Annals of Surgical Oncology, 3(6):521–525
Published by Lippincott-Raven Publishers

Kinetics of Primary Tumor Regression with Chemotherapy: Implications for the Timing of Surgery

Irene Medary, MD, Daniel Aronson, MD, Nai-Kong V. Cheung, MD, PhD, Fereshteh Ghavimi, MD, William Gerald, MD, and Michael P. La Quaglia, MD

Purpose: The kinetics of tumor regression during administration of chemotherapy has relevance to the timing of surgery. The aim of this study was characterization of the time course of primary tumor regression in initially unresectable rhabdomyosarcoma, hepatoblastoma, and neuroblastoma patients. We also estimated the total cell number in the primary tumor at diagnosis.

Methods: Tumor volumes of 24 pediatric patients with either unresectable rhabdomyosarcoma, hepatoblastoma, or neuroblastoma were determined by using computerized three-dimensional reconstruction from serial computed tomography (CT) scans during chemotherapy. Cell densities were calculated by counting cell numbers in high-power fields and dividing by area and section thickness. Cell number at diagnosis was then calculated.

Results: Median tumor volumes at diagnosis were 175 cc, 748 cc, and 738 cc for rhabdomyosarcoma, neuroblastoma, and hepatoblastoma, respectively. The median tumor cell counts were 31, 68, and 59 $\times$ 10^{10} cells/tumor for rhabdomyosarcoma, neuroblastoma, and hepatoblastoma, respectively. The tumor regression was most rapid during the first two cycles, and little change in volume was observed after three cycles.

Conclusion: Rapid initial reduction in primary tumor volume with chemotherapy was observed in rhabdomyosarcoma, neuroblastoma, and hepatoblastoma. These data suggest that second-look resection may be feasible after two to three cycles of chemotherapy. This hypothesis may be tested by randomizing the timing of second-look surgical intervention.

Key Words: Kinetics—Regression—Timing of surgery—Pediatric cancer.

Patients with primarily unresectable rhabdomyosarcoma, hepatoblastoma, or neuroblastoma generally have chemoresponsive tumors, and surgery is often done after several cycles of therapy. If the disease is responding, chemotherapy may be continued over an extended course, until no further decrease in tumor volume is appreciated. However, further chemotherapy courses might allow time for the selection of resistant clones with little benefit in tumor-volume reduction. Theoretically, a characterization of the kinetics of tumor regression would allow identification of the point when the maximum rate of chemotherapeutic response had been achieved. A surgical resection might be more effective just after that maximum rate of cytoreduction.

The purpose of our study was determination of tumor volume in the primary site of several pediatric solid cancers both at diagnosis and serially during chemotherapy by using uniform disease-specific protocols. An estimate of the total number of cells in the primary site was also obtained.

MATERIALS AND METHODS

All patients in this study were younger than 21 years at diagnosis and were first seen between July 28, 1987 and January 30, 1995. Patient data was

Received June 1, 1995; accepted October 2, 1995.

Departments of Pediatric Surgery (I.M., D.A., M.P.L.), Pediatrics (N.V.C., F.G.), and Pathology (W.G.), Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

Address correspondence and reprint requests to Dr. M. P. LaQuaglia, Department of Pediatric Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.

Presented at the 48th Annual Cancer Symposium of The Society of Surgical Oncology, Boston, Massachusetts, March 23–26, 1995.

obtained by review of hospital records, pathology reports, and surgical notes. Included were consecutive cases of primarily unresectable rhabdomyosarcoma ($n = 16$), neuroblastoma ($n = 5$), or hepatoblastoma ($n = 3$), in which each patient received a uniform, disease-specific protocol. Resectability was usually determined by imaging studies. All rhabdomyosarcoma patients were treated under a single disease-specific institutional protocol. The same was true for those with neuroblastoma. Patients with hepatoblastoma were treated by using Children's Cancer Group protocols. All patients in each disease category were treated with similar dose intensities.

Patients in this study had at least three computerized axial tomograms (CTs) during chemotherapy (median, four; range, three to seven). Tumor volumes were measured by computer-aided three-dimensional reconstruction. In each case, the tumor perimeter was carefully outlined with a cursor by using a transilluminated digitizing tablet (Jandel Scientific, Corte Madera, CA, USA) interfaced with an IBM-compatible personal computer. Each cross-sectional image was then entered into a labeled tracefile by using a software package (PC-3D, Jandel Scientific) capable of calculating the area of the digitized image. The computer could reconstruct the tumor in three dimensions as a series of stacked polygonal slices corresponding to each digitized CT scan image (Fig. 1). A value for volume was generated, which depended on the cross-sectional areas of consecutive slices multiplied by section thickness and corrected for image magnification. In most studies, a slice thickness of 10 mm had been used (range, 5–10 mm). The size of the scanned region determined the dimensions of the field-of-view and thus the image magnification. This value was manually measured by using the scale available on the hard copy scan. The median number of sections containing a tumor in each scan was nine (range, three to 22). The accuracy and reproducibility of this method were established by Wheatley et al. (1). Tumor volumes were then plotted versus time from initiation of therapy to illustrate volume decay with treatment.

All patients had an initial pathology review to verify diagnosis. Pathologic sections at diagnosis were available in the archives for 22 patients and were used to estimate primary tumor cell density. In two patients with rhabdomyosarcoma, initial slides and blocks had been returned to the referring institutions and were not available. Four representative high-power fields with known area were captured by thermal imager, hard copies made, and cells counted manually (coefficient of variation = 0.9 to 2.0%). Thin-section cell densities were measured, and cell number at diagnosis was calculated by multiplying primary tumor volume by cell density.

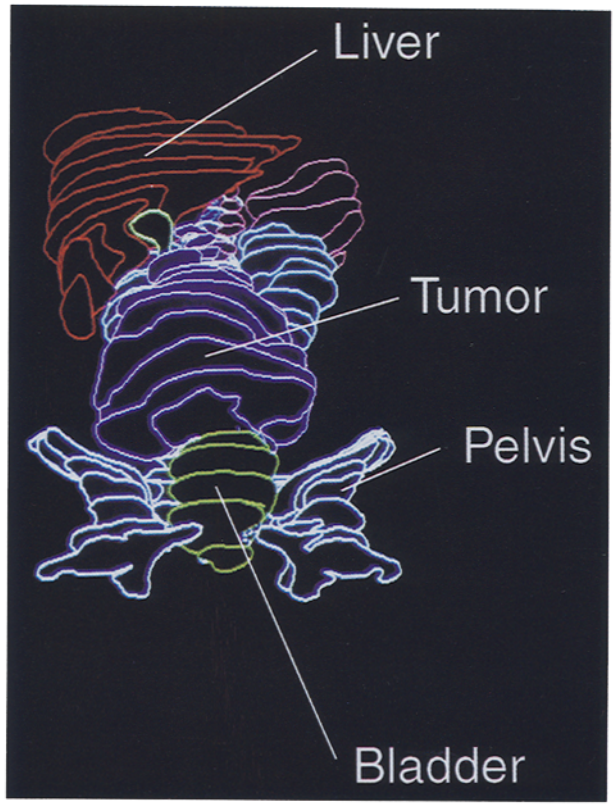

FIG. 1. Three-dimensional, computer-generated reconstruction of tumor and surrounding organs.

RESULTS

Included in this analysis were 16 patients with a diagnosis of rhabdomyosarcoma, five with neuroblastoma, and three with hepatoblastoma. Patient data are summarized in Table 1.

Rhabdomyosarcoma

Rhabdomyosarcoma primary sites included truncal (8 points), genitourinary (3 points), extremity (3 points), and head and neck (2 points). Median tumor volume and cell count at diagnosis were 257 cc and 21.3×10^{10} cells/tumor, respectively. These patients exhibited a wide range of tumor volumes and, consequently, primary tumor cell number at diagnosis (Table 1, Fig. 2). Despite this variation, cell density in the primary tumor was within the same magnitude, 10^9/cc.

TABLE 1. *Patient characteristics and clinical data*

	Rhabdomyosarcoma	Neuroblastoma	Hepatoblastoma
No. of patients	16	5	3
Median age (yr)	14	4	0.5
Sex (M : F)	6 : 10	2 : 3	2 : 1
Stage	5 : II, 2 : III, 9 : IV	4: stage IV, 1 : 3	3 : III
Median tumor volume (range)	175 cc (16–405 cc)	748 cc (665–867 cc)	739 cc (595–1,750 cc)
Mean tumor volume (±SEM)	196 ± 35 cc	761 ± 39 cc	1,027 ± 364 cc
Median cell count[a] (range)	31 × 10^{10} (3–58)	68 × 10^{10} (55–70)	59 × 10^{10} (48–929)
Mean cell count (±SEM)	29 ± 5	65 ± 3	345 ± 3

[a] Reported cell counts were obtained at diagnosis.

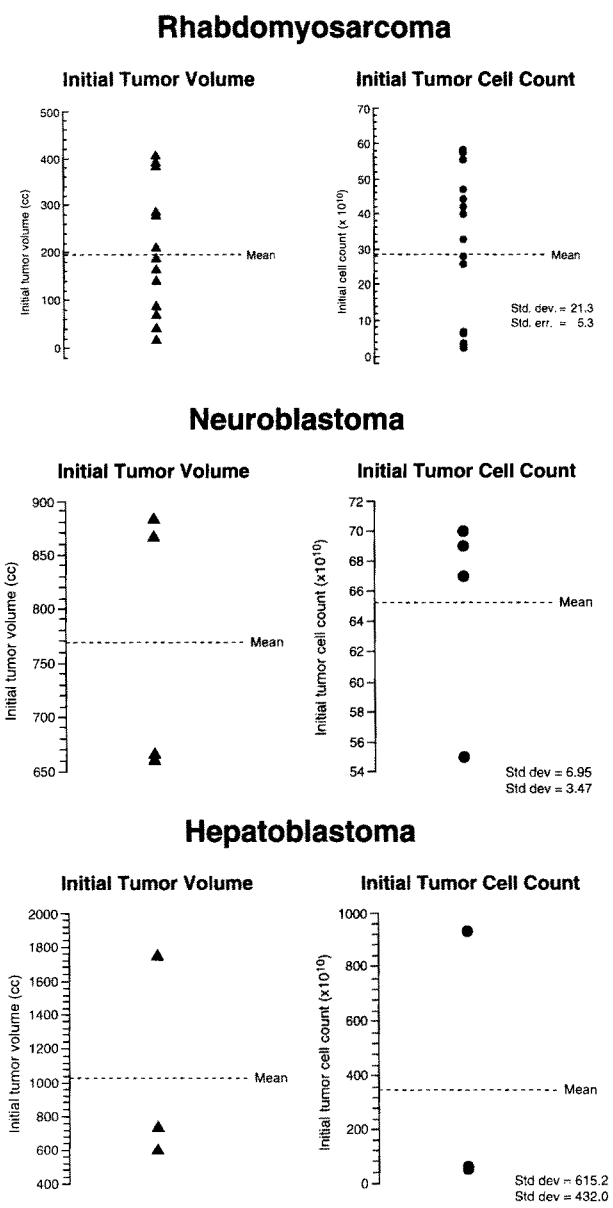

FIG. 2. Tumor volumes and tumor cell counts of rhabdomyosarcoma, neuroblastoma, and hepatoblastoma patients at diagnosis.

A plot of rhabdomyosarcoma tumor volume versus time from initiation of therapy shows early rapid tumor regression (Fig. 3), with 67 to 100% of volume decay occurring within the first two cycles of chemotherapy. The exponential decay in volume suggests first-order kinetics. After three cycles, the rate of volume decay is much slower and often seems to plateau.

Neuroblastoma

Median primary tumor volume and cell count were 641 cc and 66 × 10^{10} cells/tumor, respectively (Table 1, Fig. 2). Neuroblastoma volume decay with chemotherapy also showed an early rapid decrease that became much slower after two to three cycles of therapy with no subsequent change (Fig. 4). Similar to the rhabdomyosarcoma regression, 75 to 92% of total regression occurs within the first two cycles.

Hepatoblastoma

Median primary tumor volume and cell count at diagnosis were 740 cc and 345 × 10^{10} cells/tumor in

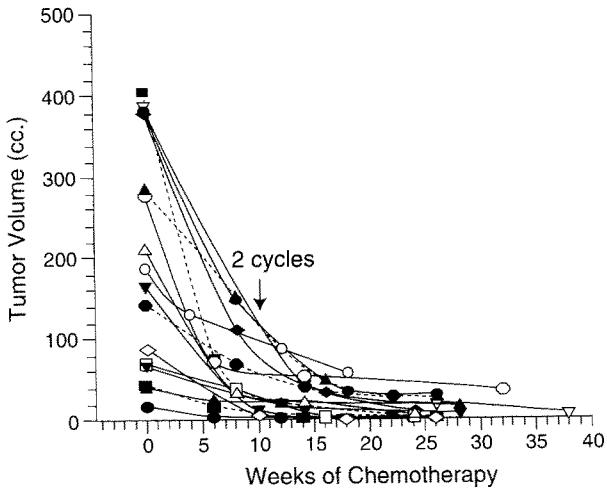

FIG. 3. Tumor volumes of rhabdomyosarcoma patients (n = 16) monitored over time. On average, two cycles are completed by week 10.

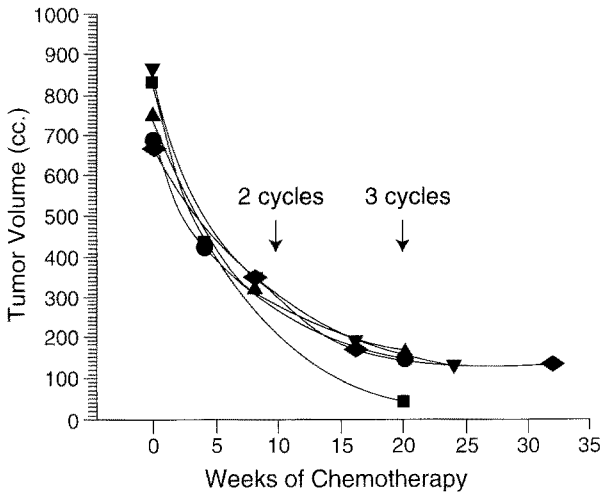

FIG. 4. Tumor volumes of neuroblastoma patients ($n = 5$) monitored over time. Two cycles were usually completed by week 10 and three cycles by week 16.

the three hepatoblastoma patients studied (Table 1, Fig. 2). The shape of the volume–decay curve was similar to those observed in rhabdomyosarcoma and neuroblastoma (Fig. 5). Of the volume reduction, 67 to 98% was noted after completion of the first two cycles of chemotherapy.

DISCUSSION

The treatment of unresectable pediatric solid tumors including rhabdomyosarcoma, high-risk neuroblastoma, and hepatoblastoma remains difficult (2). Significant tumor regression can be expected after administration of chemotherapeutic agents, allowing subsequent resections of previously unapproachable primary tumors. Previous reports have documented the benefit of a gross total resection in stage IV neuroblastoma and rhabdomyosarcoma (2–4).

Previous guidelines for the timing of postchemotherapy (second-look) resections were not based on accurate assessments of tumor regression with treatment (5). Prior studies by Friedman et al. (6) and Cohen et al. (7) confirmed the accuracy of tumor volumes measured by CT scans. No previous studies have monitored tumor volumes during chemotherapy and plotted tumor regression. Measurements of cellular metabolisms such as DNA synthesis, S-phase duration, or glycolysis are often used to analyze tumor kinetics and to calculate a growth fraction but have not been used to document the decay of neoplasms. Metabolic measures have little application to surgery except to identify a point at which the growth fraction is low and therefore chemotherapy would be less effective. Tumor markers such as carcinoembryonic antigen (CEA), CA-125, and CA-19-9, which are released during cell lysis, have also been monitored as markers of tumor necrosis or recurrence and might show similar decay (8,9). This study was undertaken to develop data regarding tumor-volume decay with chemotherapy and to use these findings to postulate the optimal timing for postchemotherapy resections.

Our data show an initial rapid diminution in tumor volume followed by a more gradual decline or often a plateau, suggesting first-order (exponential) kinetics. The changeover from this initial rapid volume decay to the slower regression occurs within the first two to three chemotherapeutic cycles. This suggests that second-look operation should be done after two to three cycles because little further tumor regression can be expected. Although we did not assess other determinants of resectability like vascularity or invasiveness, a logical assumption is that they are correlated with the tumor volume. If the mass of tumor decreases, the blood supply to that mass must eventually decrease. Similarly, if the tumor shrinks in all dimensions, microscopic and macroscopic areas of invasion must also regress. These data suggest that surgical resection is feasible after two or three cycles of chemotherapy. This is of interest because present protocols usually recommend second-look surgery after four or five cycles. We propose that future studies include a randomization of the timing of surgical intervention. For instance,

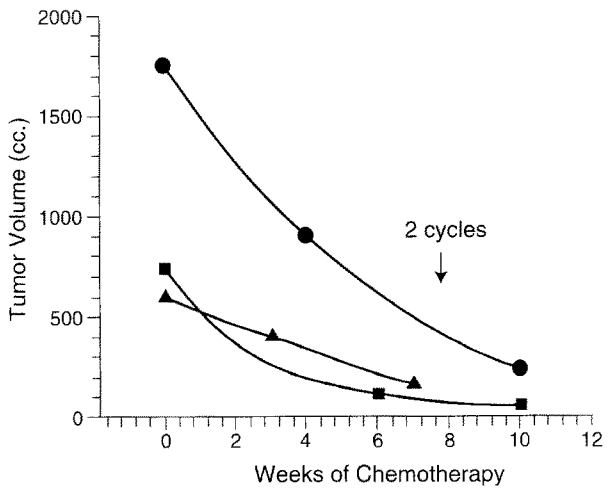

FIG. 5. Tumor volumes of hepatoblastoma patients ($n = 3$) monitored over time. Two cycles were completed by week 6 and three cycles by 13 weeks.

the effect of second-look surgery after two cycles of chemotherapy could be compared with that after four or five cycles. These studies would determine the feasibility of earlier resections and the effect on outcomes.

A second study aim was an estimate of the total number of cells in the primary tumor at diagnosis. It is presently hypothesized that treatment failure depends on the development of a drug-resistant clone that, according to the Goldie–Coldman hypothesis, depends on mutation rate and number of cell divisions (10,11). In turn, the number of cell divisions depends on the total number of cells per tumor and the growth fraction. Mutation rates typically range from 10^{-6} to 10^{-3} per cell division. Our data show that there are $\sim 10^9$ cells/cc of tumor tissue. This finding agrees with widely published documentation of $\sim 10^9$ cells/g of tumor tissue (12). Assuming the lowest mutation rate and that 1% of cells compose the growth fraction, ~1–10 cells/ g of the tumor might develop resistance to present therapy. Because overall survival in rhabdomyosarcoma is only ~50%, and survival in high-risk (stage IV, N-*myc* amplified) neuroblastoma is much less, treatment failure may be partially explained by proliferation of these resistant cells. It is thought that only one clonogenic cell has the capacity to reestablish a tumor that has initially responded to therapy.

In summary, we observed that the most rapid primary tumor-volume decay occurred after the first two to three cycles of chemotherapy. This suggests that second-look resection should be done at this time. Initial cell count data show that many resistant cells are statistically possible, underscoring the necessity of rapid cell reduction by using dose-intensive chemotherapy and aggressive attempts at a resection.

REFERENCES

1. Wheatley JM, Rosenfeld NS, Heller G, Feldstein D, La Quaglia MP. Validation of a technique of computer-aided tumor volume determination. *J Surg Res* 1995;59:621–6.
2. Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study–II. *Cancer* 1993;71: 1904–22.
3. Matsumura M, Atkinson JB, Hays DM, et al. An evaluation of the role of surgery in metastatic neuroblastoma. *J Pediatr Surg* 1988;23:448–53.
4. La Quaglia MP, Kushner BH, Heller G, Bonilla MA, Lindsley KL, Cheung NK. Stage IV neuroblastoma diagnosed at more than 1 year of age: gross total resection and clinical outcome. *J Pediatr Surg* 1994;29:1162–6.
5. Sitarz A, Finklestein J, Grosfeld J, et al. An evaluation of the role of surgery in disseminated neuroblastoma: a report from the Children's Cancer Study Group. *J Pediatr Surg* 1983;18:147–51.
6. Friedman MA, Resser KJ, Marcus FS. How accurate are computed tomographic scans in assessment of changes in tumor size? *Am J Med* 1983;75:193–8.
7. Cohen MD, Weber TR, Grosfeld J. Preoperative evaluation of pediatric abdominal tumors by computerized tomography. *J Pediatr Surg* 1984;19:273.
8. Gattani A, Chesser MR, Cuttner J, Bruckner HW. Serial assays of CA-125, CA-19-9, and CEA in newly treated patients with pancreatic cancer [Abstract]. *Proc Annu Meet Am Assoc Cancer Res* 1992;33:A1305.
9. Cruickshank DJ, Terry PB, Fullerton WT. CA125-Response assessment in epithelial ovarian cancer. *Int J Cancer* 1992;51(1):58–61.
10. Goldie JH, Coldman AJ. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979;63:1727–33.
11. Goldie JH, Coldman AJ. Quantitative model for multiple levels of drug resistance in clinical tumors. *Cancer Treat Rep* 1983;67:923–31.
12. De Vita VT Jr. Principles of chemotherapy. In: De Vita VT Jr, Hellman SA, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. Philadelphia: JB Lippincott, 1985: 257–83.