Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2007 November 15; 69(4): 1117–1123. doi:10.1016/j.ijrobp.2007.04.070.

PROGNOSTIC VALUE OF ABNORMAL p53 EXPRESSION IN LOCALLY ADVANCED PROSTATE CANCER TREATED WITH ANDROGEN DEPRIVATION AND RADIOTHERAPY: A STUDY BASED ON RTOG 9202

Mingxin Che, M.D., Ph.D.[*], **Michelle DeSilvio, Ph.D.**[†], **Alan Pollack, M.D., Ph.D.**[‡], **David J. Grignon, M.D.**[*], **Varagur Mohan Venkatesan, M.D.**[§], **Gerald E. Hanks, M.D.**[‡], and **Howard M. Sandler, M.D.**[¶]

[*] Department of Pathology, Wayne State University and Barbara Ann Karmanos Cancer Institute, Detroit, MI

[†] American College of Radiology, Philadelphia, PA

[‡] Fox Chase Cancer Center, Philadelphia, PA

[§] University of Western Ontario, London, ON

[¶] University of Michigan Medical Center, Ann Arbor, MI

Abstract

Purpose—The goal of this study was to verify the significance of p53 as a prognostic factor in Radiation Therapy Oncology Group 9202, which compared short-term androgen deprivation (STAD) with radiation therapy (RT) to long-term androgen deprivation + RT in men with locally advanced prostate cancer (Pca).

Methods and Materials—Tumor tissue was sufficient for p53 analysis in 777 cases. p53 status was determined by immunohistochemistry. Abnormal p53 expression was defined as 20% or more tumor cells with positive nuclei. Univariate and multivariate Cox proportional hazards models were used to evaluate the relationships of p53 status to patient outcomes.

Results—Abnormal p53 was detected in 168 of 777 (21.6%) cases, and was significantly associated with cause-specific mortality (adjusted hazard ratio [HR] = 1.89; 95% confidence interval (CI) 1.14 – 3.14; $p = 0.014$) and distant metastasis (adjusted HR = 1.72; 95% CI 1.13–2.62; $p = 0.013$). When patients were divided into subgroups according to assigned treatment, only the subgroup of patients who underwent STAD + RT showed significant correlation between p53 status and cause-specific mortality (adjusted HR = 2.43; 95% CI = 1.32–4.49; $p = 0.0044$). When patients were divided into subgroups according to p53 status, only the subgroup of patients with abnormal p53 showed significant association between assigned treatment and cause-specific mortality (adjusted HR = 3.81; 95% CI 1.40–10.37; $p = 0.0087$).

Conclusions—Abnormal p53 is a significant prognostic factor for patients with prostate cancer who undergo short-term androgen deprivation and radiotherapy. Long-term androgen deprivation may significantly improve the cause-specific survival for those with abnormal p53.

Reprint requests to: Mingxin Che, M.D., Ph.D., Department of Anatomic Pathology, Quest Diagnostics Incorporated, 506 E State Pkwy, Schaumburg, IL 60173. Tel: (847) 885–5235; Fax: (847) 885–5588; mingxinche@hotmail.com.

Presented in part at the 2005 Multidisciplinary Prostate Cancer Symposium, Orlando, FL, February 17–19, 2005.

Conflict of interest: none.

Keywords

p53; Immunohistochemistry; Prognostic factor; RTOG 9202; Locally advanced prostate cancer; Androgen deprivation and radiotherapy

INTRODUCTION

It is well known that p53 protein plays a central role in modulating cellular responses to cytotoxic stresses by contributing to cell-cycle arrest, programmed cell death, and double-strand DNA repair. p53 gene mutations, which are typically associated with nuclear accumulation of p53 protein (1,2), occur in approximately half of all human malignancies (3). It has been shown that p53 gene mutation and nuclear accumulation of p53 protein are associated with aggressive phenotypes in several human cancers, including breast cancer (4, 5), lung cancer (6), and colorectal carcinoma (7,8).

In prostate cancer (Pca), studies have described an association between p53 nuclear accumulation and poor differentiation, progression, metastasis, and androgen-independent growth (9–12). Furthermore, *in vitro* and *in vivo* studies showed that restoration of p53 with adenoviral vectors could increase radiation sensitivity in prostate cancer (13,14). In the patients with Pca who underwent radiation therapy, some studies showed that p53 nuclear accumulation was associated with biochemical failure (15,16). An important study of the prognostic value of p53 was based on an analysis of Radiation Therapy Oncology Group (RTOG) 8610 (17).

RTOG 8610 was a phase III, randomized, clinical trial that tested the benefit of short-term androgen deprivation (STAD) begun 2 months before and continued during external beam radiation therapy (RT) for locally advanced Pca. Abnormal p53 expression, defined as ≥20% positive nuclear staining, was detected in 23 (18%) of 129 cases and independently correlated with decreased overall and progression-free survivals and increased distant metastasis.

More evidence is needed to verify the prognostic value of p53 expression in Pca and further explore the relationship between p53 status and combined androgen deprivation and RT. In this report, we analyzed p53 protein expression in diagnostic material from a large cohort of patients participating in RTOG 9202. RTOG 9202 was a phase III randomized trial that was an extension of RTOG 8610, comparing STAD + RT with long-term androgen deprivation (LTAD) given for an additional 24 months after RT (18).

METHODS AND MATERIALS

Study population

RTOG 9202 began in June 1992 and was completed in April 1995, accruing 1,514 assessable patients (18). Tumor tissue was sufficient for p53 analysis in 777 cases, with 398 (51.2%) and 379 (48.8%) from LTAD + RT and STAD + RT treatment arms, respectively. All of the cases with determined p53 status had information about pre-treatment serum prostate-specific antigen (PSA) and clinical T stage. An institutional Gleason score was available in 721 (92.8%) of the cases, whereas a centrally reviewed Gleason score was available in 562 (72.3%) of the cases. To include maximal number of patients and increase the statistical power for detecting clinically meaningful differences, the institutional Gleason score was used for analysis.

Immunohistochemistry

The p53 status was determined by immunohistochemistry using monoclonal antibody directed against mutant and wild-type p53 (clone DO7; Novocastra, Burlingame, CA) according to the technique described previously (17). Briefly, paraffin-embedded tissue sections (5 mL) were

deparaffinized in xylene and then rehydrated in graded ethyl alcohol. Antigen retrieval was performed by heating the sections in 10 mM citrate buffer (pH 6.0) in a pressure cooker. Endogenous peroxidase activity was blocked with 3% H_2O_2, and nonspecific antibody binding was blocked with horse and bovine serum albumin. The slides were then incubated with the primary antibody (DO7, 1:100 dilution) for 20 min at room temperature. Immune complexes were detected by ABC method with 3-amino-9-ethylcarbazole as the chromogen. A colon carcinoma with a known p53 mutation was used as a positive control. Sections stained with omission of the primary antibody were used as a negative control.

The p53 status was evaluated without knowledge of patient outcome. Only apparent nuclear immunoreactivity was considered to represent positive staining. The percentage of nuclei in neoplastic cells with positive staining was manually recorded for each case. Cases with 20% or more positive nuclei were considered to have abnormal p53 expression, as described previously for protocol 8610 (17).

Definition of endpoints

The failure event for overall survival was defined as death from any cause. The following was considered as a failure event in assessing cause-specific survival and mortality: death certified as resulting from Pca, complications of treatment, unknown causes with active malignancy (clinical disease relapse), or other cancer with documented bone metastases attributed to Pca before the appearance of the second independent cancer. Local failure was assessed by palpation and defined as tumor growth of 25% or local persistence of palpable tumor beyond 18 months. Distant metastasis was defined as the clinical evidence of distant disease (by any method). Biochemical failure was defined according to American Society for Therapeutic Radiology and Oncology consensus definition as three consecutive rises or the institution of hormone treatment for a rising PSA or a posttreatment PSA nadir level >4.0 ng/mL. The failure event for disease-free survival and any failure was defined as the first occurrence of local, regional nodal, distant, or biochemical (PSA) failure, or death due to any cause. All time events, with the exception of biochemical failure, were measured from the date of randomization to the date of their occurrence or last follow-up. Biochemical failure was measured from the date of randomization to the midpoint date between the postirradiation date of nadir PSA and the date of the first of the three consecutive rises following the American Society for Therapeutic Radiology and Oncology consensus guidelines.

Statistical analysis

All pretreatment characteristics, except Gleason score, were dichotomized. Age was dichotomized by the median age in the entire cohort; PSA and stage were dichotomized by their stratification groupings (PSA ≤30 ng/mL vs. >30 ng/mL; stage T2c vs. T3-4). Gleason score was arranged into three groups as 2–6, 7, and 8–10. Statistical comparisons to assess whether missing p53 data was dependent on pretreatment characteristics, assigned treatment, or outcome were carried out using the chi-square test and the Cox proportional hazards model (19). p53 expression was dichotomized as normal (<20%) versus abnormal (≥20%). Cox proportional hazards models were used to identify the impact of p53 expression on overall and cause-specific mortalities, distant metastasis, and any local and biochemical failures. For figure presentations, actuarial estimates for overall, cause-specific, and disease-free survivals were calculated using Kaplan-Meier methods (20), and the cumulative incidence method (21) was used to estimate the local failure, biochemical failure, and distant metastasis.

RESULTS

Clinical and pathologic characteristics of patients with determined and missing p53 data

Of the total 1,514 assessable patients who entered in RTOG 9202, 777 (51.3%) had determined p53 data. Table 1 displays the distribution of patients by baseline variables and treatment arms for those with determined and missing p53 data. There was no statistically significant difference in any of the parameters studied including age, Gleason score, pretreatment PSA, clinical stage, or assigned treatment, although a borderline significant relationship was seen with Gleason score. Of those with determined p53 data, 28.2% had a Gleason score of 8–10, as opposed to 22.9% for those without p53 data ($p = 0.07$).

The median follow-up time was 71.0 months for patients with p53 data (range, 0.5–105.2 months), as well as those without p53 data (range, 2.1–107.1 months). At end of the follow-up period, 540 (69.5%) were alive in the group with determined p53 data and 525 (71.2%) in the group with missing p53 data. Univariate Cox proportional hazards model was used to evaluate the differences in all six outcomes (overall and cause-specific mortalities, distant metastasis, and any local and biochemical failures) between the two groups by p53 status. The hazard ratios (HR) of the group with determined p53 data versus that with missing p53 data ranged from 0.94 to 1.18 for these end points, and none of the differences reached statistical significance. In summary, the population analyzed for p53 status was not significantly different from those in RTOG 9202 in whom p53 was not done.

Clinical and pathologic characteristics of patients with abnormal p53 expression

Of the 777 cases with determined p53 data, 168 (21.6%) had abnormal p53 expression, defined as ≥20% cells with positive nuclear staining (Figure 1). As shown in Table 2, among the variables studied, the distribution of patients by p53 status was significantly related to Gleason score. Of those with abnormal p53 expression, 41.1%, 32.5%, and 26.5% had a Gleason score 8–10, 7, and 2–6, respectively ($p = 0.0001$). These data confirm the relationship between abnormal p53 expression and poor differentiation in Pca. There was no significant difference in age, pretreatment PSA, clinical stage, or assigned treatment between the two groups by p53 status.

Prognostic value of abnormal p53 expression

Among the six end points studied, univariate analyses showed that abnormal p53 expression was significantly associated with increased cause-specific mortality (unadjusted HR, 1.92; 95% confidence interval (CI), 1.18–3.11; $p = 0.0084$) and distant metastasis (unadjusted HR, 1.92; 95% CI, 1.29–2.85; $p = 0.0013$) (Table 3). The estimated rate of 5-year cause-specific mortality was 13.0% in cases with abnormal p53 vs. 5.3% in those with normal p53. The estimated rate of 5-year distant metastases was 19.3% in cases with abnormal p53 versus 10.5% in those with normal p53. A borderline significant relationship was seen with biochemical failure. Of those with abnormal p53 expression, 41.9% (69 of 166) had biochemical failure, as opposed to 35.3% (203 of 604) for those with normal p53 status (HR 1.31; 95% CI 0.99–1.72; $p = 0.06$).

In the multivariate analyses controlling for Gleason score, PSA, clinical stage, and assigned treatment, p53 status remained an independent predictor for cause-specific mortality (adjusted HR, 1.89; 95% CI, 1.14 – 3.14; $p = 0.014$) and distant metastasis (adjusted HR 1.72; 95% CI 1.13; $p = 1.13–2.62$; $p = 0.013$) (Table 3). Figure 2 illustrates that the reduction in cause-specific survival in the patients with abnormal p53 status corresponded to their shortened time to develop distant metastasis. No significant association between p53 status and overall mortality, or any, local or biochemical failure was observed in the multivariate analyses.

Interaction between duration of hormone therapy and p53 status

First, we analyzed the prognostic value of p53 in the subgroup of patients assigned to STAD + RT or LTAD + RT. As shown in Table 4, in the subgroup of STAD + RT, 19 of 84 (22.62%) patients with abnormal p53 in contrast to 27 of 295 (9.15%) patients with normal p53 died of Pca; the abnormal p53 was significantly associated with cause-specific mortality (adjusted HR, 2.43; 95% CI, 1.32–4.49; $p = 0.0044$). On the contrary, in the subgroup of LTAD + RT, 6 of 84 (7.14%) patients with abnormal p53 compared with 22 of 314 (7.01%) patients with normal p53 died of Pca; abnormal p53 was no longer associated with cause-specific mortality (adjusted HR, 0.87; 95% CI, 0.32–2.37; $p = 0.7797$).

The improved treatment efficacy of LTAD + RT vs. STAD + RT was further analyzed in subgroup of patients with normal (<20%) or abnormal (≥20%) p53 status (Table 5). In the subgroup of patients with abnormal p53 expression, 6 of 84 (7.14%) patients with LTAD + RT in contrast to 19 of 84 (22.62%) those with STAD + RT died of prostate cancer; LTAD + RT was significantly associated with reduced cause-specific mortality (adjusted HR, 3.81; 95% CI, 1.40–10.37; $p = 0.0087$). On the contrary, in the subgroup of patients with normal p53 status, 22 of 314 (7.01%) with LTAD + RT compared with 27 of 295 (9.15%) those with STAD + RT died of Pca; LTAD + RT was no longer associated with cause-specific mortality (adjusted HR, 1.41; 95% CI, 0.79–2.54; $p = 0.248$). These results indicate that patients with abnormal p53 status would be especially benefited from long-term hormone therapy in combination with radiation therapy. However, this possible interaction between p53 status and hormone therapy was only obvious with respect to cause-specific mortality. It must be emphasized that interpretation of the subgrouping data in Tables 4 and 5 need be cautious. The sizes of study population and events of failure were reduced significantly and unevenly in the subgroups, which could variably affect their power of statistical analysis.

DISCUSSION

In this RTOG 9202 study, we verified the significance of p53 as a prognostic factor in Pca. The abnormal expression of p53 was related to about a 2× increased risk of death from Pca and the development of distant metastasis at 5 years. To our knowledge, this is the largest analysis of p53 ever performed in men with Pca and the first in men treated with RT + LTAD.

Although there is little doubt concerning the relationships between p53 immunoreactivity and unfavorable histology or advanced disease in Pca, the prognostic value has been uncertain. Shurbaji *et al.* (22) evaluated 109 patients who received curative radiotherapy, hormonal therapy, or watchful waiting with a mean follow-up of 3.8 years. Multivariate analyses showed p53 reactivity was significant with Wilcoxon test only but not with log–rank and Cox tests. Similarly, in a study of 186 Pca patients treated with transurethral resection and subsequent surveillance, Stattin *et al.* (23) demonstrated a significant correlation between p53 staining and shorter survival only with univariate, but not with multivariate analyses. More recently, Quinn *et al.* studied p53 in 263 men with localized Pca treated uniformly with radical prostatectomy and found that the p53 status was an independent predictor for relapse in multivariate analysis (24).

Only a few studies have focused on the prognostic value of detecting abnormal p53 in Pca treated with radiation therapy. As mentioned previously, in the study of RTOG 8610, Grignon *et al.* demonstrated that p53 status was a significant independent prognostic indicator for time to distant metastases, progression-free survival and overall survival (17). However, Stattin *et al.* (25), who studied 60 patients with Pca treated with definitive external beam therapy, found that p53 did not correlate with tumor grade or cancer-specific survival. Other studies, which analyzed p53 as well as bcl-2 in Pca treated with radiation therapy, showed conflicting results also (15,26). Recently, Ritter *et al.* (16) investigated p53 expression in favorable-to-

intermediate-risk Pca treated with radiotherapy. Abnormal p53 was found to be strongly and independently correlated with the actuarial biochemical failure at 5 years with a hazard ratio of 2.3.

Several issues should be considered in the interpretation of these results. A major concern is the statistical power of the studies for detecting a survival difference between the patients with an abnormal p53 status and those with a normal one. Other issues that need to be considered are the cutoff point for p53 positivity, patient characteristics, treatment, and follow-up. Visakopi showed that only high-level p53 accumulation with staining in more than 20% of tumor cells was associated with a poor outcome (27). Quinn *et al.* also demonstrated that a stratum of 20% was an effective cutoff point in predicting cancer specific death for patients underwent radical prostatectomy (24). Grignon *et al.* further demonstrated that among three cutoff points studied, including *(1)* presence of any detectable cells, *(2)* more than 1%, and *(3)* 20% or more, the last cutoff point (≥20%) was the best one for assessing prognostic value of p53 in Pca (17). In this study, using the 20% cut point, p53 was confirmed to be an independent predictor for distant metastasis and cause-specific mortality.

In addition, a possible interaction between p53 and hormone therapy was observed in this study. In the analysis of RTOG 8610, which also included men treated with STAD + RT, p53 status was significantly associated with a poor prognosis, with respect to time to distant metastases (17). In this study, we confirmed that for patients treated with STAD + RT, p53 was significantly associated with cause-specific mortality. There is a borderline significant relationship of p53 status with distant metastasis ($p = 0.06$) and a more significant relationship to cause specific mortality. A possible explanation of this difference is that after distant metastasis occurs, progression to death from prostate cancer is more rapid when p53 is abnormal. An example of this phenomenon is seen in an analysis of DNA-ploidy, wherein non-diploid tumors treated with STAD + RT (28) had a reduced survival, but no difference in metastasis; these tumors were less responsive to salvage androgen deprivation.

Furthermore, our results showed that the improved efficacy of LTAD + RT with respect to cause-specific mortality was much more significant in the patients with abnormal p53 status. These results indicate a possible mechanism of long term hormone therapy in reversing or bypassing the p53-dependent pathway in prostate cancer. However, these findings require further confirmation by prospective studies.

In summary, our results indicate that patients with abnormal p53 who undergo STAD and RT are associated with poor prognosis; long-term androgen deprivation appears to improve outcome. Our study provides strong evidence for using p53 as a marker stratifying patients in future trials aimed at evaluation of androgen deprivation adjuvant to RT.

Acknowledgments

Supported in part by the Pennsylvania Department of Health and CA101984 (from Alan Pollack, M.D., Ph.D.).

References

1. Finlay CA, Hinds PW, Tan TH, et al. Activating mutations for transformation by p53 produce a gene product that forms an hsc70-p53 complex with an altered half-life. Mol Cell Biol 1988;8:531–539. [PubMed: 2832726]
2. Bartek J, Iggo R, Gannon J, et al. Genetic and immunochemical analysis of mutant p53 in human breast cancer cell lines. Oncogene 1990;5:893–899. [PubMed: 1694291]
3. Kirsch DG, Kastan MB. Tumor-suppressor p53: Implications for tumor development and prognosis. J Clin Oncol 1998;16:3158–3168. [PubMed: 9738588]

4. Umekita Y, Kobayashi K, Saheki T, et al. Nuclear accumulation of p53 protein correlates with mutations in the p53 gene on archival paraffin-embedded tissues of human breast cancer. Jpn J Cancer Res 1994;85:825–830. [PubMed: 7928628]
5. Tsuda H, Hirohashi S. Association among p53 gene mutation, nuclear accumulation of the p53 protein and aggressive phenotypes in breast cancer. Int J Cancer 1994;57:498–503. [PubMed: 7910151]
6. Hiyoshi H, Matsuno Y, Kato H, et al. Clinicopathological significance of nuclear accumulation of tumor suppressor gene p53 product in primary lung cancer. Jpn J Cancer Res 1992;83:101–106. [PubMed: 1544866]
7. Buglioni S, D'Agnano I, Vasselli S, et al. p53 nuclear accumulation and multiploidy are adverse prognostic factors in surgically resected stage II colorectal cancers independent of fluorouracil-based adjuvant therapy. Am J Clin Pathol 2001;116:360–368. [PubMed: 11554164]
8. Manne U, Myers RB, Moron C, et al. Prognostic significance of Bcl-2 expression and p53 nuclear accumulation in colorectal adenocarcinoma. Int J Cancer 1997;74:346–358. [PubMed: 9221816]
9. Stapleton AM, Timme TL, Gousse AE, et al. Primary human prostate cancer cells harboring p53 mutations are clonally expanded in metastases. Clin Cancer Res 1997;3:1389–1397. [PubMed: 9815823]
10. Navone NM, Troncoso P, Pisters LL, et al. p53 protein accumulation and gene mutation in the progression of human prostate carcinoma. J Natl Cancer Inst 1993;85:1657–1669. [PubMed: 7692074]
11. Bookstein R, MacGrogan D, Hilsenbeck SG, et al. p53 is mutated in a subset of advanced-stage prostate cancers. Cancer Res 1993;53:3369–3373. [PubMed: 8324747]
12. Eastham JA, Stapleton AM, Gousse AE, et al. Association of p53 mutations with metastatic prostate cancer. Clin Cancer Res 1995;1:1111–1118. [PubMed: 9815901]
13. Colletier PJ, Ashoori F, Cowen D, et al. Adenoviral-mediated p53 transgene expression sensitizes both wild-type and null p53 prostate cancer cells in vitro to radiation. Int J Radiat Oncol Biol Phys 2000;48:1507–1512. [PubMed: 11121656]
14. Cowen D, Salem N, Ashoori F, et al. Prostate cancer radiosensitization in vivo with adenovirus-mediated p53 gene therapy. Clin Cancer Res 2000;6:4402–4408. [PubMed: 11106260]
15. Scherr DS, Vaughan ED Jr, Wei J, et al. BCL-2 and p53 expression in clinically localized prostate cancer predicts response to external beam radiotherapy. J Urol 1999;162:12–17. [PubMed: 10379729]
16. Ritter MA, Gilchrist KW, Voytovich M, et al. The role of p53 in radiation therapy outcomes for favorable-to-intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2002;53:574–580. [PubMed: 12062599]
17. Grignon DJ, Caplan R, Sarkar FH, et al. p53 status and prognosis of locally advanced prostatic adenocarcinoma: A study based on RTOG 8610. J Natl Cancer Inst 1997;89:158–165. [PubMed: 8998185]
18. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003;21:3972–3978. [PubMed: 14581419]
19. Cox DR. Regression models and life-tables. J Roy Stat Soc Series B 1972;34:187–202.
20. Kaplan EL, Meier P. Nonparameteric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
21. Kalbfleish, JD.; Prentice, RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980.
22. Shurbaji MS, Kalbfleisch JH, Thurmond TS. Immunohistochemical detection of p53 protein as a prognostic indicator in prostate cancer. Hum Pathol 1995;26:106–109. [PubMed: 7821906]
23. Stattin P, Bergh A, Karlberg L, et al. p53 immunoreactivity as prognostic marker for cancer-specific survival in prostate cancer. Eur Urol 1996;30:65–72. [PubMed: 8854070]
24. Quinn DI, Henshall SM, Head DR, et al. Prognostic significance of p53 nuclear accumulation in localized prostate cancer treated with radical prostatectomy. Cancer Res 2000;60:1585–1594. [PubMed: 10749127]

25. Stattin P, Damber JE, Modig H, et al. Pretreatment p53 immunoreactivity does not infer radioresistance in prostate cancer patients. Int J Radiat Oncol Biol Phys 1996;35:885–889. [PubMed: 8751397]

26. Huang A, Gandour-Edwards R, Rosenthal SA, et al. p53 and bcl-2 immunohistochemical alterations in prostate cancer treated with radiation therapy. Urology 1998;51:346–351. [PubMed: 9495727]

27. Visakorpi T, Kallioniemi OP, Heikkinen A, et al. Small subgroup of aggressive, highly proliferative prostatic carcinomas defined by p53 accumulation. J Natl Cancer Inst 1992;84:883–887. [PubMed: 1350643]

28. Pollack A, Grignon DJ, Heydon KH, et al. Prostate cancer DNA ploidy and response to salvage hormone therapy after radiotherapy with or without short-term total androgen blockade: An analysis of RTOG 8610. J Clin Oncol 2003;21:1238–1248. [PubMed: 12663710]

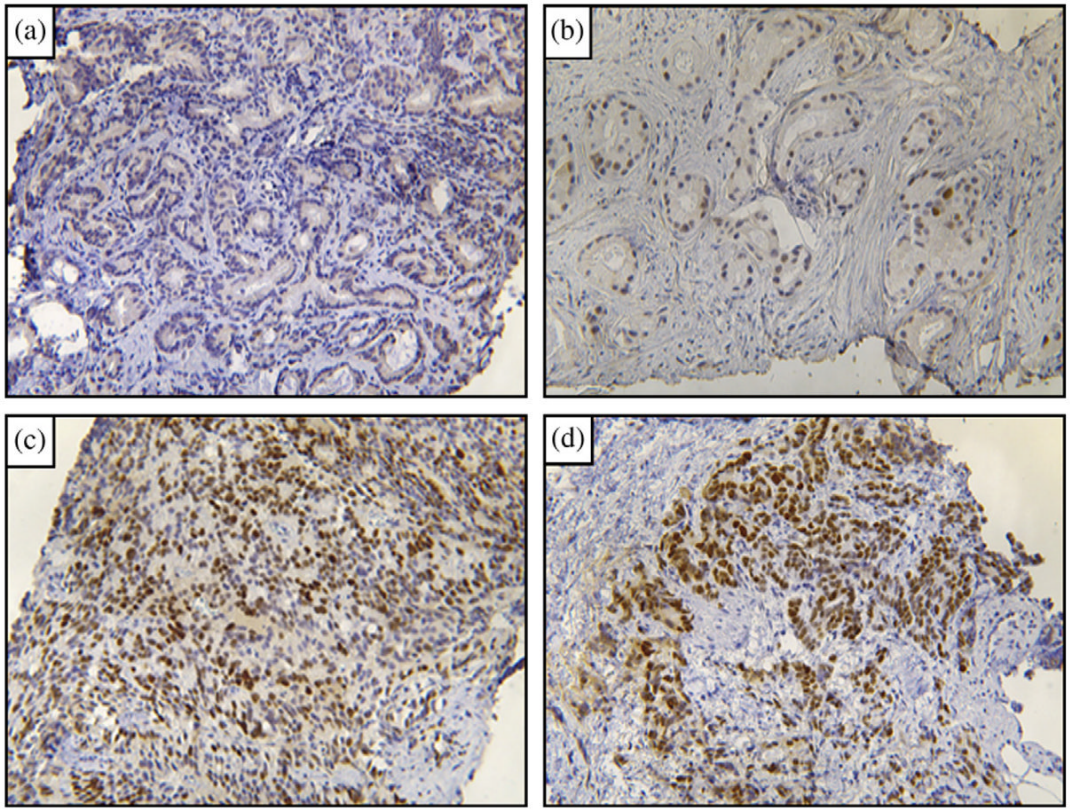

Fig. 1.
p53 nuclear accumulation in prostate cancer (Pca). Normal p53 status with no (a) and rare (b) brown nuclear staining in two samples of Pca with Gleason score 6. Abnormal p53 nuclear accumulation with 50% (c) and 80% (d) brown nuclear staining in two samples of Pca with Gleason score 8.

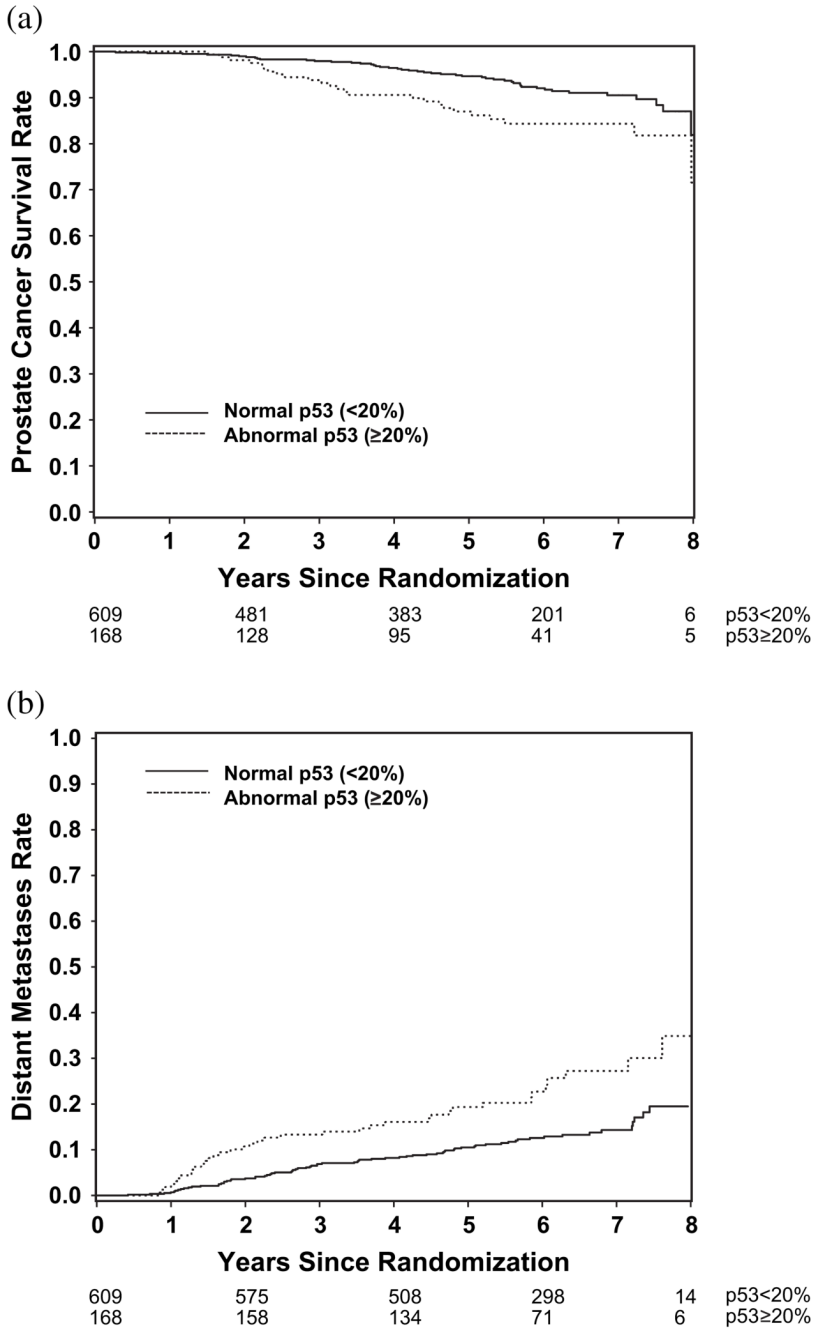

Fig. 2.

(a) Kaplan-Meier curve for cause-specific survival according to p53 expression. (b) Time to distant metastasis according to p53 expression. The numbers at risk at 0, 2, 4, 6, and 8 years are shown.

Table 1

Characteristics of patients entered in RTOG 9202 with determined or missing p53 data

Characteristics	Missing p53 data	Determined p53 data	
	Number of patients (%)	Number of patients (%)	*p**
Eligible	737 (48.7)	777 (51.3)	—
Age (y)			
<70	342 (46.4)	333 (42.9)	0.17
≥70	395 (53.6)	444 (57.1)	
Gleason score†			
2–6	292 (42.3)	285 (39.5)	0.07
7	241 (34.9)	233 (32.3)	
8–10	158 (22.9)	203 (28.2)	
PSA (ng/mL)			
≤30	494 (67.0)	517 (66.5)	0.84
>30	243 (33.0)	260 (33.5)	
Clinical stage			
T2c	322 (43.7)	364 (46.8)	0.22
T3-4	415 (56.3)	413 (53.2)	
Assigned treatment			
LTAD + RT	355 (48.2)	398 (51.2)	0.23
STAD + RT	382 (51.8)	379 (48.8)	

Abbreviations: RTOG = Radiation Therapy Oncology Group; PSA = prostate-specific antigen; LTAD = long-term androgen deprivation; STAD = short-term androgen deprivation.

* *P* value from chi-square test.

† Forty-six (6.2%) and 56 (7.2%) cases with missing and determined p53 data, respectively, have unknown institutional Gleason scores.

Table 2

Characteristics of patients entered in RTOG 9202 with normal (<20%) or abnormal (≥20%) p53 expression

Characteristic	Normal p53 (< 20%) Number of patients (%)	Abnormal p53 (≥20%) Number of Patients (%)	*p* *
Eligible	609 (78.4)	168 (21.6)	—
Age (y)			
<70	253 (41.5)	80 (47.6)	0.16
≥70	356 (58.5)	88 (52.4)	
Gleason score†			
2–6	245 (43.0)	40 (26.5)	0.0001
7	184 (32.3)	49 (32.5)	
8–10	141 (24.7)	62 (41.1)	
PSA (ng/mL)			
≤30	406 (66.7)	111 (66.1)	0.88
>30	203 (33.3)	57 (33.9)	
Clinical stage			
T2c	294 (48.3)	70 (41.7)	0.13
T3-4	315 (51.7)	98 (58.3)	
Assigned treatment			
LTAD + RT	314 (51.6)	84 (50.0)	0.72
STAD + RT	295 (48.4)	84 (50.0)	

See Table 1 for abbreviations.

* *P* value from chi-square test.

† Thirty-nine (6.4%) and 17 (10.1%) cases with normal and abnormal p53 expression, respectively, have unknown institutional Gleason scores.

Table 3

Hazard ratio of p53 expression: normal (<20%) versus abnormal (≥20%)

Endpoint	p53 expression	Failures/total	5-y rate* (%)	Unadjusted		Adjusted	
				HR† (95% CI)	p‡	HR† (95% CI)	p‡
Overall mortality	<20%	183/609	20.4	1.10 (0.81–1.48)	0.56	1.06 (0.77–1.46)	0.73
	≥20%	54/168	23.4				
Cause-specific mortality	<20%	49/609	5.3	1.92 (1.18–3.11)	0.0084	1.89 (1.14–3.14)	0.0142
	≥20%	25/168	13.0				
Distant metastasis	< 20%	74/609	10.5	1.92 (1.29–2.85)	0.0013	1.72 (1.13–2.62)	0.013
	≥20%	37/168	19.3				
Local failure	<20%	61/609	9.1	1.25 (0.76–2.08)	0.38	1.16 (0.68–1.97)	0.59
	≥20%	20/168	9.9				
Biochemical failure§	<20%	203/604	35.3	1.31 (0.99–1.72)	0.06	1.23 (0.92–1.64)	0.16
	≥20%	69/166	41.9				
Any failure	<20%	349/609	62.6	1.15 (0.92–1.43)	0.21	1.07 (0.85–1.35)	0.54
	≥20%	104/168	65.7				

Abbreviations: HR = hazard ratio; CI = confidence interval.

*Actuarial estimates for overall and cause-specific mortalities and any failure were calculated using Kaplan-Meier methods and the cumulative incidence method was used to estimate local and biochemical failures and distant metastasis.

†A ratio of 1 indicates no difference between the two subgroups.

‡*P* value from chi-square test using the Cox proportional hazards model.

§Seven cases have unknown biochemical failure status.

Table 4

Adjusted hazard ratios of p53 expression (normal vs. abnormal) by assigned treatment

		STAD + RT			LTAD + RT		
Endpoint	**p53**	**Failures/total**	**HR* (95% CI)**	***p*†**	**Failures/total**	**HR* (95% CI)**	***p*†**
Overall mortality	<20%	88/295	1.15 (0.74–1.78)	0.5426	95/314	0.85 (0.52–1.37)	0.4947
	≥20%	29/84			25/84		
Cause-specific mortality	<20%	27/295	2.43 (1.32–4.49)	0.0044	22/314	0.87 (0.32–2.37)	0.7797
	≥20%	19/84			6/84		
Any failure	<20%	198/295	1.09 (0.81–1.47)	0.5828	151/314	0.99 (0.68–1.44)	0.9537
	≥20%	61/84			43/84		
Distant metastases	<20%	45/295	1.67 (0.97–2.86)	0.0636	29/314	1.44 (0.73–2.84)	0.2951
	≥20%	22/84			15/84		
Local failure	<20%	40/295	1.23 (0.65–2.33)	0.5196	21/314	0.85 (0.32–2.31)	0.7563
	≥20%	14/84			6/84		
Biochemical failure	<20%	133/295	1.34 (0.96–1.88)	0.0885	70/309	0.89 (0.50–1.60)	0.7029
	≥20%	50/83			19/83		

Abbreviations: HR = hazard ratio; CI = confidence interval; STAD = short-term androgen deprivation; LTAD = long-term androgen deprivation; RT = radiation therapy; PSA = prostate-specific antigen.

*A ratio of 1 indicates no difference between the two subgroups. The adjusted HR is from the model adjusting for PSA, Gleason score (institutional), stage, and age (overall survival model only).

†*P* value from chi-square test using the Cox proportional hazards model.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2009 October 30.

Table 5

Adjusted hazard ratios of treatment arms (LTAD + RT vs. STAD + RT) by p53 expression

Endpoint	Treatment arm	Normal p53 expression (<20%)			Abnormal p53 expression (≥20%)		
		Failures/total	HR* (95% CI)	*p*†	Failures/total	HR* (95% CI)	*p*†
Overall mortality	STAD + RT	88/295	1.02 (0.75–1.37)	0.9166	29/84	1.51 (0.84–2.71)	0.1698
	LTAD + RT	95/314			25/84		
Cause-specific mortality	STAD + RT	27/295	1.41 (0.79–2.54)	0.2480	19/84	3.81 (1.40–10.37)	0.0087
	LTAD + RT	22/314			6/84		
Any failure	STAD + RT	198/295	1.86 (1.50–2.32)	<0.001	61/84	2.44 (1.58–3.76)	<0.001
	LTAD + RT	151/314			43/84		
Distant metastases	STAD + RT	45/295	1.66 (1.02–2.72)	0.0429	22/84	1.60 (0.79– 3.24)	0.1945
	LTAD + RT	29/314			15/84		
Local failure	STAD + RT	40/295	2.00 (1.17–3.41)	0.0110	14/84	2.98 (1.05–8.48)	0.0402
	LTAD + RT	21/314			6/84		
Biochemical failure	STAD + RT	133/295	2.83 (2.10–3.83)	<0.001	50/83	5.11 (2.82–9.26)	<0.001
	LTAD + RT	70/309			19/83		

See Table 4 for abbreviations.

*A ratio of 1 indicates no difference between the two subgroups. The adjusted hazard ratio is from the model adjusting for PSA, Gleason score (institutional), stage, and age (overall survival model only).

†*P* value from chi-square test using the Cox proportional hazards model.