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Low p21Waf1/Cip1 Protein Level Sensitizes Testicular Germ Cell Tumor Cells to Fas-Mediated Apoptosis

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(odds ratio (OR): 0.70, 95% confidence interval (CI): 0.46–1.1). Most of the screening tests were DREs, and it was not possible to assess the separate influence of PSA screening.

Conclusions: The results of this study suggest that men who have been screened for prostate cancer have a reduced risk of dying as a result of this disease.

Editorial Comment: This study, which was carried out in the pre-PSA era, demonstrates that patients who underwent a digital rectal examination had a 40% reduction in prostate cancer mortality (OR 0.60, 95% CI 0.38 to 0.93).

Patrick C. Walsh, M.D.

Delayed Intraoperative Hydration Limits Blood Loss During Radical Retropubic Prostatectomy

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Urology, **64**: 712–716, 2004

Objectives. To evaluate the effects of limiting hydration during prostate mobilization on intraoperative blood loss.

Methods. The patient records of 519 consecutive men undergoing radical retropubic prostatectomy by a single surgeon from January 2000 through April 2003 were reviewed. In the initial 328 cases, intravenous fluids were not limited throughout the case (constant hydration group). In the next 189 cases, intravenous fluids were limited to a target of 1500 mL during prostate dissection (delayed hydration group). After the prostate was removed, hydration was brisk for an additional target of 3500 mL. The patient characteristics, perioperative events, and postoperative recovery were evaluated.

Results. Delayed hydration resulted in a statistically significant reduction in estimated blood loss compared with the constant hydration group, averaging 700 mL versus 965 mL, respectively. The immediate postoperative hematocrit values were also significantly greater in the delayed hydration group (31.5%) than in the constant hydration group (30.2%). Furthermore, the delayed hydration group had significantly fewer cases of blood loss greater than 1500 mL and fewer patients needed intraoperative transfusions. No statistically significant difference was found in total intravenous fluids given and no increased morbidity occurred with delayed hydration.

Conclusions. Delayed hydration appears to reduce blood loss during radical retropubic prostatectomy. In the hemodynamically stable patient, limiting intravenous fluids before complete dissection of the prostate is feasible without increasing morbidity.

Editorial Comment: For a number of years I have instructed our anesthesiologists to limit the amount of crystalloids administered to patients prior to removal of the prostate. This study proves the wisdom of that approach. These authors were able to reduce blood loss by almost 30% by limiting the replacement of crystalloids to 1,500 ml prior to removal of the prostate followed by brisk rehydration. They point out in their discussion that this approach has been successful both in liver transplantation and in the critical care setting where hydration is limited until there is control of significant hemorrhage.

Patrick C. Walsh, M.D.

UROLOGICAL ONCOLOGY: TESTIS CANCER AND ADVANCES IN ONCOLOGICAL THERAPY

Low p21^{Waf1/Cip1} Protein Level Sensitizes Testicular Germ Cell Tumor Cells to Fas-Mediated Apoptosis

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Oncogene, **23**: 4862–4872, 2004

In the present study, we investigated the relation between p21 expression and the sensitivity of testicular germ cell tumor (TGCT) cells to apoptotic stimuli. Despite similar cisplatin-induced wild-type

p53 accumulation, the TGCT cell lines Tera and Scha expressed low p21 protein and mRNA levels in comparison to A2780 ovarian cancer cells. Inhibition of the proteasome complex with MG-132 increased p21 protein levels in TGCT cells but much more in A2780 cells, whereas cisplatin had no additional effect on p21 protein levels. Inhibition of caspase-3 activity in TGCT cells with the broad-spectrum caspase inhibitor zVAD-fmk had no effect on p21 levels and also not upon cisplatin treatment. A similar induction of p53 irradiation, in contrast to cisplatin, substantially increased both p21 mRNA and protein expression in Tera cells. Cisplatin-treated Tera cells expressing low p21 protein levels were Fas-sensitive, while irradiation-induced p21, which was mainly localized in the cytosol, rendered irradiated Tera cells resistant to Fas-induced apoptosis. Sensitivity of irradiated Tera cells to Fas-induced apoptosis was restored by short interfering RNA-specific suppression of p21 expression. These results strongly indicate that the low p21 protein levels are caused by reduced p21 gene transcription and sensitize cisplatin-treated TGCT cells to the Fas death pathway.

Editorial Comment: The tumor suppressor protein p53 has been shown to be important in the response of cancer cells to DNA damage. However, p53 mutations rarely occur in human testicular germ cell tumors. Previous studies by the authors have demonstrated that sensitivity of testicular germ cell tumors to cisplatin is related to the presence of a functional p53 as well as a Fas dependent death pathway or apoptosis. Most testicular germ cell tumors lack p21 protein expression as well, a downstream factor related to p53. Decreased p21 expression in testicular germ cell tumors may fail to prevent rapid apoptosis that occurs with DNA damage, and may be a partial explanation for the sensitivity of testicular germ cell tumors to apoptotic stimuli.

The authors studied the relationship of p21 expression and sensitivity of testicular germ cell tumors to apoptotic stimuli. They evaluated potential mechanisms involved in the decreased p21 protein levels. Low p21 protein expression on cisplatin exposure relates to a decreased p21 gene transcription rather than an increased caspase mediated breakdown. Testicular germ cell tumor cells treated with cisplatin and expressing low p21 protein tend to be Fas sensitive. However, in irradiated testicular germ cell tumors increased p21 protein levels tend to make these cells more resistant to Fas induced apoptosis. This interesting article may help explain why some patients who have undergone radiation therapy tend to be locally resistant to chemotherapeutic treatments.

Jerome P. Richie, M.D.

UROLOGICAL ONCOLOGY: BLADDER, PENIS AND URETHRAL CANCER, AND BASIC PRINCIPLES OF ONCOLOGY

Histologic Grading of Noninvasive Papillary Urothelial Tumors. Validation of the 1998 WHO/ISUP System by Immunophenotyping and Follow-Up

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Am J Clin Pathol, **121**: 679–687, 2004

Cytokeratin (CK) 20, Ki-67, and p53 were applied to 84 noninvasive papillary urothelial tumors graded by the 1973 World Health Organization (WHO) and 1998 WHO/International Society of Urological Pathology (ISUP) systems. In the WHO/ISUP classification, all benign lesions showed normal CK20 staining and all carcinomas showed abnormal staining. The Ki-67 index was significantly different between benign and malignant lesions ($P < .05$) and between low- and high-grade carcinomas ($P < .001$). p53 was negative in all benign lesions, with a significant difference between low- and high-grade carcinomas ($P < .001$). Tumor recurrence was significantly different between low- and high-grade carcinomas (no recurrences among the papillary urothelial neoplasms of low malignant potential). By the 1973 WHO classification, normal CK20 staining was present both in benign lesions and in carcinomas. Ki-67 staining did not distinguish between grade 2 and grade 3 carcinomas ($P > .05$), and there was no difference in p53 staining in grades 1 and 2 carcinomas ($P > .05$). Recurrences were not different between grades 1, 2, and 3 carcinomas. All biologic markers studied and tumor recurrences