MDM2 overexpression is associated with short survival in adults with medulloblastoma¹

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In adult medulloblastoma, postoperative radiotherapy is significantly effective in prolonging time to recurrence and survival time; however, the response of individual cases to radiotherapy, that is the total survival, is different. Apoptosis is an important cellular response to radiation. It can be hypothesized that the individual radiosensitivity of medulloblastomas depends on the individual capability to undergo apoptosis. p53 protein is involved in the apoptotic response to ionizing radiation; loss of function of p53 can be the consequence not only of *TP53* mutations, but also of amplification and/or overexpression of the *MDM2* gene. We have analyzed cerebellar medulloblastomas from 51 adults (>16 years of age) for *MDM2* gene amplification (by differential polymerase chain reaction assay), *TP53* gene mutation (by polymerase chain reaction single-strand conformation polymorphism analysis of exons 5-8), and immunohistochemical expression of p53 (clone DO1) and *MDM2* (clone IF2). The results have been evaluated in relation to age, tumor location, classic or desmoplastic type, MIB-1 labeling index, and total survival. No tumor had *MDM2* amplification. Ten tumors had *MDM2*-positive tumor cells. One case had a mutated *TP53* gene; 16/51 cases had intense p53 immunostaining. Only 2 *MDM2* protein-positive

tumors were also p53-positive. Both subgroups of *MDM2*- and p53-positive tumors had a significantly shorter postoperative survival. In conclusion, the overexpression of *MDM2* protein and the accumulation of wild-type p53 are unrelated in adult medulloblastoma; they may result in a reduced apoptotic response after radiotherapy and contribute to a shortened survival. Also, *MDM2* amplification and *TP53* gene mutation are rare events in medulloblastomas of adults. *Neuro-Oncology* 4, 115–122, 2002 (Posted to *Neuro-Oncology* [serial online], Doc. 01-062, February 27, 2002. URL <neuro-oncology.mc.duke.edu>)

Medulloblastoma is a malignant tumor of the cerebellum, occurring commonly in children and less frequently in adults. It is characterized by a favorable response to radiation therapy. Long postoperative remission-free survival is achieved with an adequate radiation treatment (Bloom and Bessel, 1990; Hartsell et al., 1992). Although in children this therapeutic option may be limited by severe complications, in adults it is unanimously recognized as a factor responsible for survival rates of 50% to 60% at 5 years and 40% to 50% at 10 years (Carrie et al., 1994; Giordana et al., 1995; Hartsell et al., 1992), especially when administered in a short time period and starting after a short median time after surgery (Chan et al., 2000).

An important cellular response to radiation is apoptosis that may be mediated by the activation of the p53 pathway through DNA fragmentation occurring in medulloblastoma cells in response to ionizing radiation (Dee et al., 1995). Cell lines of medulloblastoma bearing a dominant negative mutant *TP53* have a reduced level of radiation-induced apoptosis (Dee et al., 1995). This indicates that p53 plays an important role in radiation-induced apoptosis of medulloblastomas.

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³Abbreviations used are as follows: LI, labeling index; PCR, polymerase chain reaction.

Our hypothesis was that the individual sensitivity of medulloblastomas to radiation may be related to the individual capability to undergo p53-related apoptosis.

Inactivation of p53 can follow *TP53* gene mutation. This is a highly infrequent event in the medulloblastomas of children (Adesina et al., 1994). Few data are available about the uncommon adult medulloblastoma. The pro-apoptotic activity of p53 may be inactivated also by amplification or overexpression of the *MDM2* gene product; the MDM2 protein is able to form oligomeric complexes with p53 protein and, when experimentally overexpressed, to abolish the transactivating capability of p53 (Momand et al., 1992).

There are few reports on the analysis of the *MDM2* gene in medulloblastomas (Adesina et al., 1994; Batra et al., 1995), and none evaluates adult medulloblastomas separately from pediatric medulloblastomas.

We investigated *MDM2* and *TP53* gene status and expression at the protein level in 51 adult medulloblastomas and analyzed the results in relation to clinical and pathologic features and duration of postoperative survival after radiotherapy.

Materials and Methods

Neurosurgical specimens of 51 cerebellar medulloblastomas from adult patients (33 males, 18 females) consecutively operated on in the 1976-1999 time period in the Neurosurgical Unit of the Department of Neuroscience of the University of Turin, Italy, were analyzed. Age range of the patients was 18 to 62 years with a mean age of 32.5 years; all patients were Caucasian. The patients received postoperative radiotherapy on the whole CNS, with a posterior fossa dose of 30 to 55 Gy. Patients were followed until December 2000.

Analysis of the *MDM2* Gene

MDM2 gene amplification was investigated with multiplex PCR.³ PCR amplifications were performed with 200 ng DNA, 200 mM dNTPs, 1.5 mM MgCl₂, and 1 U Taq polymerase (Boehringer, Mannheim, Germany), in a final volume of 20 ml. PCR cocktails were used for all reactions and contained 0.2 mM primers for *MDM2* coamplified with 0.5 mM primers for γ -interferon.

After DNA was denatured at 95°C for 5 min, 30 cycles of denaturation (94°C), annealing (53°C), and extension (72°C) were done on an automated DNA thermal cycler.

Oligonucleotide primers were designated to amplify a 143-base pair fragment of *MDM2* (P1 5'-GAGGGCTTTGATGTTCTGA-3' and P2: 5'-GCTACAGAAGTTGATGGC-3') and to amplify a control 150-base pair sequence of γ -interferon (P1 5'-AGTGATGGCTGAAGTCTCGC-3' and P2 5'-CTGGGATGCTCTTCGACCTC-3') (Piva et al., 1998).

The amplified PCR products were electrophoresed on a 4% agarose gel and visualized by UV light after ethidium bromide staining. Gels were photographed using Polaroid (St. Albans, U.K.) film and the intensity of the *MDM2* fragment and reference sequence were measured by means of a densitometer GS-670 (Bio-Rad, Hercules,

Calif.). A ratio of more than 4 for *MDM2*/ γ -interferon was considered as indicative of *MDM2* amplification.

Analysis of the *TP53* gene

DNA was extracted from 20 mm-thick paraffin sections after deparaffinization and resuspension in Tris-EDTA (pH 8.0) by heating at 95°C for 10 min. Analysis of the *TP53* gene was performed by the PCR single-strand conformation polymorphism method and sequencing. The following *TP53* primers were used: exon V P1: 5'-ACCCTGGGCAACCAGCCCTGT-3' and P2: 5'-TTCCTCTCCTGCAGTACTC-3'; exon VI P3: 5'-ACAGGGCTGGTTGCCAGGGT-3' and P4: 5'-AGTTGCAAACCAGACCTCAG-3'; exon VII P5: 5'-GTGTTGTCTCCTAGGTTGGC-3' and P6 5'-GTCA GAGGCAAGCAGAGGCT-3'; exon VIII P7: 5'-TATCC TGAGTAGTGGAATC-3' and P8: 5'-AAGTGAATCT GAGGCATAAC-3'.

PCR amplifications were performed with 200 ng DNA, 25 pM of each primer, 200 mM dNTP, 1.5 mM MgCl₂, and 1 U Taq polymerase (Boehringer), in a final volume of 50 ml. As control, genomic DNA obtained from peripheral blood leukocytes of patients without neoplasm was added to each set of PCR reactions. Thirty-five cycles of denaturation (95°C), annealing (63°C for exon V, VI, and VII, and 58°C for exon VIII) and extension (72°C) were done on an automated DNA thermal cycler. Products were then analyzed by single-strand conformation polymorphism. The PCR products were denatured and loaded onto a nondenaturing polyacrilamide gel (Pharmacia Biotech, Amersham, Uppsala, Sweden) and subjected to electrophoresis at 10°C for 2 h. After electrophoresis, the gel was stained with a silver staining kit for DNA (Pharmacia Biotech). In those cases in which mobility shifts were identified by PCR single-strand conformation polymorphism, DNA was amplified and sequenced.

Immunohistochemical Study

The expression of p53 and MDM2 protein were immunohistochemically investigated. The following antibodies were used on sections fixed in Carnoy solution and embedded in paraffin: monoclonal antihuman p53 protein, clone DO1, (Oncogene Science, Darmstadt, Germany, 1:50); monoclonal antihuman MDM2 protein, clone IF2, (Oncogene Research Product, Darmstadt, Germany, 1:100).

After cutting, sections were deparaffinized in xylene and rehydrated through graded alcohol to water and incubated with 0.3% hydrogen peroxide in distilled water for 20 min at room temperature to inhibit endogenous peroxidase. After being washed with Tris-buffered saline 1×, the sections were completely immersed in 0.01 M citrate buffer (pH 6.0) and processed in a microwave oven set at 600 W, 3 min × 5 to enhance the immunoreactivity. Sections were saturated with 10% normal serum for 20 min and incubated at 4°C for 18 to 22 h with primary antibodies. Biotinylated antibody and strept-ABC (Vectastain, Vector Laboratories Inc., Burlingame, Calif.) were successively applied at room

temperature for 30 min each. The immune reactions were developed with diaminobenzidine as a chromogen. Sections were counterstained with hematoxylin. Staining without primary antibodies served as negative control, whereas paraffin sections of a liposarcoma with *MDM2* amplification were used as positive control.

MDM2 protein expression is undetectable in normal nerve tissue (Korkolopoulou et al., 1997); immunoreactivity to *MDM2* has been considered as due to up regulation of its expression, occurring both with or without gene amplification (Biernat et al., 1997). Also, p53 is undetectable by standard immunohistochemistry because of its low cellular levels and very short half-life (Finlay et al., 1989). Mutations of the *TP53* gene, or other events leading to the production of a more stable, nonfunctional protein, are responsible for the immunohistochemical detectability of the accumulated protein (Iggo et al., 1990).

The percentage of p53- and *MDM2*-positive tumor cells was estimated in each case by counting the number of immunoreactive cells in 10 high-power microscopic fields of areas showing the highest immunopositivity at visual analysis. Cases with less than 5% immunopositive tumor cells were scored as negative. Cases with 5% to 20% positive cells were scored as +; 21%-50% ++; more than 50% +++.

Data obtained from the molecular and immunohistochemical study of *MDM2* and p53 were evaluated by considering tumor type (classic versus desmoplastic), tumor location (median versus lateral), proliferation potential evaluated by MIB-1 LI, and overall survival. Clone MIB-1 (AMAC Inc., Westbrook, Me, 1:100) was used. The LI of each tumor was evaluated as previously described (Giordana et al., 1995): The percentage of tumor cells with MIB-1 positive nuclei were counted in the areas showing the highest density of positive nuclei at visual analysis. Ten microscopic fields at magnification $\times 1000$ were examined.

Statistical Evaluation

Correlation between *MDM2* or p53 immunoreactivity and tumor type, location, and proliferation potential was performed by a 2×2 analysis. Survival curves were calculated with the Kaplan-Meier method (Kaplan and Meier, 1958), excluding cases with a postoperative survival shorter than 2 months. Significance of difference was evaluated with the log-rank test (Peto et al., 1977). Multivariate analysis was performed with the Cox method.

Results

Age, sex, tumor type, location, postoperative survival, *MDM2* and p53 immunoreactivity, and the MIB-1 LI of all cases are shown in Table 1. The MIB-1 LI ranged from 2% to 64.7% (median 30.6%).

MDM2 gene amplification was not found in any case. Differential PCR results showed a similar intensity of *MDM2* and reference amplified products in all studied specimens (Fig. 1).

MDM2 immunohistochemical expression was observed in the nuclei of tumor cells. Ten medulloblastomas (19.6%) showed *MDM2*-positive tumor cells. The score was + in 7 cases ++ in 2, +++ in 1. *MDM2*-positive cells were either collected in clusters or evenly distributed within the tumor (Fig. 2A and 2B).

TP53 gene analysis demonstrated an alteration in the electrophoretic pattern in case No. 8 (Fig. 3A). The mutation was located in exon 7. Sequence analysis showed a C→T transition in position 57 (Fig. 3B).

The immunohistochemical expression of p53 was found in the nuclei of tumor cells in 17/51 (33.3%) cases; 6 had +, 4 had ++, and 7 had +++ staining intensity. The case with a mutated gene had +++ p53-positive cells. In classic medulloblastomas, p53-positive tumor cells were scattered in the tumor (Fig. 2C), whereas in desmoplastic medulloblastomas, they were in central areas of pale islands (Fig. 2D).

In 2 cases only, the immunohistochemical expression of p53 and *MDM2* coexisted. No correlation was found between *MDM2* and p53 immunoreactivity and the location, tumor type, age, and MIB-1 LI parameters.

Survival Analysis

Survival time was significantly lower in *MDM2*-positive tumors (median time, 11 months) than in *MDM2*-negative tumors ($P < 0.01$) (Fig. 4). The survival time of p53-positive tumors was significantly shorter than those that were p53 negative ($P < 0.05$) (Fig. 5). Results of the Cox multivariate analysis are shown in Table 2. The only significant variable was *MDM2* immunoreactivity.

Discussion

Among 51 medulloblastomas from adult patients, we identified 8 cases in which the *MDM2* protein was immunohistochemically overexpressed in the absence of either *TP53* gene mutation or p53 expression and 16 cases that had p53 expression without *TP53* gene mutation or *MDM2* amplification or overexpression. In one case, *TP53* mutation and overexpression coexisted with *MDM2* overexpression. Both subgroups of medulloblastomas, the p53- and the *MDM2*-immunopositive cases, had an overall postoperative survival shorter than the negative cases.

These results show that the 2 markers are uncorrelated in the study series of adult medulloblastomas; the expression of *MDM2* and the accumulation of p53 wild-type are independent events, both possibly indicating a derangement of the p53-linked apoptotic pathway, responsible for the shorter survival after radiotherapy.

The functional relationship between *TP53* and *MDM2* gene product has been investigated in malignant gliomas in which the *MDM2* gene represents the second most amplified gene, after the *EGFR* gene (Reifenberger et al., 1995). In glioblastomas, *MDM2* amplification is found in cases without *TP53* mutation, supporting the hypothesis that *MDM2* amplification and overexpression are alternative mechanisms for p53 inactivation

Table 1. Demographic, clinical, and immunohistochemical features of adults with medulloblastoma

	Sex, age	Survival	Status at December 2000	Type	Tumor location	MDM2 ^a	P53 ^a	MIB-1 LI
1	F, 36 yrs	Surgical death	Dead	Classic	Hemisphere	+	–	38.8
2	M, 32 yrs	6 mo	Dead	Desmoplastic	Hemisphere	++	+	42.9
3	M, 27 yrs	11 mo	Dead	Desmoplastic	Hemisphere	+	–	51.2
4	F, 23 yrs	Surgical death	Dead	Classic	Vermis	+	–	–
5	M, 41 yrs	Surgical death	Dead	Classic	Vermis	+	–	–
6	M, 62 yrs	2 mo	Dead	Desmoplastic	Hemisphere	++	–	28.5
7	M, 31 yrs	2 mo	Dead	Classic	Hemisphere	+++	–	–
8 ^b	F, 19 yrs	3 yrs 9 mo	Dead	Desmoplastic	Vermis	+	+++	30.6
9	F, 50 yrs	Surgical death	Dead	Classic	Vermis	+	–	39.6
10	M, 40 yrs	11 yrs	Alive	Desmoplastic	Vermis	+	–	34.5
11	M, 37 yrs	3 yrs 4 mo	Dead	Classic	Hemisphere	–	+	51.2
12	F, 32 yrs	1 yr 4 mo	Dead	Desmoplastic	Hemisphere	–	++	64.7
13	M, 28 yrs	2 mo	Dead	Classic	Vermis	–	+++	28.3
14	M, 43 yrs	1 mo	Lost	Desmoplastic	Vermis	–	+	63.7
15	F, 31 yrs	2 mo	Lost	Classic	Vermis	–	+++	23
16	F, 21 yrs	Surgical death	Dead	Desmoplastic	Hemisphere	–	++	17.4
17	M, 54 yrs	4 mo	Dead	Classic	Hemisphere	–	+	28.9
18	M, 30 yrs	21 yrs	Alive	Desmoplastic	Hemisphere	–	++	10.3
19	M, 40 yrs	4 yrs 3 mo	Dead	Desmoplastic	Vermis	–	+	33.1
20	F, 38 yrs	1 yr 7 mo	Dead	Desmoplastic	Vermis	–	++	42.5
21	M, 18 yrs	2 yrs 2 mo	Dead	Desmoplastic	Hemisphere	–	+++	32.6
22	M, 33 yrs	Recurred as #23	Alive	Desmoplastic	Hemisphere	–	+++	24.3
23	M, 50 yrs	17 yrs	Alive	Desmoplastic	Hemisphere	–	+++	55.5
24	M, 21 yrs	10 mo	Alive	Classic	Hemisphere	–	+	33.7
25	F, 33 yrs	7 mo	Alive	Desmoplastic	Vermis	–	+++	43.6
26	F, 32 yrs	33 yrs	Alive	Classic	Hemisphere	–	–	2
27	M, 30 yrs	Surgical death	Dead	Classic	Hemisphere	–	–	21.5
28	M, 30 yrs	2 yrs 6 mo	Dead	Desmoplastic	Hemisphere	–	–	15
29	F, 33 yrs	Surgical death	Dead	Classic	Hemisphere	–	–	20.2
30	M, 19 yrs	3 yrs 4 mo	Dead	Classic	Hemisphere	–	–	38.4
31	M, 40 yrs	3 mo	Dead	Classic	Vermis	–	–	63.7
32	M, 35 yrs	5 yrs	Dead	Desmoplastic	Hemisphere	–	–	18.3
33	F, 35 yrs	18 yrs	Alive	Classic	Hemisphere	–	–	49.4
34	M, 18 yrs	8 yrs 3 mo	Dead	Desmoplastic	Vermis	–	–	35.7
35	M, 25 yrs	17 yrs	Alive	Classic	Vermis	–	–	16.9
36	M, 23 yrs	Surgical death	Dead	Classic	Vermis	–	–	23.3
37	M, 26 yrs	16 yrs	Alive	Classic	Vermis	–	–	28
38	F, 21 yrs	15 yrs	Alive	Classic	Hemisphere	–	–	37.3
39	M, 22 yrs	11 yrs	Alive	Desmoplastic	Vermis	–	–	30.2
40	M, 19 yrs	10 yrs	Alive	Desmoplastic	Vermis	–	–	9.6
41	M, 20 yrs	8 mo	Dead	Desmoplastic	Hemisphere	–	–	10.4
42	M, 32 yrs	1 yr 10 mo	Dead	Desmoplastic	Hemisphere	–	–	18
43	F, 35 yrs	6 yrs	Alive	Classic	Hemisphere	–	–	21
44	M, 45 yrs	6 yrs	Alive	Desmoplastic	Hemisphere	–	–	42
45	F, 31 yrs	4 yrs 11 mo	Alive	Desmoplastic	Vermis	–	–	18
46	F, 25 yrs	2 yrs 5 mo	Alive	Classic	Hemisphere	–	–	40
47	M, 36 yrs	3 yrs	Lost	Desmoplastic	Hemisphere	ND ^c	ND	ND
48	F, 35 yrs	2 mo	Lost	Desmoplastic	Vermis	ND	ND	ND
49	M, 56 yrs	2 mo	Lost	Classic	Vermis	ND	ND	ND
50	M, 26 yrs	2 yrs 6 mo	Lost	Classic	Vermis	ND	ND	ND
51	F, 32 yrs	1 mo	Lost	Desmoplastic	Hemisphere	ND	ND	ND

^a+, 5%-20%; ++, 21%-50%; +++, more than 50%; –, no reactivity.^bCase with mutated *TP53*.^cND: not done.

Fig. 1. Multiplex PCR analysis of adult medulloblastoma DNA (lanes 1-7) for amplification of the *MDM2* gene. The γ -interferon gene is used as a reference. One pediatric medulloblastoma with *MDM2* amplification is shown in lane 10.

Fig. 2. Immunostaining in adult medulloblastomas. A and B. *MDM2* protein immunostaining. C and D. p53 Immunoreactivity in classic (C) and desmoplastic (D) tumors. 3,3'-Diaminobenzidine stain. Original magnification, A and C $\times 150$, B $\times 250$, and D $\times 100$.

(Biernat et al., 1997; Reifenberger et al., 1993; Riemschneider et al., 1999; Schiebe et al., 2000). Additionally, a significant correlation of *MDM2* gene amplification with short survival was reported in glioblastomas (Schiebe et al., 2000).

Amplification of *MDM2* has never been found in the medulloblastomas found in children (Adesina et al., 1994; Batra et al., 1995). The present results report the same finding in adult medulloblastomas and confirm that *MDM2* amplification is not a major event in medulloblastoma tumorigenesis.

The relation between *MDM2* amplification and overexpression is complex, because tumors may show simul-

taneous amplification and overexpression, amplification without overexpression, or overexpression without amplification (Cordon-Cardo et al., 1994). In glioblastomas, the incidence of *MDM2* overexpression at the protein level is significantly higher than *MDM2* gene amplification (Biernat et al., 1997). The absence of *MDM2* amplification in tumors with protein overexpression may be due in part to a dilution effect: Gene amplification in a low number of tumor cells may not be detectable by differential PCR. Alternatively, *MDM2* overexpression may be due to enhanced translation, as observed in a choriocarcinoma cell line (Landers et al., 1994). The expression of *MDM2* in medulloblastomas

Fig. 3. *TP53* gene analysis. A. PCR single-strand conformation polymorphism analysis of exon 7: Sample 4 shows an altered pattern. B. Sequence analysis of case No. 10 showing the altered pattern demonstrates a C→T transition in position 57.

Fig. 4. Survival curves according to MDM2 immunoreactivity in adult medulloblastomas.

Fig. 5. Survival curves according to p53 immunoreactivity in adult medulloblastomas.

has never been investigated. These results show that a subgroup of them expresses MDM2 protein in the absence of gene amplification.

Although the functional significance of MDM2 overexpression in malignant gliomas remains to be explained, the same finding in medulloblastomas may relate to the role of *MDM2* in modulating the pro-

apoptotic activity of p53 (Haupt et al., 1996). MDM2 overexpression reduces the p53 response to DNA damage (Kubbutat et al., 1997) and can be responsible for a lower tumor radiosensitivity. The association of MDM2 overexpression with shorter overall survival in the present series of adult medulloblastomas supports this hypothesis. Because the present study is retrospective,

Table 2. Cox multivariate analysis of survival for patients with adult medulloblastoma

Variable ^a	Result	HR	95% CI	P
MDM2	Negative	1		0.01
	Positive	2.65	1.77-3.53	
p53	Negative	1		NS
	Positive	1.68	0.70-2.66	

Abbreviations: HR, hazard ratio; CI, confidence interval; NS, not significant.

^a Sex, age, location, and type were not significant in univariate and multivariate analyses. Therapy was not included in the model because all patients received the same treatment.

we have not been able to collect data about tumor dissemination outside the posterior fossa and residual tumor after surgery. Both are major prognostic factors in pediatric medulloblastomas (Packer et al., 1994; Zeltzer et al., 1999); however, they were not of prognostic significance in adult medulloblastomas (Kunschner et al., 2001).

A different subgroup of our adult medulloblastomas showed p53 immunohistochemical expression without *TP53* gene mutation; an association with short survival was found also for this subgroup of patients. Intense p53 staining turned out to be a valuable prognostic indicator of poor prognosis in the medulloblastomas of children (Woodburn et al., 2001). A similar prognostic value in adult cases is shown by these results.

Tumor suppressor gene *TP53* has undergone intensive investigation in a wide range of neoplasms. Wild-type p53 protein is present at low levels in normal cells and is generally undetectable by immunohistochemistry. High levels of detectable p53 protein would suggest prolongation of half life of this protein, resulting from a mutation of the *p53* gene or from deregulation of other genes influencing p53 activity. Our results confirm the very uncommon occurrence of *TP53* mutations in the

medulloblastomas of adults, similarly to pediatric medulloblastomas. Medulloblastoma has basically the same biologic features in children and adults (Giordana et al., 1997). At variance from astrocytic gliomas, *TP53* mutation is not a major target for neoplastic transformation in medulloblastomas.

Nonmutational p53 overexpression is found in 40% to 60% of astrocytomas (Lang et al., 1994). It has been suggested that p53 immunoreactivity in the absence of gene mutation may indicate stabilization of the wild-type protein through interaction with the MDM2 protein (Ohkoudo et al., 1998). This latter mechanism is not the case in our series of medulloblastomas, in which the immunohistochemical expression of p53 was independent of MDM2 overexpression. Mutations in the *TP53* gene outside the conserved region cannot be excluded (Kyritsis and Saya, 1993). Another mechanism responsible for immunohistochemical detectability may be a derangement of proteolytic degradation of p53, operated by the proteasome pathway (Maki et al., 1996).

In conclusion, here we show that in adult medulloblastomas the immunohistochemical expressions of MDM2 protein and p53 protein are mutually exclusive and both are associated with a shorter survival. This association may be due to a disruption of the p53 apoptotic pathway caused by 2 distinctive, still unclarified events, leading to accumulation of wild-type p53 protein and overexpression of MDM2 protein and producing a reduced response to radiotherapy.

Adult medulloblastoma is a rare tumor. No definite prognostic variable has so far been identified (Kunschner et al., 2001), and optimal postsurgical treatment remains to be clarified (Chan et al., 2000). Taking into account the prognostic role of MDM2 and p53 expression may help when evaluating the efficacy of any treatment regimen.

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