time of local recurrence. There was a positive correlation between the extent of GS change and the interval to local recurrence. □

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