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THE RELATIONSHIP AMONG MULTIPLE RECURRENCES, PROGRESSION AND PROGNOSIS OF PATIENTS WITH STAGES TA AND T1 TRANSITIONAL CELL CANCER OF THE BLADDER FOLLOWED FOR AT LEAST 20 YEARS

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ABSTRACT

A retrospective study was done on 176 patients with primary stages Ta and T1 bladder cancer treated between 1963 and 1972. One patient was lost to followup after 6 years, while the remainder were followed to death or for at least 20 years. In 1993, 13 patients had no evidence of disease, 39 died of bladder cancer and 123 died of intercurrent disease. Of 77 patients with a primary noninfiltrating tumor and 99 with a primary lamina propria invasive tumor 9 (11%) and 30 (30%), respectively, died of bladder cancer. Recurrences were noted on 10 or more cystoscopic studies in 16 patients and 10 died of bladder cancer 3.5 to 19 years after the primary transurethral resection. A total of 14 patients received repeated thiotepa instillations, all continued to have recurrences and 10 subsequently died of bladder cancer. Only 1 upper tract tumor was diagnosed on routine followup excretory urography. Invasive transitional cell carcinoma of the bladder developed in only 1 of 59 patients who had been tumor-free for 5 years.

The results indicate that patients with recurrences on 10 or more cystoscopic studies will continue to have recurrences until death or cystectomy. Recurrence more than 4 years after the primary tumor operation is another ominous sign. Repeated thiotepa instillations did not influence the course of the disease in patients with a history of multiple recurrences. Followup cystoscopy may be discontinued 5 to 10 years after the last recurrence, at least in patients with a solitary low grade primary tumor. Routine followup urographic studies are neither cost-effective, clinically indicated nor justified in patients with superficial bladder cancer.

KEY WORDS: bladder neoplasms, recurrence, follow-up studies, thiotepa

Superficial bladder cancer (stages Ta and T1) is diagnosed primarily and treated by transurethral bladder resection. More than 50% of the patients will have recurrences, and 2 to 6% of those with noninfiltrating grades 1 and 2 tumors and 21 to 48% with grades 2 and 3 tumors invading the lamina propria will eventually have progression and die of the disease.[1,2] The ideal situation would be if the prognosis of the individual patient could be predicted early in the course of the disease so that patients with potentially progressive cancer could be treated more aggressively early. Patients who would be clinically cured after a few transurethral resections could then be spared intravesical therapy and radical operations. The number, size, stage and grade of the primary tumor provide valuable prognostic information but the disease course in the individual case seems to be highly variable.[3] The presence of urothelial dysplasia in apparently tumor-free areas of the bladder also has a significant impact on prognosis.[4] Flow cytometry, mitosis count and tumor markers to date have been shown to be of limited clinical usefulness.[3] Therefore, studies on long-term prognosis are important. However, relatively few studies exist in which patients have undergone repeated transurethral resections and fulgurations over a long period.[2,5–9] The fate of patients subjected to repeated resections is seldom reported, probably due to the limited followup in the literature. As a matter of fact, the natural history with regard to tumor recurrence and progression after transurethral resections has not been well documented since there seem to be no reports with followup of longer than 15 years.[2]

During the last 30 years at our hospital stages Ta and T1 bladder cancer has primarily been treated by repeated transurethral bladder resection, while cystectomy was performed in patients with multiple or large lamina propria invasive tumors, muscle or vascular invasion and extensive carcinoma in situ. When the age or general condition of the patient prevented cystectomy, radiotherapy was the treatment of choice. Intravesical chemotherapy was rarely used with the exception of thiotepa instillations between 1969 and 1975, and bacillus Calmette-Guerin (BCG) instillations were not given before 1986. Since anecdotal cases indicated that repeated recurrences are ominous signs for prognosis, we decided to review a large series of patients with stages Ta and T1 bladder cancer who also had long-term followup.

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PATIENTS AND METHODS

Between 1963 and 1972, 230 patients with a histopathological diagnosis of bladder cancer without muscle invasion (stages Ta and T1) were treated. These cases were reviewed in 1977.[10] The histological material could not be retained in 8 cases and invasive growth could not be evaluated in 13. More advanced disease (muscle invasion or metastases) was found in 24 patients. The bladder tumor diagnosis could not be verified in 3 cases. Three patients with upper tract tumors and 2 with carcinoma in situ of the bladder were also excluded. The 5 to 10-year followup of the remaining 177 patients has been reported previously.[10] During 1993, all of the clinical records were reviewed again. Only 1 patient was lost to followup after 6 years. The new histopathological material (transurethral bladder resection specimens, cystectomy and autopsy material) obtained after the 1977 review was evalu-

ated by the same pathologist (S. L. J.) as the initial material. All tumors were of transitional cell origin, and graded according to the principles of Bergqvist et al[11] and staged according to the TNM classification.[12]

At the end of 1993, 163 patients had died and autopsy was done in 82 cases. More than 80% of the patients died at hospitals or extended care facilities, including nursing homes. The majority of the patients had undergone cystoscopy within 1 year of death. In 1993, 9 patients were alive with a cystoscopically normal bladder. All but 1 patient underwent endoscopy every year or every other year despite the fact that the last recurrence among them was diagnosed in 1973. In addition, 5 cystectomy patients were alive in 1993, 4 of whom were followed regularly. Two patients refused regular followup and denied any symptoms of bladder cancer. One of them was a man initially diagnosed with bladder cancer but shown to have an inverted papilloma upon review of the slides. This patient was excluded from further discussion.

The term recurrence in this study covers true recurrences and new occurrences. If the tumor(s) was not completely removed at 1 operation and additional surgery was needed, the case was counted as 1 recurrence. Fulguration without biopsy was also counted as 1 recurrence.

RESULTS

Stage Ta (noninvasive tumors). Grade 1 (22 patients): One patient underwent cystectomy for large primary tumors. Two patients were treated with radiotherapy, since grade and stage initially were considered to be higher and both died of intestinal perforation with peritonitis. Six patients had no recurrences after the resection and all died of intercurrent disease at a median of 8 years (range 0.5 to 26) after the primary operation. A total of 9 patients died of intercurrent disease after 2 to 9 recurrences (1 of them underwent cystectomy after 6 grade 1 recurrences). No patient with less than 10 recurrences had progression in stage. More than 10 recurrences were noted in 4 patients.

Grade 2 (46 patients): One patient underwent cystectomy for large primary tumors and 2 underwent cystectomy after 1 year due to repeated stage Ta recurrences. A total of 15 patients had no recurrence after the primary resection and they survived 3 to 28 years (median 13), while 19 had 1 to 8 recurrences and died of intercurrent disease. Only 1 patient with less than 10 recurrences had progression in stage 5 years after the primary operation (recurrence 7). A total of 8 patients had more than 10 recurrences.

Grade 3 (9 patients): Two patients underwent cystectomy as primary treatment and 1 underwent radiotherapy. Of 6 patients who underwent partial bladder resection or transurethral bladder resection 2 had recurrences: 1 had a small grade 1 tumor 6 months after the primary operation, and 1 underwent cystectomy due to incontinence and decreased bladder capacity after recurrence 7. Histopathological examination revealed muscle invasion. No other patient had progression in stage.

Stage T1 (lamina propria invasion). Grade 2 (41 patients): A total of 16 patients underwent cystectomy or external beam radiotherapy during year 1 after diagnosis, 5 (30%) of whom died of metastatic bladder cancer. There were no recurrences after the primary resection in 8 patients and they survived 4 to 16 years (median 11). Of 13 patients with 1 to 8 recurrences 10 died of intercurrent disease and only 1 underwent cystectomy (after 6 stage Ta recurrences within 2 years). In 1 patient the primary tumor showed lymphatic invasion and he died of metastases after 33 months. Two patients had progression in stage after 2 and 5 years, respectively (with 4 and 1 recurrences, respectively). Four patients had 10 or more recurrences.

Grade 3 (48 patients): Of 30 patients who underwent cystectomy or external beam radiotherapy during year 1 after the diagnostic operation 12 (40%) died of metastatic bladder cancer. Two patients were lost to followup after the primary operation and returned after 1 to 3 years: 1 with lymphatic invasion and 1 with perivesical growth. Both patients underwent cystectomy but died of metastases. Of 16 patients who underwent transurethral resection or partial bladder resection 4 had no recurrences, while 12 had 1 to 9 recurrences and 9 of them are alive or had died of intercurrent disease. One patient had progression in stage after 1.5 years and 1 after 4 years. Carcinoma in situ developed after 12 years in 1 man who was treated with thiotepa but he died of invasive bladder cancer 14 years after the primary operation.

Grade 4 (10 patients): Cystectomy was done within 1 year after diagnosis in 4 patients and 6 underwent external beam radiotherapy. A total of 5 patients (50%) died of bladder cancer, 3 died of intercurrent disease and 1 cystectomy patient was alive in 1993. One cystectomy patient was lost to followup after 6 years.

Patients with recurrences at 10 or more cystoscopic examinations. A total of 16 patients had recurrent tumor on 10 or more cystoscopic studies. The tumor volume was not determined but the impression, after having evaluated the surgical reports, was that the larger the number and volume of the recurrent tumors, the shorter the survival. Three of 12 patients with primary stage Ta, grades 1 to 2 tumors lacked histopathological evidence of invasion before metastases were diagnosed. Of the 16 patients with 10 or more positive cystoscopic studies 11 were treated with intravesical thiotepa and 9 of them died of metastatic bladder cancer at a median of 4 years (range 0.5 to 15) after the first 6 instillations.

Primary Stage Ta, Grade 1 Tumor: One patient had 22 recurrences of 1 to 2 small tumors and died of intercurrent disease with tumor in the bladder 16 years after the primary resection. Three patients died of bladder cancer after 20, 28 and 33 recurrences, respectively (6, 12 and 16 years after the primary resection). They had multiple tumors on almost every cystoscopic study and were treated with thiotepa without effect.

Primary Stage Ta, Grade 2 Tumor: Of the patients 8 had 10 to 34 recurrences, and 6 of them had progression in stage and died of metastatic bladder cancer 4 to 19 years after the primary operation. One man underwent cystectomy after 12 years and 20 recurrences, and was alive 25 years after the primary operation. One woman died of pyelonephritis after 14 years and 32 small recurrences.

Primary Stage T1, Grade 2 Tumor: One man had 10 stage T1 recurrences and died of pyelonephritis 6 weeks after transurethral bladder resection for a recurrence, while 1 had 12 stage Ta, grades 1 to 2 recurrences and died of a stroke 4 months after the last episode. A patient with progression to muscle invasion after 20 stage Ta, grade 2 recurrences underwent cystectomy and died of metastatic rectal adenocarcinoma 4 years later. A patient with 30 stage Ta, grades 1 to 2 recurrences had progression to prostate invasion after 14 years, and died of bladder cancer and uremia.

Patients with recurrences more than 4 years after the primary operation. Primary Stage Ta, Grades 1 to 2 Tumors: Six patients had 12 to 16 tumors within 4 years after the primary operation and recurrence continued to develop. Of these 6 patients 5 died of bladder cancer 5 to 11 years after the primary operation and 1 had a small bladder tumor at autopsy 14 years postoperatively. Four patients had 2, 4, 4 and 7 tumors, respectively, within 4 years and progression in stage after 7, 22, 22 and 27 recurrences, respectively. Two patients had 8 and 9 recurrences within 4 years after the primary operation: 1 underwent cystectomy after 12 more recurrences, while 1 had 12 more tumors and died of intercurrent disease. Five patients underwent resections or fulgurations of single grade 1 or 2 tumors with 2 to 4-year inter-

vals and died of intercurrent disease 7 to 17 years after the primary operation.

Primary Stage T1, Grades 2 to 3 Tumors: Two patients with 4 and 11 tumors within 4 years had 3 and 2 more recurrences but died within months after the last episode. A total of 3 patients with 7 to 9 stage Ta recurrences within 4 years had progression in stage after 1, 12 and 23 more recurrences. Two patients had been free of tumor since the primary operation but late recurrences developed: 1 had a muscle invasive tumor after 5 years (at autopsy) and 1 had carcinoma in situ after 12 years.

Over-all 24 patients with primary stage Ta or T1 tumors had recurrences more than 4 years after the primary operation and 14 of them had progression to muscle invasion or metastases.

Thiotepa treatment. A total of 13 patients with multiple tumors at every cystoscopic study and 1 with carcinoma in situ were treated with 1 to 10 series of 6 instillations of 20 to 50 mg. thiotepa every other day. All 14 patients had recurrences after the thiotepa treatment and 10 later died of bladder cancer.

Number of primary tumors. Stage Ta, Grades 1 to 2: No disease recurred in 22 patients who underwent transurethral bladder resection or partial bladder resection: 18 (86%) had solitary primary tumors and 4 (14%) had 2 primary tumors. Disease recurred in 44 patients with primary grades 1 to 2 tumors. Two or more primary tumors were present in 21 of 44 patients (48%) with recurrences. At least 4 primary tumors were present in 8 patients: 3 underwent cystectomy, 3 died of bladder cancer and 2 had repeated recurrences until death. Of the 16 patients with 10 or more recurrences 8 had solitary, 1 had 2 and 7 had 4 or more primary tumors.

Followup cystoscopy. A total of 59 patients had no recurrences at followup endoscopy for 5 years or longer. Disease later recurred in 2 of them: 1 had a solitary grade 1 recurrence after a tumor-free period of 6 years and 1 had carcinoma in situ diagnosed 12 years after resection of a grade 3 tumor with invasion into the lamina propria. The bladder capacity was decreased and the mucosa was described as inflamed at least 3 years before the diagnosis of carcinoma in situ. The remaining 57 patients survived 6 to 29 years (median 13) after the last recurrence and had negative cystoscopic results until 1993 or death. Of the patients 8 were alive in 1993 and were examined with cystoscopy every year or every other year but the last recurrence was in 1973.

Upper tract tumors. During the observation period, only 1 patient had a renal pelvic tumor diagnosed on routine followup excretory urography (IVP). Nephroureterectomy was performed and histopathological examination showed noninvasive grade 2 cancer. The patient died of metastatic bladder cancer 1 year later. Two patients presented with hematuria and IVPs showed a renal pelvic tumor in 1 and ureteral tumors in 1 despite previously normal routine followup IVPs.

DISCUSSION

Of the 176 patients with a primary stage Ta/T1 bladder cancer 20% did not have recurrences after the initial transurethral or open resection. Of our patients 18 who were treated with transurethral bladder resection or partial bladder resection only had recurrences but eventually became tumor-free within 4 years and lived for more than 10 years without further recurrences. Barnes et al reported on 28 similar patients in a long-term followup study and suggested that they had acquired an immunity to the tumor.[5] On the other hand, our patients with recurrences more than 4 years after the primary operation continued to have recurrent tumors until death, unless cystectomy was performed. Some of them had relatively benign disease with recurrent solitary low grade tumors and an interval of many years. Others had frequent recurrences of multifocal tumors that finally progressed and killed the patient.

Our report further showed that patients with stage Ta, grades 1 to 2 recurrences on 10 or more cystoscopic studies continued to have recurrent disease until death or cystectomy and most of them died of bladder cancer 3.5 to 19 years (median 9.5) after the primary operation. The larger the number and volume of the tumors the earlier the progression. Several other studies have also shown that patients with multiple recurrences have an increased risk of progression.[7-9,13] Thus, as early as 1950, Deming found that 67% of patients with more than 10 tumors per year later had progression to invasive disease.[13] We could confirm previous observations of a high risk of recurrent tumors in patients with at least 2 primary tumors.[1,7,8] Furthermore, all of our patients with 4 or more primary neoplasms either underwent cystectomy or died with or of bladder cancer.

There sometimes are marked difficulties in clinically and histopathologically identifying an invasive tumor in a bladder that is scarred and deformed after multiple resections, which may explain the dismal prognosis in these patients. The majority of our patients with more than 10 recurrences also seemed to have had problems with incontinence and decreased bladder capacity. Whether this was related to the treatment or the unrecognized presence of urothelial dysplasia/carcinoma in situ cannot be stated in this retrospective study, since mapping biopsies generally were not performed.

Due to the fact that many patients with lamina propria invasion underwent cystectomy or radiotherapy, the results may not be valid for current treatment policy, which is based on transurethral resections and intravesical instillations.[1,2,14] Neither was the depth of the lamina propria invasion determined in our study, a factor that recently has been shown to have an important impact on prognosis.[15]

Only 3 upper tract cancers were found among 176 patients followed from the primary operation until death or for at least 20 years. Routine followup IVPs were performed at various intervals but only 1 of the upper tract tumors was detected by this method. Walzer and Soloway found only 1 upper tract tumor in 337 patients followed for up to 9 years and considered such routine IVPs neither cost-effective nor necessary, a statement with which we fully agree.[16] Recently, however, Herr et al found an 18% risk of upper tract cancer in patients with superficial bladder tumors treated with BCG and followed for 10 years. It may be that BCG alters the natural course of the disease and surveillance of the upper urinary tract seems to be needed in such patients.[14]

Serial thiotepa instillations were given only to patients with repeated multiple recurrences and this treatment seemed to have been of limited value or of no value at all. The lack of effect of thiotepa in our patients sharply contrasts with the report by England et al, who claimed good results after similar thiotepa treatment regimens in patients with multiple superficial bladder recurrences.[17] There are few reports on the long-term outcome of patients given intravesical cytostatic agents.[18] In an analysis of multiple randomized clinical trials Herr concluded that thiotepa only had an 8% better prophylactic effect than placebo compared to BCG, which had a 42% better effect than placebo.[19] Our results seem to support his analysis regarding the limited benefit of thiotepa. According to our experience, most patients with noninvasive bladder cancer will be cured by 1 or a few transurethral resections and, therefore, do not need intravesical therapy. Patients with multiple recurrences need intravesical therapy and BCG clearly is the preferred treatment. However, the long-term effect of BCG is far from known.[14] Whether BCG is effective in patients with recurrences on 10 or more cystoscopic studies is unknown, since the number of recurrences before the start of BCG treatment was not stated in most reports. In the study by Kavoussi et al, for example, only 2 of 104 patients had 10 or more recurrences before BCG

treatment.[20] It was suggested recently that BCG treatment was less successful and serious side effects were more common in patients who were treated more than 4 years after the primary operation.[21]

Our study results indicate that it may be reasonable to discontinue followup cystoscopy 5 to 10 years after the last recurrence, at least in patients with a solitary low grade primary tumor. Previous studies have shown an increased risk of late invasive recurrences in smokers[22] and in BCG treated patients,[14] and it appears justified not to discontinue followup.

CONCLUSIONS

The implications of our study are that patients with stage Ta, grades 1 to 2 bladder cancer with recurrences after 4 years and/or on 10 or more cystoscopic studies will continue to have bladder tumors. Patients with small recurrent grade 1 neoplasms may be treated with repeated cystodiathermy but those with large and/or multiple tumors should be treated more aggressively, much earlier than after 10 recurrences. Serial thiotepa instillations have not been shown to be beneficial in such patients. Our results confirmed previous reports that demonstrated routine followup IVPs to be neither necessary nor cost-effective.

Ms. Lena Wiman, Department of Urology and Ms. Karin Karlsson, Department of Pathology, Sahlgrenska University Hospital assisted with the study. Valuable information was provided by Mr. Erik Holmberg, Oncology Center for Western Sweden, Ms. Mona Agroth, Department of Pathology, Sahlgrenska University Hospital, and Drs. Karl-Henrik Leissner, Mölndal; Viggo Sörensen, Sante Olling and Anders Olsfors, Göteborg; Björn Kihl, Karlstad; Lennart Roxvall and Jan Hammarsten, Varberg; Thomas Ranch, Uddevalla; Håkan Kleist and Torkel Wahlin, Trollhättan; Lennarth Holmgren, Falköping; Margareta Andersson, Kungälv; Per-Olof Magnusson, Tidaholm; Nils Wedel, Kungsbacka; Anders Tholén, Alingsås, and Clas Eriksson, Skövde, Sweden.

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EDITORIAL COMMENT

Again, the Swedish urologists have produced an excellent review detailing the long-term followup of a sizeable population with a urological neoplasm. In this instance the tumor is bladder cancer, specifically stages Ta and T1 transitional cell carcinoma, and the study consists of a 20-year followup after the initial endoscopy and tumor resection. One wonders why there are so few long-term studies emanating from the United States? There is 1 obvious difference between the 2 societies. The Swedes traditionally live most of their lives in 1 city and their medical care is centralized within the National Health Service. In contrast, we in the United States live in a mobile society. It is not uncommon for a man or woman to initiate medical care in New York and within several years move to Florida or Arizona, where they will live the rest of their lives. Multiple physicians and even specialists are not uncommon.

Although the conclusions are not surprising, they provide some important messages that may well influence our patient management. Of their patients 22%, if followed for a sufficient interval, eventually died of bladder cancer. Consistent with other reports, three-quarters of the patients who died of transitional cell carcinoma initially had invasion of the lamina propria (stage T1). Hopefully, if we can decide earlier which of these patients would benefit from cystectomy we can improve upon this 30% death rate for stage T1 transitional cell carcinoma.

Patients who continue to have recurrences were at a higher risk of dying of transitional cell carcinoma. Thus, it seems prudent to use effective intravesical therapy early for the patient with multiple tumors, high grade transitional cell carcinoma or a stage T1 tumor. In my experience approximately 40 to 50% of such patients will have an excellent result after complete transurethral resection followed by BCG or mitomycin C. Those who continue to have recurrent high

grade transitional cell carcinoma should be considered for cystectomy.

I was not surprised with the data on the diagnostic value of routine upper tract studies in patients with stages Ta and T1 transitional cell carcinoma of the bladder. Except for patients with carcinoma in situ of the lower urinary tract, no more than 5% (possibly closer to 1 to 2%) of such patients will have an upper tract tumor. Of equal importance, even routine every 6-month radiographic studies of the upper urinary tract do not reliably detect the tumors that develop. Others have also found that hematuria is still a common presenting sign despite routine monitoring.

This excellent article raises several issues that can immediately impact on our management decisions. Will the 20-year followup for stages Ta and T1 transitional cell carcinoma treated between 1994 and 1995 prove to be any better? Hopefully, the addition of fiberoptic and video endoscopy, and the appropriate use of BCG for high grade transitional cell carcinoma will make a difference. The development of bladder replacement procedures has lessened the quality of life impact of radical cystectomy and provides an alternative for patients who refuse cystectomy because they do not want to wear a bag. Our challenge is to determine if we can improve upon the result reported.

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