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TRANSITIONAL CELL CARCINOMA INVOLVING THE PROSTATE: A CLINICOPATHOLOGICAL RETROSPECTIVE STUDY OF 76 CASES

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ABSTRACT

Purpose: We reviewed the degree to which extension from transitional cell carcinoma into the prostate affects survival. We also compared whether prostatic stromal invasion occurring via direct extension through the bladder wall differs from stromal invasion arising intraurethrally.

Materials and Methods: A total of 76 men who underwent radical cystectomy for transitional cell carcinoma also had prostate involvement. Patients were separated into group 1–18 with primary bladder tumor extending transmurally through the bladder wall to invade the prostate and group 2—58 with prostate involvement arising from within the prostatic urethra. In the latter group the degree of prostate invasion was classified as urethral mucosal involvement, ductal/acinar involvement and stromal invasion.

Results: The 5-year overall survival and recurrence-free rate were 22% and 28% in group 1 versus 43% and 45% in group 2, respectively. In group 2 survival rates were similar in those with prostatic urethral and ductal tumors (without stromal invasion). Five-year overall survival rates without and with stromal invasion were 49% and 25%, respectively ($p = 0.024$). Prostate involvement decreased survival, which varied according to primary bladder stages (Pis, P1, P2a/b and P3a/b, $p = 0.004$) or superficial (Pis, Pa and P1) and muscle invasive (P2a/b and P3/b, $p = 0.045$), disease in 2 groups. Those with positive lymph nodes experienced poorer outcomes in each group. The 5-year overall survival rate in the 19 men with positive lymph nodes was 13% and it was 44% with negative lymph nodes ($p = 0.034$). The major prognostic factors were age, degree of prostate invasion and lymph node involvement.

Conclusions: The invasion pathways of prostate invasion in patients with transitional cell bladder carcinoma have a statistically significant prognostic role in survival. Transitional cell carcinoma of the bladder extending into the prostate through the bladder wall and bladder carcinoma that did not directly infiltrate the prostate through the bladder wall are 2 distinct clinicopathological entities that should not be included in the same staging grade.

KEY WORDS: prostate; bladder neoplasms; carcinoma, transitional cell; cystectomy; neoplasm invasiveness

Transitional cell carcinoma extending into the prostate was first reported in 1952 by Melicow and Hollowell, who described carcinoma in situ of the prostate coexistent with bladder transitional cell carcinoma as Bowen's disease.[1] Since this description, many reports of prostate invasion from transitional cell carcinoma have been published, allowing urologists to classify better this entity. However, confusion remains regarding optimal treatment in patients with transitional cell carcinoma involving the prostate, the degree to which this extension affects the overall prognosis and its impact on the prognosis.

The incidence of prostate involvement from transitional cell carcinoma varies widely. Schellhammer et al originally described a 12% incidence in 350 patients undergoing radical cystectomy for primary bladder cancer.[2] Using a whole mount step sectioning technique Wood et al noted a 43% incidence.[3] In that study lateral verumontanal prostate biopsy with prostatic transurethral resection was 90% accurate in detecting the presence or absence of prostatic extension. In a prospective study of 246 consecutive patients using transurethral resection before cystectomy Donat et al showed that lateral verumontanal prostatic biopsy as part of preoperative evaluation for urethral involvement could accurately detect prostatic involvement in 81% of patients.[4] Men with direct transmural invasion of the prostate by bladder transitional cell carcinoma experienced a worse outcome than those in whom bladder transitional cell carcinoma was present with prostate carcinoma but showing no sign of direct infiltration.[5]

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MATERIALS AND METHODS

Between January 1982 and April 2000, 283 consecutive patients underwent radical cystectomy for transitional cell carcinoma, of whom 76 (27%) also showed prostate involvement on retrospective review of all pathological records. The cystoprostatectomy specimens were inflated with 10% formalin solution for 24 to 72 hours. The bladder and prostate were cut sagitally. Each half of the bladder was cut in 0.5 cm. serial sections for macroscopic examination. A specimen was obtained at the upper and lateral faces of the bladder, at each half of the trigone and in the prostate. Other specimens were obtained into the urethra. Standard hematoxylin and eosin staining was done after paraffin embedding on 5 μm. sections.

These patients had involvement of the prostatic urethra, ducts or stroma. We separated them into group 1—18 (24%) in whom primary bladder transitional cell carcinoma extended through the bladder full-thickness wall to invade the stroma of the prostate extravesically (stage pT4a) and group 2—58 (76%) in whom prostate involvement arose from within the prostatic urethra.[6] As reported by Hardeman and Soloway,[7] and Esrig et al[6] the group 2 was divided into

3 subgroups, including 1 with prostatic urethral tumor, 1 with prostatic duct involvement without stromal invasion and 1 with stromal invasion. Stroma invasive tumors showed basal membrane invasion from the prostatic urethral or ductal tumors. Of the 76 patients 19 (25%) had associated lymph node metastases. Lymph nodes were positive in 5 of the 18 patients (28%) with stage P4a tumors and in 13 of the remaining 58 (22%).

Median age at cystectomy was 65 years (range 35 to 83). Patients were followed at 3-month intervals during postoperative year 1, every 6 months during years 2 and 3, and yearly thereafter. Followup included a biochemical profile, physical examination and computerized tomography. Whole body bone scan and chest x-ray were also performed to exclude disease recurrence. Transitional cell carcinoma recurrence and causes of death were determined from office and hospital records, and telephone contact with the patient or family.

Survival rates were estimated according to the Kaplan-Meier product limit method with the standard errors. Comparisons between groups were performed by the log rank test. The Cox proportional hazards model was used for multivariate survival analysis with backward selection of variables by the Wald test.

RESULTS

Of the 283 evaluable cases 76 (27%) had transitional cell carcinoma with prostate involvement. In 18 group 1 patients (24%) primary transitional cell carcinoma extended throughout the full-thickness bladder wall to invade the prostatic stroma (stage P4a). In 58 group 2 patients (76%) transitional cell carcinoma arose from within the prostatic urethra only (26) or there were ductal tumors without stromal invasion (10) and stromal invasive tumors (22). Table 1 shows primary bladder and prostate tumor stage in 76 patients with prostate transitional cell carcinoma.

The overall mean 5-year survival rate ± SE in the 76 patients was 38% ± 7%. The overall mean survival and recurrence-free rates were 22% ± 13% and 28% ± 13%, in the stage P4a group compared with 43% ± 9% and 45% ± 9%, respectively, in the remaining 58 patients ($p = 0.023$). Table 2 lists 5-year overall survival and recurrence-free rates based on the extent of prostate involvement by transitional cell carcinoma in the 58 group 2 patients. Figure 1 shows the impact of the stage P4a designation in terms of overall survival compared with that of prostatic involvement originating from within the prostate. Combining group 2 patients with stromal invasion with the 40 who had stage P4a in group 1 produced a mean 5-year overall survival of 25% ± 10% versus 49% ± 11% in those with acinar and ductal involvement ($p = 0.024$). No statistically significant difference in survival was observed in men with ductal and acinar involvement.

Primary bladder stage in the 76 patients was divided into 2 groups (superficial stages Pis, Pa and P1, and muscle invasive P2a/b and P3a/b) or into 4 groups (stages Pis, P1, P2a/b and P3a/b) ($p = 0.045$ and 0.004, respectively, fig. 2). Figure 3 shows the overall survival rate in patients with superficial and muscle invasive tumors ($p = 0.004$). Lymph node status affected survival. The 5-year overall mean survival rate was 44% ± 9% in lymph node negative patients compared with 13% ± 12% in those with positive lymph nodes ($p = 0.034$). Figure 4 shows the impact of lymph node involvement on survival. In addition to prostate transitional cell carcinoma, 10 and 14 patients also had intraepithelial neoplasia and adenocarcinoma of the prostate, respectively. A Cox proportional hazards model of survival and recurrence-free survival selected age ($p = 0.003$ and 0.001, respectively), lymph node involvement ($p = 0.01$ and 0.05) and the degree of prostate invasion ($p = 0.003$ and 0.01) as independent prognostic variables.

TABLE 1. *Bladder and prostate tumor stage*

	No. Pts. (%)
Bladder tumor:	
P0, Pa, P1, Pis	23 (30)
P2, P3a	19 (25)
P3b	34 (45)
Prostate invasion:	
Urethral mucosa	26 (34)
Ductal/acinar	10 (13)
Stromal	22 (29)
Extracapsular	18 (24)

TABLE 2. *Five-year overall and recurrence-free survival in 58 group 2 patients*

	% Overall ± SE	% Recurrence-Free ± SE
Urethral tumor	46 ± 12	45 ± 12
Ductal involvement	64 ± 17	70 ± 14
Stromal invasion	29 ± 15	35 ± 16

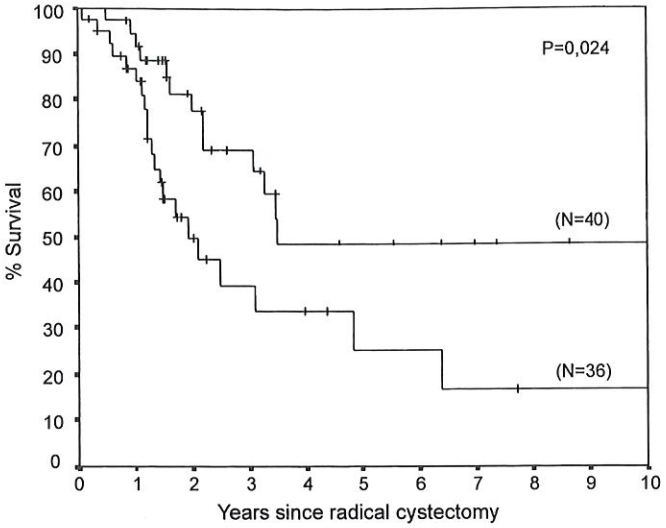

FIG. 1. Overall mean 25% ± 10% versus 49% ± 11% survival rate in 40 patients with stromal invasion in group 2 and with stage P4a in group 1 versus 36 with acinar and ductal involvement ($p = 0.024$).

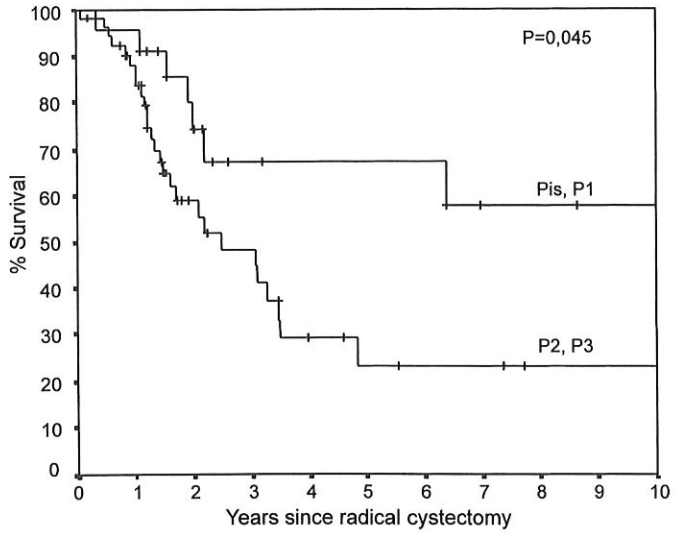

FIG. 2. Survival in 76 patients divided into superficial stages Pis, Pa and P1, and muscle invasive stages P2 and P3 stratified by primary bladder stage ($p = 0.045$).

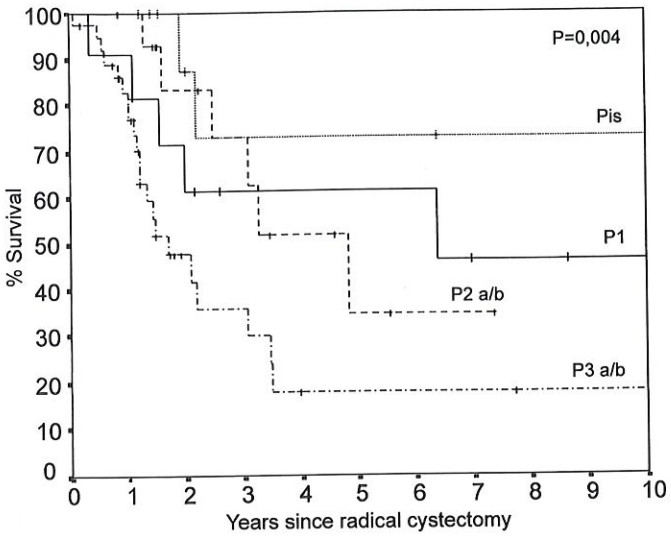

FIG. 3. Survival in 76 patients stratified by primary bladder stages Pis, P1, P2a/b and P3a/b) (p = 0.004).

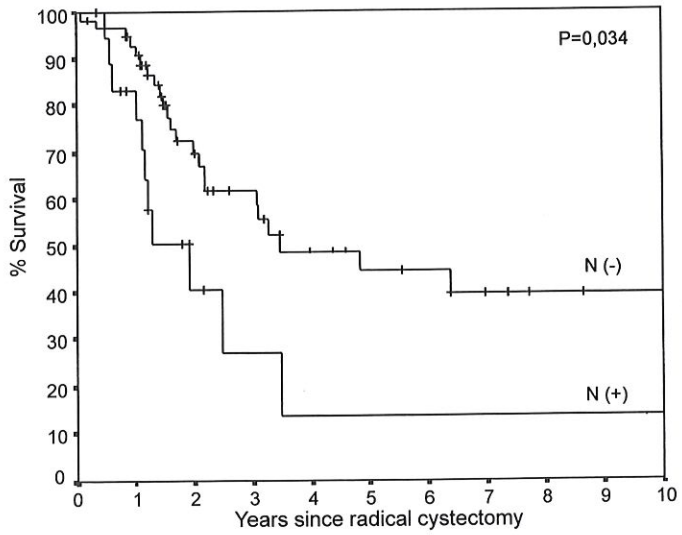

FIG. 4. Survival according to lymph node positive (*n (+)*) and negative (*n (−)*) disease (p = 0.034).

DISCUSSION

The incidence of primary transitional cell carcinoma of the prostate is thought to represent 1% to 4% of all prostate malignancies.[8–10] On the other hand, transitional cell carcinoma extending into the prostate with concurrent bladder cancer is more common, occurring in 7% to 43% of cases.[2,3] The staging system of Jewett and Strong[11] subsequently modified by Marshall[12] classifies any prostate invasion as stage D1. The TNM classification categorizes it as stage P4aN0M0.[13] Neither of these classification schemes distinguishes stromal invasion secondary to prostatic urethral or ductal basement membrane invasion and large extravesical primary bladder tumors invading the prostatic stroma.[6] However, the prognosis is different for superficial bladder transitional cell carcinoma with ductal extension and stromal invasion. Pagano[14] and Esrig[6] et al reported that prostate involvement by transitional cell carcinoma can be separated into 2 distinct clinicopathological entities that should not be included in the same stage. These clinical observations suggest that when prostatic stromal involvement is discovered early and treated aggressively with radical cystoprostatectomy, it may translate into better survival. Our study shows that stage P1 bladder tumors with prostatic stromal invasion occurring intraurethrally confer better survival than those with extravesical tumor extension into the prostate. Therefore, a separate designation is required.

After transitional cell carcinoma of the prostate is diagnosed controversy persists about appropriate management. Bretton et al from Memorial Sloan-Kettering Cancer Center reported a 87% complete response rate for prostatic urethral transitional cell carcinoma to after bacillus Calmette-Guerin but only 4 of 23 patients had ductal involvement and none had stromal invasion.[15] Others believed that minimal ductal involvement by transitional cell carcinoma does not preclude a trial of bacillus Calmette-Guerin but careful followup and prostate biopsies are mandatory.[16] However, as noted by Matzkin et al, it is difficult to determine on transurethral biopsy demonstrating ductal involvement that underlying stromal invasion is not also present.[17] When one considers transurethral resection of primary bladder tumor as definitive therapy for high grade lesions, deep transurethral resection biopsies of the prostatic urethra should be done to evaluate possible ductal or stromal involvement. However, Donat et al observed that the specificity, sensitivity and positive predictive value of transurethral resection biopsy for predicting the degree of involvement at cystectomy was low.[4]

Schellhammer et al first reported a difference in survival based on the presence or absence of stromal invasion.[2] The 5-year survival rate for prostatic mucosal involvement was 50% versus 22% for stromal invasion. We confirmed these observations in our combined cohort of men with mucosal and ductal involvement versus stromal invasion (49% versus 29%).

In the series of Esrig et al it was proposed that primary bladder tumor stage significantly affects survival.[6] For tumors with and without stromal invasion primary bladder stage affected survival. In our series we divided bladder stage in all patients into carcinoma in situ, lamina propria invasion, muscle invasion and extravesical disease. The survival rate for muscle invasive (stages P2a/b) and extravesical (stages P3a/b) disease was less than that of stages P1 and Pis.

Our statistical analysis of the survival rate according to the degree of prostatic invasion shows that patients with noncontiguous stage P4a disease by direct extension from the urethra have a better prognosis and more favorable outcome than those with bladder tumor invading the prostatic stroma via extension through the whole bladder wall. Age and lymph node involvement were also prognostic factors.

CONCLUSIONS

The staging system for transitional cell carcinoma of the prostate is impractical due to a lack of consensus on which staging criteria should be applied. Degrees of prostate invasion by transitional cell carcinoma are currently not classified according to prognostic value. No distinctions have been made in staging classifications according to the different pathways of prostate involvement, that is by direct extension from the bladder wall or via the urethra. Currently transitional cell carcinoma of the prostate is always considered advanced disease. Patients with high grade superficial disease at or around the bladder neck and trigone should be evaluated for early prostatic involvement because it can suggest the possibility of silent stromal invasion and may provide an indication for early cystectomy to improve survival.

We observed that the current staging system of this feature is not predictive of patient outcome. Bladder and prostate tumors should be staged separately. Consequently another specific staging system of prostate involvement is warranted.

REFERENCES

1. Melicow, M. M. and Hollowell, J. W.: Intra-urothelial cancer: carcinoma in situ, Bowens's disease of the urinary system: discussion of thirty cases. J Urol, **68:** 763, 1952
2. Schellhammer, P. F., Bean, M. A. and Whitmore, W. F., Jr.: Prostatic involvement by transitional cell carcinoma: pathogenesis, patterns and prognosis. J Urol, **118:** 399, 1977
3. Wood, D. P., Jr., Montie, J. E., Pontes, J. E., Vanderburg Medendorp, S. and Levin, H. S.: Transitional cell carcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. J Urol, **141:** 346, 1989
4. Donat, S. M., Genega, E. M., Herr, H. W. and Reuter, V. E.: Mechanisms of prostatic stromal invasion in patients with bladder cancer: clinical significance. J Urol, **165:** 1117, 2001
5. Pagano, F., Bassi, P., Prayer Galetti, T., Meneghini, A., Milani, C., Artibani, W. et al: Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastasis classification. J Urol, **145:** 45, 1991
6. Esrig, D., Freeman, J. A., Elmajian, A. D., Stein, J. P., Chen, S.-C., Groshen, S. et al: Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. J Urol, **156:** 1071, 1996
7. Hardeman, S. W. and Soloway, M. S.: Transitional cell carcinoma of the prostate: diagnosis, staging and management. World J Urol, **6:** 170, 1988
8. Rubeinstein, A. B. and Rubnitz, M. E.: Transitional cell carcinoma of the prostate. Cancer, **24:** 543, 1969
9. Wolfe, J. H. and Lloyd-Daviies, R. W.: The management of transitional cell carcinoma of the prostate. Br J Urol, **53:** 253, 1981
10. Bates, H. R., Jr.: Transitional cell carcinoma of the prostate. J Urol, **101:** 206, 1969
11. Jewett, H. J. and Strong, G. H.: Infiltrating carcinoma of the bladder: relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J Urol, **55:** 366, 1946
12. Marshall, V. F.: The relation of the preoperative estimate to the pathologic demonstration of the extent of vesical neoplasm. J Urol, **68:** 714, 1952
13. Sobin, L. H. and Wittekind, C.: TNM Classification of Malignant Tumours, 5th ed. New York: International Union Against Cancer, 1997
14. Pagano, F., Bassi, P., Drago Ferrante, G. L., Piazza, N., Abatangelo, G., Pappagallo, G. L. et al: Is stage PT4a (D1) reliable in assessing transitional cell carcinoma involvement of the prostate in patients with a concurrent bladder cancer? A necessary distinction for contiguous or non contiguous involvement. J Urol, **155:** 244, 1996
15. Bretton, P. R., Herr, H. W., Whitmore, W. F., Jr., Badalament, R. A., Kimmel, M., Provet, J. et al: Intravesical bacillus Calmette-Guerin therapy for in situ transitional cell carcinoma involving the prostate urethra. J Urol, **141:** 853, 1989
16. Montie, J. E., Wood, D. P., Jr., Mendendorp, S. V., Levin, H. S. and Pontes, J. E.: The significance and management of transitional cell carcinoma of the prostate. Semin Urol, **8:** 262, 1990
17. Matzkin, H., Soloway, M. S. and Hardeman, S.: Transitional cell carcinoma of the prostate. J Urol, **146:** 1207, 1991