Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy for Diffuse Malignancy Peritoneal Mesothelioma

a report by

Paul H Sugarbaker, MD, FACS, FRCS *and* **Tristan D Yan, BSc (Med), MBBS**

Program in Peritoneal Surface Oncology, Washington Cancer Institute, Washington Hospital Center

DOI: 10.17925/OHR.2006.00.02.30

Paul H Sugarbaker, MD, FACS, FRCS is Director of Surgical Oncology at the Washington Cancer Institute. He originated the now worldwide program in cancer dissemination to peritoneal surfaces. His innovations include peritonectomy procedures and heated intra-operative intra-peritoneal chemotherapy; these combined treatments now cure patients with gastrointestinal cancer previously considered incurable.

Malignant mesothelioma arises from the serosal lining of the pleural, peritoneal, and pericardial cavities.[1–6] It is a rare neoplasm and has been implicated to be associated with asbestos exposure.[1–5] The rising worldwide incidence of malignant mesothelioma is not expected to peak for another 10–20 years.[5] Diffuse malignant peritoneal mesothelioma (DMPM) represents one-quarter of all mesotheliomas with an annual incidence of DMPM of 300–400 cases in the US.[2–3] It is characterized macroscopically by thousands of whitish tumor nodules of variable size and consistency that may coalesce to form plaques or masses, or layer out to uniformly cover the entire peritoneal surface. Although association of asbestos exposure with DMPM has been observed, the pathogenesis of this disease is largely unknown.[7–8] In addition, DMPM has been reported following radiation therapy, mica exposure, recurrent peritonitis, and administration of thorium dioxide.[9–13]

A great majority of patients present with abdominal pain and distension caused by the accumulation of tumors and ascitic fluid.[14] Without aggressive treatments the disease is rapidly fatal.[15] In the past, DMPM was treated at most cancer centers with a combination of systemic chemotherapy, palliative surgery, and, in a few patients, total abdominal radiation. However, the patients did not seem to respond to these treatments in that the median survival was approximately one year (see *Table 1*).[16–22] No randomized trials have been attempted but it is likely that the survival associated with these palliative treatments was little different from the natural course of the disease.

In most patients DMPM remains localized within the abdominopelvic cavity throughout its course. An aggressive treatment plan to surgically eradicate gross disease combined with peri-operative intraperitoneal chemotherapy (PIC) to control residual disease has a strong locoregional treatment rationale.[23–25] This combined modality has been used with success in patients with pseudomyxoma peritonei and peritoneal carcinomatosis from other gastrointestinal and gynecologic malignancies.[26–31] Treatment of peritoneal carcinomatosis through the use of intraperitoneal chemotherapy was declared standard of practice by the National Cancer Institute, Bethesda, US after a recent phase III study in ovarian cancer.[32] Especially in the last five years, as the cytoreductive surgical (CRS) approach combined with PIC was expanded, the results of treatment for DMPM have dramatically improved compared with historical controls. The median survival has approached five years.[14,33–49]

Assessment of Survival

The effectiveness of CRS and PIC on survival of patients with DMPM is demonstrated in *Table 2*.[39,42,45,47–49]

The rising worldwide incidence of malignant mesothelioma is not expected to peak for another 10–20 years.

The median survival ranged from 34 to 92 months.[39,42,47,48] The median survival was not reached in two of the studies.[45,49] The one-, two-, three-, five- and seven-year survival rates varied from 60% to 88%, 60% to 77%, 43% to 65%, 29% to 59%, and 33% to 39%, respectively.[39,42,45,47–49] One study reported disease status in 49 patients, which showed that 29 patients had no evidence of disease; 10 patients were alive with disease; and 10 patients had died from disease.[45]

Assessment of Peri-operative Outcomes

The effectiveness of CRS and PIC on peri-operative outcomes is demonstrated in *Table 3*.[38,42,45,47–49] The overall morbidity rate varied from 25% to 40%.[38,39,42,45,47,49] Hematological toxicity rate varied from 8% to 26%.[38,42] Blood loss was reported to be 590.[38] Mean operative duration ranged from 6.5 hours to 9.6 hours.[38,42,49] Re-operation rates for post-operative adverse events were 4–11%.[38,42,49] The overall mortality rates ranged from 0% to 8%.[38,42,45,47–49] The median and mean hospital stay were 16 days[47] and 22–23 days,[38,49] respectively.

Discussion

DMPM represents one-third of all mesotheliomas and in the past attracted little attention.[2-3] Traditionally there was a historic agreement among practitioners that peritoneal malignancy was virtually untreatable and therefore considered a pre-terminal condition. The patients were managed with systemic chemotherapy and palliative surgery. However, eventually nearly all patients died from the disease as a result of intestinal obstruction and/or terminal starvation.[16–22] As shown in *Table 1*, the median survival in these patients prior to the year 2000 was less than one year. Recently, as shown in *Table 2*, there has been a re-examination of the peritoneal malignancy and its treatments involving CRS and PIC with a curative intent.

CRS is an important first step in the combined treatment that attempts a removal of all peritoneal tumors together with complete lysis of adhesions between the bowel loops.[23] This provides an optimal situation for adjuvant intra-peritoneal chemotherapy, which is given before the formation of any adhesions, allowing direct chemotherapy and tumor-cell contact, minimizing systemic toxicity.[24–25] Hyperthermia has been known to have direct cytotoxic effects in both a temperature- and time-dependent manner.[50–51] It also has been shown that a greater depth of penetration of the chemotherapy agents into the tumors is achieved;[52] in addition, heat synergizes the cytotoxic drugs selected for intraperitoneal use at the time of surgery.[53]

Table 1: Median Survival of Diffuse Malignant Peritoneal Mesothelioma Using Traditional Treatment Modalities (Combined Pleural and Peritoneal Mesothelioma)*

Authors	Year	No. of patients	Median survival (months)
Chailleux et al.[16]	1988	11/167	10*
Antman et al.[17]	1988	37/180	15*
Sridhar et al.[18]	1992	13/50	9.5*
Markman et al.[19]	1992	19	9
Yates et al.[20]	1997	14/272	14*
Neumann et al.[21]	1999	74	12
Eltabbakh et al.[22]	1999	15	12.5

Table 2: Results of Treatment with Cytoreductive Surgery Combined with Peri-operative Intraperitoneal Chemotherapy for Diffuse Malignant Peritoneal Mesothelioma

Chief investigator	n	Median survival (months)	Survival rates (%) 1-year	2-year	3-year	5-year	7-year
Sugarbaker[39]	100	52	78	64	55	46	39
Alexander[42]	49	92	86	77	59	59	-
Deraco[45]	49	NA	88	74	65	57	-
Glehen[47]	15	36	69	58	43	29	-
Loggie[48]	12	34	60	60	50	33	33
Morris[49]	15	NA	76	63	63	-	-

NA = median survival was not reached.

Many unanswered questions remain regarding the surgical options in the management of DMPM. What can be stated with assurance is that this disease, which in the past was considered a pre-terminal condition, can now be treated with CRS and PIC with benefit in terms of long-term survival. Perhaps it is safe to suggest that this new treatment option, using combined therapy, is a new standard of care with which all other treatment options should now be compared.[54] However, it is also important to note that the results achieved by international experts in this field may not be replicated in routine clinical practice. In the current literature, unfortunately, there are limited data, but with increased recognition of this new treatment for DMPM, more clinical evidence will be available. ■

Table 3: Morbidity and Mortality of Cytoreductive Surgery Combined with Peri-operative Intraperitoneal Chemotherapy for Peritoneal Mesothelioma

Chief Investigator	n	Morbidity (%)	Hematological toxicity (%)	Blood loss(cc)	Op duration (hours)	Reoperation (%)	Mortality (%)	Hospital stay (days)
Sugarbaker[38]	70	36	8	590	8.0*	11	3	23*
Alexander[42]	49	25	26	-	6.5*	4	0	-
Deraco[45]	49	27	-	-	-	-	0	-
Glehen[47]	15	40	-	-	-	-	0	16
Loggie[48]	12	-	-	-	-	-	8	-
Morris[49]	15	36	-	-	9.6*	7	7	23*

References

1. *Wagner JC, Sleegs CA, Marchand P, "Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province",* Br J Int Med *(1960);17: pp. 260–271.*
2. *McDonald AD, MacDonald JC, "Epidemiology of malignant mesothelioma", Antman K, Aisner J (eds.),* Asbestos-related Malignancy *(1987), Orlando: Grune & Stratton, pp. 31–35.*
3. *Price B, "Analysis of current trends in the United States mesothelioma incidence",* Am J Epidemiol *(1997);145: pp. 221–218.*
4. *Scott B, Mukherjee S, Lake R, et al., "Malignant mesothelioma", Hanson H (ed),* Textbook of Lung Cancer *(2000), London: Martin Dunitz, pp. 273–293.*
5. *Robinson BWS, Lake RA, "Advances in malignant mesothelioma",* N Engl J Med *(2005);353: pp. 1591–1603.*
6. *Miller J, Wynn H, "A malignant tumor arising from the endothelium of the peritoneum and producing a mucoid ascitic fluid",* J Pathol Bacteriol *(1908);12: p. 267.*
7. *Price B, Ware A, "Mesothelioma trends in the Unites States: an update based on surveillance, epidemiology and end results program data from 1973 through 2003",* Am J Epidemiol *(2004);159: pp. 107–112.*
8. *Welch LS, Acherman YIZ, Haile E, et al., "Asbestos and peritoneal mesothelioma among college-educated men",* Int J Occup Envirn Health *(2005);11: pp. 254–258.*
9. *Antman KH, Corson JM, Li FP, et al., "Malignant mesothelioma following radiation exposure",* J Clin Oncol *(1983);1: pp. 695–700.*
10. *Chahinian AP, Pajak TF, Holland JF, et al., "Diffuse malignant mesothelioma. Prospective evaluation of 69 patients",* Ann Intern Med *(1982);96: pp. 746–755.*
11. *Riddel RH, Goodman MJ, Moosa AR, "Peritoneal malignant mesothelioma in a patient with recurrent peritonitis",* Cancer *(1981);48: pp. 134–139.*
12. *Maurer R, Egloff B, "Malignant peritoneal mesothelioma after cholangiography with Thorotrast",* Cancer *(1975);36: pp. 1381–1385.*
13. *Peterson JT, Greenberg SD, Buffler PA, "Non-asbestos related malignant mesothelioma",* Cancer *(1984);54: pp. 951–960.*
14. *Acherman YIZ, Welch LS, Bromley CM, et al., "Clinical presentation of peritoneal mesothelioma",* Tumori *(2003);89: pp. 269–273.*
15. *Moertel CG, "Peritoneal mesothelioma",* Gastroenterology *(1972);63: pp. 346–350.*
16. *Chailleux E, Dabouis G, Pioche D, et al., "Prognostic factors in diffuse malignant pleural mesothelioma. A study of 167 patients",* Chest *(1988);93: pp. 159–162.*
17. *Antman K, Shemin R, Ryan L, et al., "Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965–1985",* J Clin Oncol *(1988);6: pp. 147–153.*
18. *Sridhar KS, Doria R, Raub WA Jr., et al., "New strategies are needed in diffuse malignant mesothelioma",* Cancer *(1992);70: pp. 2969–2979.*
19. *Markman M, Kelsen D, "Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma",* J Cancer Res Clin Oncol *(1992);118: pp. 547–550.*
20. *Yates DH, Corrin B, Stidolph PN, et al., "Malignant mesothelioma in south east England: clinicopathological experience of 272 cases",* Thorax *(1997);52: pp. 507–512.*
21. *Neumann V, Muller KM, Fischer M, "Peritoneal mesothelioma—incidence and etiology",* Pathologe *(1999);20: pp. 169–176.*
22. *Eltabbakh GH, Piver MS, Hempling RE, et al., "Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma",* J Surg Oncol *(1999);70: pp. 6–12.*
23. *Sugarbaker PH, "Peritonectomy procedures",* Ann Surg *(1995);221: pp. 29–42.*
24. *Katz MH, Barone RM, "The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies",* Surg Oncol Clin N Am *(2003);12: pp. 673–688.*
25. *Sticca RP, Dach BW, "Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents",* Surg Oncol Clin N Am *(2003);12: pp. 689–701.*
26. *Sugarbaker PH, "New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome",* Lancet Oncol *(2006);7: pp. 69–76.*
27. *Bryant J, Clegg AJ, Sidhu MK, et al., "Systematic review of the Sugarbaker procedure for pseudomyxoma peritonei",* Br J Surg *(2005);92: pp. 153–158.*
28. *Glehen O, Kwiatkowski F, Sugarbaker PH, et al., "Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study",* J Clin Oncol *(2004);22: pp. 3284–3292.*
29. *Verwaal VJ, van Ruth S, Witkamp A, et al., "Long-term survival of peritoneal carcinomatosis of colorectal origin",* Ann Surg Oncol *(2005);12: pp. 65–71.*

30. *Verwaal VJ, van Ruth S, de Bree E, et al., "Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal origin",* J Clin Oncol *(2003);21: pp. 3737–3743.*
31. *Look M, Chang D, Sugarbaker PH, "Long-term results of cytoreductive surgery for advanced and recurrent epithelial ovarian cancers and papillary serous carcinoma of the peritoneum",* Int J Gynecol Cancer *(2004);14: pp. 35–41.*
32. *Armstrong DK, Bundy B, Wenzel L, et al., "Intraperitoneal cisplatin and paclitaxel in ovarian cancer",* N Engl J Med *(2006), 354: pp. 77–79.*
33. *Sebbag G, Yan H, Shmookler BM, et al., "Results of treatment of 33 patients with peritoneal mesothelioma",* Br J Surg *(2000); 87: pp. 1587–1593.*
34. *Sugarbaker PH, Acherman YIZ, Gonzalez-Moreno S, et al., "Diagnosis and treatment of peritoneal mesothelioma: the Washington Cancer Institute experience",* Semin Oncol *(2002);29: pp. 51–61.*
35. *Sugarbaker PH, Welch LS, Mohamed F, et al., "A review of peritoneal mesothelioma at the Washington Cancer Institute",* Surg Oncol Clin N Am *(2003);12: pp. 605–621.*
36. *Yan TD, Popa E, Brun EA, et al., "Sex difference in diffuse malignant peritoneal mesothelioma",* Br J Surg *DOI: 10.1002/bjs.5377.*
37. *Yan TD, Brun EA, Carlos AC, et al., "Prognostic indicators for patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma",* Ann Surg Oncol *DOI: 10.1245/s10434-006-9169-7.*
38. *Yan TD, Alderman R, Edwards G, et al., "Morbidity and mortality assessment of cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma – a prospective study of 70 consecutive cases",* Ann Surg Oncol *DOI: 10.1245/s10434-006-9187-5.*
39. *Yan TD, Yoo D, Sugarbaker PH, "Significance of lymph node metastasis in patients with diffuse malignant peritoneal mesothelioma"* Eur J Surg Oncol *DOI: 10.1016/j.ejso.2006.05.009.*
40. *Ma GY, Bartlett DL, Reed E, et al., "Continuous hyperthermic peritoneal perfusion with cisplatin for the treatment of peritoneal mesothelioma",* Cancer J Sci Am *(1997);3: pp. 174–179.*
41. *Park BJ, Alexander HR, Libutti SK, et al., "Treatment of primary peritoneal mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP)",* Ann Surg Oncol *(1999);6: pp. 582–590.*
42. *Feldman AL, Libutti SK, Pingpank JF, et al., "Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy",* J Clin Oncol *(2003);21: pp. 4560–4567.*
43. *Deraco M, Casali P, Inglese MG, "Peritoneal mesothelioma treated by induction chemotherapy, cytoreductive surgery and intraperitoneal hyperthermic perfusion",* J Surg Oncol *(2003);83: pp. 147–153.*
44. *Nonaka D, Kusamura S, Baratti D, et al., "Diffuse malignant mesothelioma of peritoneum: a clinicopathologic study of 35 patients treated locoregionally at a single institution",* Cancer *(2005);104: pp. 2181–2188.*
45. *Deraco M, Nonaka D, Baratti D, et al., "Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion",* Ann Surg Oncol *(2006);13: pp. 229–237.*
46. *Glehen O, Mithieux F, Osinsky D, et al., "Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study",* J Clin Oncol *(2003);21: pp. 799–806.*
47. *Brigand C, Monneuse O, Mohamed F, et al., "Malignant peritoneal mesothelioma treated by cytoreductive surgery and intraperitoneal chemohyperthermia: results of a prospective study",* Ann Surg Oncol *(2006);13: pp. 405–412.*
48. *Loggie BW, Fleming RA, McQuellon RP, et al., "Prospective trial for the treatment of malignant peritoneal mesothelioma",* Am Surg *(2001);67: pp. 999–1003.*
49. *Yan TD, Links M, Morris DL, "Cytoreductive surgery and perioperative intraperitoneal chemotherapy for 15 patients with diffuse malignant peritoneal mesothelioma". (Submitted for publication).*
50. *Armour EP, McEachern D, Wang Z, et al., "Sensitivity of human cells to mild hyperthermia",* Cancer Res *(1993);53: pp. 2740–2744.*
51. *Los G, Smals OAG, van Vugt MJH, et al., "A rationale for carboplatin treatment and abdominal hyperthermia in cancers restricted to the peritoneal cavity",* Cancer Res *(1992);52: pp. 1252–1258.*
52. *van de Vaart PJ, van der Vange N, Zoetmulder FAN, et al., "Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines",* Eur J Cancer *(1998);34: pp. 148–154.*
53. *Los G, Sminia P, Wondergem J, et al., "Optimization of intraperitoneal cisplatin therapy with regional hyperthermia in rats",* Eur J Cancer *(1991);27: pp. 472–477.*
54. *Janne PA, Wozniak AJ, Belani CP, et al., "Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program",* Clin Lung Cancer *(2005);7: pp. 40–46.*