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PROSTATE CANCER DETECTION, CHARACTERIZATION, AND CLINICAL OUTCOMES IN MEN AGED 70 YEARS AND OLDER REFERRED FOR TRANSRECTAL ULTRASOUND AND PROSTATE BIOPSIES

JEFFREY C. SUNG, JOHN N. KABALIN, AND MARTHA K. TERRIS

ABSTRACT

Objectives. To evaluate the diagnostic findings and treatment options chosen in men aged 70 years and older referred for prostate biopsy.

Methods. Age, prostate-specific antigen (PSA), biopsy pathology, clinical stage, treatment pursued, and treatment outcome were analyzed in 210 men age 70 years and older referred for transrectal ultrasound and prostate biopsies. All patients were followed for a mean of 46.9 months (range 28 to 63).

Results. Cancer was found in 120 (56.8%) of the patients. The cancer detection rate was significantly higher (81.0%) in patients aged 80 years and older than those younger than 80 years. Cancer patients aged 80 years and older had a higher rate of poorly differentiated cancer (64.7%) compared with the 70 to 74-year-olds (33.3%) and 75 to 79-year-olds (32.1%). The patients aged 80 years and older also had a larger proportion of high-stage cancer. The patients younger than 80 years had a significantly higher incidence of stable/falling PSA with treatment compared with the older patients. Of the 210 patients, 41 (19.4%) died within 5 years of the diagnostic procedure; 3 died of prostate cancer. The death rate was not significantly different among the three age groups evaluated. None of the patients aged 80 years and older died of prostate cancer.

Conclusions. Patients aged 80 years and older who are diagnosed with prostate cancer are less likely to respond well to treatment and usually die of unrelated causes. Aggressive diagnosis, staging, and treatment in octogenarians should be guided by the patients' symptoms, overall health, and personal preferences. UROLOGY 56: 295-301, 2000. © 2000, Elsevier Science Inc.

The Prostate Patient Outcomes Research Team (PPORT) reported the national Medicare experience with prostate cancer treatment outcomes in 1993, concluding that aggressive treatment of prostate cancer in patients aged 70 years and older was generally harmful.¹ Subsequent treatment trends have shown a dramatic drop in the number of patients aged 70 years and older who undergo radical surgery.² Even the aggressive evaluation for the presence of prostate cancer in men aged 70

years and older is discouraged because treatment options are limited.³ However, in clinical practice many men in this age group present for evaluation and counseling. We retrospectively reviewed the presentation and clinical outcome in 210 consecutive men aged 70 years and older who were referred by urologists for transrectal ultrasound and ultrasound-guided prostate biopsy in the 3 years following the PPORT recommendations.

MATERIAL AND METHODS

From March 1, 1994 to February 28, 1997, 210 men aged 70 years and older were referred to the urology clinic of the Veterans Affairs Palo Alto Health Care System for transrectal ultrasound and ultrasound-guided prostate biopsies. The men ranged in age from 70 to 88 years (mean 74, median 74). In all patients, serum for determination of prostate-specific antigen (PSA) level and digital rectal examination were obtained prior to the procedure.

PSA levels before biopsy ranged from 0.4 to 564 ng/mL (mean 23.3, median 9.4). Transrectal ultrasound and ultra-

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Submitted: December 20, 1999, accepted (with revisions): March 16, 2000

sound-guided biopsies were performed in all patients by the systematic sextant method previously described.⁴ Additional directed, transition zone, or seminal vesicle biopsies were performed when clinically indicated.⁵⁻⁸ The average number of biopsies taken was 8 (range 6 to 13). Biopsy specimens from each of the sites were labeled and submitted separately for histologic analysis. Each specimen was fixed in 10% formalin, embedded in paraffin, sectioned longitudinally, and stained with hematoxylin and eosin. Each biopsy core was carefully examined microscopically for the presence of cancer. For each patient, the Gleason grade of any cancer identified was noted. Patients with Gleason grade 3 + 4 carcinoma or less were considered well differentiated and those with Gleason grade 4 + 3 carcinoma or higher were considered poorly differentiated.⁹

Patients found to have prostate cancer underwent complete clinical staging, including uniform use of bone scintigraphy in all cases. Following initiation of their choice of treatment, patients returned for clinic visits with physical examination and PSA level every 3 to 6 months at either the Palo Alto facility or another Veterans Affairs (VA) facility sharing the VISTA (Veteran's Health Information Systems and Technology Architecture, Department of Veterans Affairs, Technical Services) network through which patients could be followed. Progression of disease was considered three serial rising PSA levels after post-treatment nadir.¹⁰ For patients on expectant management, three serial PSA rises after diagnosis were used. Those patients without prostate cancer were followed with physical examination and PSA level every 6 to 12 months. All patients were followed for a mean of 52.9 months and median of 58 months (range 34 to 69). Date and cause of death were determined according to documentation in the VISTA system.

Patients were divided into three age groups for analysis: (1) 70 to 74-year-old group ($n = 132$), (2) 75 to 79-year-old group ($n = 57$), and (3) 80-year-old and older group ($n = 21$). As shown in Table I, in the 70 to 74-year-old group, the mean age was 72 years, the PSA levels ranged from 0.4 to 564 ng/mL (median 9.1), and an average of 8 biopsies were performed per patient (range 6 to 13). In the 75 to 79-year-old group, the mean age was 76 years, the PSA levels ranged from 1.9 to 120 ng/mL (median 8.2), and an average of 8 biopsies were performed per patient (range 6 to 12). In the 80-year-old and older group, the mean age was 83 years, the PSA levels ranged from 3.4 to 360 ng/mL (median 17.7), and an average of 7 biopsies were performed per patient (range 6 to 10).

Tests for correlation were performed with the Spearman's rank correlation; these correlations were tested for statistical significance by the Mann-Whitney *U* test. Evaluations for statistically significant differences between unpaired groups were performed with the Student's unpaired two-tailed *t* test.

RESULTS

In the 210 patients aged 70 years and older referred for transrectal ultrasound and biopsies, cancer was found in 120 (56.8%). As shown in Table I, the cancer detection rate was significantly higher in the 80-year-old and older age group, with cancer detected in 17 (81.0%) of the 21 patients, compared with the 70 to 74-year-old group (cancer in 75 of 132 patients or 56.8%) and the 75 to 79-year-old group (cancer in 28 of 57 patients or 49.1%).

Table I shows that of the 75 prostate cancer patients aged 70 to 74 years, 50 (66.7%) had well-differentiated prostate cancer (grade 3 + 4 or less) and 25 (33.3%) had poorly differentiated cancer

(grade 4 + 3 or higher). Similarly, in the 28 patients aged 75 to 79 years with prostate cancer, 19 (67.9%) had well-differentiated tumors and 9 (32.1%) had poorly differentiated tumors. However, there was an inverse distribution of grade in the 17 prostate cancer patients aged 80 years and older compared with the younger age groups, with only 6 (35.3%) having well-differentiated cancers and 11 (64.7%) having poorly differentiated tumors. There was a significant positive correlation between increasing age and increasing grade ($r = 0.4$, $P < 0.0005$).

Of the 210 patients aged 70 years and older referred for transrectal ultrasound and biopsy, 41 (19.4%) died within the 2 to 5-year follow-up period (Table I); only 3 (1.4%) died of complications of their prostate cancer. In the 41 patients who died, their death was an average of 25 months after biopsy (range 3 to 50). Of the 91 patients who underwent prostate ultrasound-guided biopsy but were found to have no cancer, 18 (19.8%) died during the follow-up period. Of the 120 found to have prostate cancer, 23 (19.2%) died during the follow-up period; 3 (2.5%) died of prostate cancer. This difference was not statistically significant. In the older, 80 years and older, age group, 6 (28.6%) of 21 patients died between 6 and 37 months (mean 23.2) after biopsy. In the 75 to 79-year-old group, 14 (24.6%) of 57 patients died between 4 and 50 months (mean 27.8) after biopsy. Of the 132 patients in the 70 to 74-year-old group, 21 (15.9%) died between 2 and 39 months (mean 23) after biopsy. No significant difference was seen in the death rate or the time passage between the biopsy procedure and death in any of the three age groups when all patients (both those with and without a diagnosis of cancer) are considered. However, when only the patients with cancer are considered, there was a trend toward increasing death rate with increasing age. There was an overall death rate of 16% and a 1.3% prostate cancer-specific death rate for the 70 to 74-year-old cancer patients, 21.4% overall and 7.1% prostate cancer-specific death rate for the 75 to 79-year-old prostate cancer patients, and 29.4% overall and 0% prostate cancer-specific death rate for the 80-year-old and older prostate cancer patients (Table I).

As expected, the cancer detection rate increased with increasing PSA (Table II); the prostate cancer-specific death rates also increased with increasing PSA in patients younger than 80 years of age, but patients aged 80 years and older died of other causes regardless of PSA at presentation. Similarly, the cancer detection rate increased with increasingly suspicious digital rectal examination (Table III); the prostate cancer-specific death rate increased with worsening rectal examination findings in the patients younger than 80 years of age,

TABLE I. PSA, rectal examination findings, cancer detection rate, Gleason grade, and death rates in patients aged 70 years and older referred for transrectal ultrasound and biopsy

Age (yr) (mean)	n	Mean/ Median PSA (ng/mL) (range)	Mean Number of Biopsy Cores (range)	Abnormal DRE (%)*	Cancer Detected (%)*	Gleason Grade			Deaths		
						Grade 3 + 3 or Lower (%)†		Grade 3 + 4 or Higher (%)†	All Causes, Prostate Cancer Patients (%)†	All Causes, Cancer-Specific, Prostate Cancer Patients (%)†	All Causes, Non-Prostate Cancer Patients (%)†
						3 + 3 or Lower (%)†	Grade 3 + 4 or Higher (%)†				
70-74 (72)	132	61.1/9.1 (0.4-564)	8 (6-13)	90 (68.2)	75 (56.8)	50 (66.7)	25 (33.3)	21 (15.9)	12 (16)	1 (1.3)	9 (15.8)
75-79 (76)	57	23.2/8.2 (1.9-120)	8 (6-12)	29 (50.9)	28 (49.1)	19 (67.9)	9 (32.1)	14 (24.6)	6 (21.4)	2 (7.1)	8 (27.6)
≥80 (83)	21	72.9/17.7 (3.4-360)	7 (6-10)	18 (85.7)	17 (81.0)	6 (35.3)	11 (64.7)	6 (28.6)	5 (29.4)	0 (0)	1 (25)
Total (74)	210	68.3/9.4 (0.4-57.4)	8 (6-13)	137 (64.9)	120 (56.8)	75 (52.5)	45 (37.5)	41 (19.4)	23 (19.2)	3 (2.5)	18 (19.8)

KEY: PSA = prostate-specific antigen; DRE = digital rectal examination.

* Percent of all patients in each age group.

† Percent of cancer patients in each age group.

* Percent of noncancer patients in each age group.

TABLE II. PSA levels relative to cancer detection rates and death rates in patients aged 70 years and older referred for transrectal ultrasound and biopsy

Age (yr)	n	Mean/Median PSA (range)	PSA Level at Presentation										
			<4.0 ng/mL			4.0-10 ng/mL			>10.0 ng/mL				
			Total (%)*	Cancer Detected (%)†	Deaths (%)†	Total (%)*	Cancer Detected (%)†	Deaths (%)†	Total (%)*	Cancer Detected (%)†	Deaths (%)†		
70-74	132	61.1/9.1 (0.4-564)	24 (18.2)	7 (29.2)	3 (12.5)	49 (37.1)	24 (49.0)	5 (10.2)	0 (0.0)	60 (45.5)	44 (73.3)	4 (6.7)	1 (1.7)
75-79	57	23.2/8.2 (1.9-120)	3 (5.3)	0 (0.0)	0 (0.0)	40 (70.2)	19 (47.5)	3 (7.5)	0 (0.0)	14 (24.6)	9 (64.3)	3 (21.4)	2 (14.3)
≥80	21	72.9/17.7 (3.4-360)	2 (9.5)	0 (0.0)	1 (50)	2 (9.5)	2 (100)	1 (50)	0 (0.0)	17 (81.0)	15 (88.2)	3 (17.7)	0 (0.0)
Total	210	68.3/9.4 (0.4-57.4)	29 (13.7)	7 (24.1)	4 (13.8)	91 (43.1)	45 (49.5)	9 (9.9)	0 (0.0)	91 (43.1)	68 (74.7)	10 (11.0)	3 (3.3)

KEY: PSA = prostate-specific antigen.

* Percent of all patients in each age group.

† Percent of patients in each age and PSA range group.

however, patients aged 80 years or older died of noncancer causes regardless of the stage of disease at the time of presentation. Also seen in Table III, 22 (18.3%) of the 120 cancer patients were local Stage T1, 76 (63.3%) were local Stage T2, and 24 (20.0%) had local Stage T3 prostate cancer. Further staging evaluation revealed that 10 (8.3%) of the 120 prostate cancer patients had metastatic disease. The proportion of patients with locally advanced or metastatic disease increased with increasing age (Table III). A significant positive correlation existed between increasing age and increasing stage ($r = 0.3, P < 0.0005$).

Of the 120 patients aged 70 years and older found to have prostate cancer, 9 (7.5%) elected to undergo radical prostatectomy (Table IV). One of these 9 patients choosing radical prostatectomy had biochemical failure 32 months following surgery. There were 82 (68.3%) of the 120 prostate cancer patients who chose hormonal therapy, of which 36 (43.9%) of the 82 patients eventually demonstrated progression as measured by a rising PSA during a mean follow-up of 39.5 months. Twenty-two (18.3%) patients chose expectant management of which 8 (36.4%) progressed during a mean follow-up of 46.8 months. Seven (5.8%) chose external beam radiation therapy of which 2 (28.6%) progressed during a mean follow-up of 35.5 months. No statistically significant difference was seen in the incidence of PSA failure in the patients choosing expectant management between the 70 to 74-year-old group and the 75 to 79-year-old group, nor was there a difference in the incidence of PSA failure in the patients choosing hormonal therapy between these two age groups. The incidence of biochemical progression during expectant management in the 70 to 74-year-old group was 30.0% and in the 75 to 79-year-old group was 33.3%. In patients undergoing hormonal therapy, the PSA failure rate was 25.5% in the 70 to 74-year-old group and 27.8% in the 75 to 79-year-old group. In contrast, the 80-year-old and older group had a PSA failure rate of 53.8% for hormonal therapy; this finding was a statistically significant difference from the other two age groups ($P = 0.04$). The 80-year-old and older patients who chose expectant management also had a substantially higher PSA failure rate of 66.7%, compared with the younger age groups, although this difference did not reach statistical significance.

COMMENT

We found a higher incidence of prostate cancer, grade, and stage with increasing age as well as a poorer response to therapy. Other authors have observed similar trends. In a large study of nearly 5000 prostate cancer patients, Borek *et al.*¹¹ found

that 22.2% of patients younger than age 60 years had poorly differentiated cancer compared with 32.5% for patients aged 80 years and older. In a series of 350 radical prostatectomy specimens, Kabalin *et al.*¹² found that 75% of patients older than 70 years had Gleason grade 4 and/or 5 tumor compared with 62% of those 61 to 70 years old, 54% in the 51 to 60-year-old group, and 35% in those aged 41 to 50 years. In another series based on patients diagnosed as part of a large PSA screening program, Richie *et al.*¹³ found that the cancer was organ confined in 74% of patients younger than age 60 years and in 60% of men older than 70 years of age. Such trends persist even when only the most favorable population is considered. Carter *et al.*,¹⁴ in a study of 492 men with clinical Stage T1C disease who underwent radical prostatectomy, found that age was a strong predictor of whether or not the cancer was surgically curable on the basis of pathologic findings in the surgical specimens. Similarly, Öbek *et al.*¹⁵ have documented a higher biochemical failure rate in 41 patients older than age 70 years who underwent radical prostatectomy compared with 460 patients aged 70 years and younger (27% versus 13%), as well as a shorter time until failure (median of 48 months versus median of 60 months). In addition to cancer control concerns, complications of therapy are potentially more dramatic in the older population. Catalona *et al.*¹⁶ have shown that the complications of impotence and incontinence are more common in patients aged 70 years and older. Lu-Yao *et al.*¹⁷ in a recent review of more than 100,000 patients via Medicare claims found that the 30-day surgical mortality rate following radical prostatectomy for patients between the ages of 65 and 69 years was less than 0.5%, whereas the surgical mortality rate for patients aged 70 years and older approached 1%.

Not all authors agree that older patients will have a less favorable outcome. Corral and Bahnsen¹⁸ reviewed 101 men aged 70 to 79 years with prostate cancer with a mean follow-up of 59 months and compared the 43% who underwent radical prostatectomy with the 57% who were treated with hormonal therapy, radiation therapy, or expectant management. In their study, survival for the surgically treated group was significantly better than for the medically treated group. They concluded that men undergoing radical prostatectomy at their institution in the eighth decade of life did not frequently die of intercurrent disease and experienced acceptable morbidity and mortality. Similarly, Huguenin *et al.*¹⁹ recently showed no difference in the disease-free survival of men older than 74 years of age treated with radiation therapy for their prostate cancer when compared with matched younger patients. Pow-Sang *et al.*,²⁰ in a longitudinal study of

TABLE III. Rectal examination findings/clinical stage relative to cancer detection and death rates in patients aged 70 years and older referred for transrectal ultrasound and biopsy

Age (yr)	n	Rectal Examination Findings/Clinical Stage at Presentation											
		Normal/Enlarged (Stage T1)				Nodular (Stage T2)				Fixed Mass (Stage T3)			
		Total (%)*	Cancer Detected (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†	Total (%)*	Cancer Detected (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†	Total (%)*	Cancer Detected (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†
70-74	132	42 (31.8)	12 (28.6)	8 (19.0)	0 (0.0)	77 (57.0)	50 (64.9)	10 (13.0)	0 (0.0)	13 (9.6)	13 (23.1)	1 (7.7)	4 (3.0)
75-79	57	28 (49.1)	9 (32.1)	7 (12.3)	0 (0.0)	26 (45.6)	16 (61.5)	6 (23.1)	1 (3.9)	3 (5.3)	3 (33.3)	1 (33.3)	3 (5.3)
≥80	21	3 (14.3)	1 (33.3)	0 (0.0)	0 (0.0)	10 (47.6)	10 (100.0)	3 (30.0)	0 (0.0)	8 (38.1)	3 (37.5)	0 (0.0)	3 (14.3)
Total	210	73 (38.6)	22 (30.1)	15 (20.6)	0 (0.0)	113 (53.6)	76 (67.3)	19 (16.8)	1 (0.9)	24 (11.4)	24 (29.2)	2 (8.3)	10 (4.7)

* Percent of all patients in each age group.

† Percent of patients in each age and stage group.

TABLE IV. Treatment selection and outcome in prostate cancer patients diagnosed after reaching 70 years of age

Age (yr)	n	All Prostate Cancer Patients																			
		Expectant Management				Hormone Therapy				Radiation Therapy				Radical Prostatectomy							
		Total (%)*	Failed (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†	Total (%)*	Failed (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†	Total (%)*	Failed (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†	Total (%)*	Failed (%)†	Deaths (%)†	Prostate Cancer-Specific Deaths (%)†				
70-74	10	3 (30.0)	1 (10.0)	0 (0.0)	0 (0.0)	51 (68)	13 (25.5)	9 (17.7)	1 (2.0)	6 (8.0)	2 (33.3)	1 (16.7)	0 (0.0)	8 (10.7)	1 (12.5)	1 (12.5)	0 (0.0)	75 (55.6)	19 (25.3)	12 (16.0)	1 (1.3)
75-79	9	3 (33.3)	2 (22.2)	0 (0.0)	0 (0.0)	18 (64.3)	5 (27.8)	4 (22.2)	2 (11.1)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (48.1)	8 (28.6)	6 (21.4)	2 (7.1)
≥80	3	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	13 (76.5)	7 (53.8)	4 (30.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	17 (80.9)	9 (29.4)	5 (16.4)	0 (0.0)
Total	22	8 (36.4)	4 (18.2)	0 (0.0)	0 (0.0)	82 (68.3)	25 (30.5)	17 (20.7)	3 (2.4)	7 (5.8)	2 (28.6)	1 (14.3)	0 (0.0)	9 (7.5)	1 (11.1)	1 (11.1)	0 (0.0)	120 (56.9)	36 (30)	23 (19.2)	3 (2.5)

* Percent of all cancer patients in this age group.

† Percent of patients choosing this therapy option in this age group.

* Defined as three consecutive PSA rises.

30 high-grade, Stage IV prostate cancer patients aged 80 years or older, found that survival at 3 years was 60%, which was slightly better than patients with similar stage cancer 10 years younger (57.8%).

The patient population in our study may not represent the more advanced nature of prostate cancer in older patients but rather the hesitance of referring urologists to diagnose low-grade, low-stage prostate cancer in older patients in whom the disease will have no impact on their quantity and quality of life. Many urologists, as well as primary care providers, may appropriately follow elderly, asymptomatic men with expectant management for elevated PSA levels or with digital rectal examination abnormalities, possibly a result of prostate cancer, for which a tissue diagnosis is never made. Neither our study nor a review of the literature clearly defined how aggressive urologists should be for these elderly men. It is generally accepted that screening and aggressive case finding to seek out early, organ-confined disease is contraindicated in those with a life expectancy less than 10 years,³ but how does the urologist confirm an individual's life expectancy or exclude advanced disease without investigation?

In a study of participants in the Canada Health Survey, Eapen *et al.*²¹ found that, for prostate cancer patients aged 80 years and older, comorbidity was not a significant predictor of survival. Those researchers admonished against restricting access to PSA screening on the basis of survival probability in elderly patients. Roche *et al.*²² agree that age alone is a poor predictor of survival and an inappropriate factor by which to exclude patients from screening and clinical trials for cancer treatment. They proposed a formal geriatric assessment, including measures of cognitive, functional, and affective status in elderly patients being considered for intervention. Perhaps the most critical of current approaches to prostate cancer in the elderly is a review of several centers by Bennett *et al.*²³ that showed that patients aged 75 years and older had significantly less intensive clinical staging evaluations and discussion of treatment options when compared with patients aged 50 to 65 years. Greenfield *et al.*²⁴ have noted similar results in studies of elderly patients with other malignancies and have suggested the presence of widespread age bias in cancer diagnosis, staging, and treatment. Saltzstein *et al.*,²⁵ in an exhaustive review of more than 14,000 cancer patients older than 90 years of age from the California Cancer Registry, showed that patients older than 90 years of age were diagnosed with cancer at a more advanced stage and received a more abbreviated staging evaluation. Those patients that died, however, usually died of causes other than their cancer.²⁵

It is, unfortunately, difficult if not impossible to conduct completely objective discussions of treatment options, particularly with prostate cancer. For example, with asymptomatic, organ-confined prostate cancer, expectant management would be encouraged, and radical prostatectomy would certainly not be presented with enthusiasm as a reasonable option to patients aged 80 years and older, whereas the benefits of surgery and other treatments with curative intent would be strongly recommended to younger patients.

CONCLUSIONS

In a review of prostate cancer in the elderly by Kirk,³ he stated, "The aim always is diagnosis where appropriate, treatment which will be of benefit, and quality rather than length of life." While seemingly simple, following these elusive caveats remains a challenge as the population ages, longevity increases, and prostate cancer therapies evolve.

We discourage screening in asymptomatic elderly and/or debilitated (life expectancy estimated at less than 10 years) patients. Should an asymptomatic man with a modest PSA elevation (less than 20 ng/mL) and/or with digital rectal examination abnormality present as a referral for prostate biopsy, we counsel the patient on the low potential of prostate cancer affecting his life expectancy or quality of life as well as the possibility that procedures performed to pursue cancer diagnosis as well as subsequent treatment could significantly affect his quality of life. The final decision, however, remains with the patient.

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