

Case Analysis

Primary Adenocarcinoma of the Appendix

Po-Chuan Chen¹

Shao-Chieh Lin¹

Jenq-Chang Lee¹

Chao-Han Lai²

Bo-Wen Lin¹

¹Division of Colorectal Surgery,

²Division of Cardiovascular Surgery,

Department of Surgery, National Cheng

Kung University Hospital, Tainan, Taiwan

Key Words

Appendiceal cancer;

Pseudomyxoma peritonei;

Intraoperative intraperitoneal

hyperthermia;

Appendiceal adenocarcinoma

Purpose. Primary adenocarcinoma of the appendix is a rare condition. Institutions around the world have tried to find out the best treatment protocol for these patients. We perform a retrospective chart review, at our hospital, to analyze our treatment result of the past 15 years and compare them to those published in the literature.

Methods. A total of 16 patients are analyzed. Patient demographics, presentation, peri-operative data and total survival are compared.

Results. There is a trend of survival benefit for patients who receive operation with curative intent. A trend of survival benefit can be seen in patients who receive hyperthermia therapy for pseudomyxoma peritonei.

Conclusion. The current practice in our hospital for primary adenocarcinoma of the appendix is comparable to that published in the literature. There is a room for the practice of cytoreductive surgery with hyperthermic intraoperative intraperitoneal chemotherapy for appendiceal pseudomyxoma peritonei. Referral centers should be established in Taiwan to provide best treatment options for these patients.

[J Soc Colon Rectal Surgeon (Taiwan) 2012;23:168-174]

The first reported primary adenocarcinoma of the appendix is by Berger in 1882. It is most commonly classified into colonic-type adenocarcinoma and mucinous-type adenocarcinoma, which is differentiated by the production of mucin. For a perforated mucinous adenocarcinoma, intraperitoneal gelatinous material is termed "pseudomyxoma peritonei" because the material is not composed of true mucin. Primary adenocarcinoma of the appendix is a rare disease, accounting for 0.2-0.5% of all gastrointestinal tumors and 4-6% of primary malignant neoplasms of the appendix.¹ Over the years, institutions around the world have published their treatment results for appendiceal cancer but conclusions are still controversial. Traditionally, major debulking surgery with intravenous chemotherapy has been used to treat patients with pseudomyxoma peritonei. Since Sugarbaker's

publication of peritonectomy procedure in 1987² and 1995,³ the treatment strategy is gradually replaced by cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy.^{3,4} Many institutions around the world have tried to replicate their results, including institutions in England, Australia, Italy, France, Netherland, and the United States.⁵ To evaluate the treatment result, we perform a retrospective chart review of the 15 year experience of treating primary adenocarcinoma of the appendix at National Cheng Kung University Hospital.

Material and Method

Seventeen patients with a clinical and pathological diagnosis of appendiceal adenocarcinoma were

Received: March 1, 2012.

Accepted: July 2, 2012.

Correspondence to: Dr. Bo-Wen Lin, Division of Colorectal Surgery, Department of Surgery, National Cheng Kung University Hospital, No. 138, ShengLi Road, Tainan City 704, Taiwan. Tel: +886-6-235-3535, ext. 5181; Fax: +886-6-276-6676; E-mail: linbw@mail.ncku.edu.tw

treated at National Cheng Kung University Hospital during the period from July 1996 to September 2010. One patient was excluded because appendiceal adenocarcinoma was noted incidentally while treating the synchronous descending colon cancer with carcinomatosis. In the end, a total of sixteen patients were analyzed in this review, which included three colonic-type adenocarcinoma and thirteen mucinous-type adenocarcinoma. Pseudomyxoma peritonei were noted in ten mucinous-type adenocarcinoma patients. Survival plot was constructed using Kaplan-Meier analysis. The χ^2 test or Fisher's exact test was used for comparing categorical variables and was performed by using the Statistical Package for the Social Sciences for Windows, Version 12.0 (SPSS, Chicago, IL, USA). $p < 0.05$ was considered significant.

Result

The clinical data and presentation were summarized in Table 1. The median age at presentation was 67 years (range, 39 to 87 years). Male to female ratio was 3:13. Five patients presented as acute appendicitis (31.3%). One patient presented as retroperitoneal abscess with persistent fever (6.3%). One patient presented as cecal tumor (6.3%). One patient presented as intraabdominal tumor (6.3%). Two patients were diagnosed preoperatively to have massive ascites (12.6%). A total of six patients (37.5%) presented as either pelvic or ovarian tumors (four pelvic tumors, two ovarian tumors) and we were consulted intraoperatively by gynecologists to deal with these situations.

Three colonic-type adenocarcinoma and thirteen mucinous adenocarcinoma were identified. Ten out of thirteen mucinous adenocarcinoma patients presented with diffuse pseudomyxoma peritonei. The over-all 1-, 2- and 5-year survival rates of these 16 patients were 75%, 75% and 50% respectively (Fig. 1). When two histologic types were compared, no survival difference could be seen. No survival difference could be seen whether patients had pseudomyxoma peritonei or not (Table 2).

Eight patients (50%) received right hemicolectomy and the other eight patients received appendectomy at their initial presentation. No survival differ-

Table 1. Patient characteristics and clinical presentations

Variables	Number (n = 16)	%
Age (Median, range)	67, 39-87	
Male gender	3	18.8
Preoperative diagnosis		
Acute appendicitis	5	31.3
Pelvic tumor	6	37.4
Others	5	31.3
Histologic type		
Colonic-type	3	18.8
Mucinous-type	13	81.2
Surgical procedure		
Appendectomy	8	50
Right hemicolectomy	8	50
AJCC Staging		
I	2	12.5
II	3	18.8
III	0	0
IV	11	68.8
Postoperative chemotherapy for stage IV patients	7	43.8
Carcinomatosis		
Yes	1	6.3
No	5	31.3
Pseudomyxoma peritonei	10	62.6
With hyperthermia therapy	7	43.8
Without hyperthermia therapy	3	18.8
Operation with curative intent	14	87.5

Note. Values are patient numbers unless indicated otherwise.

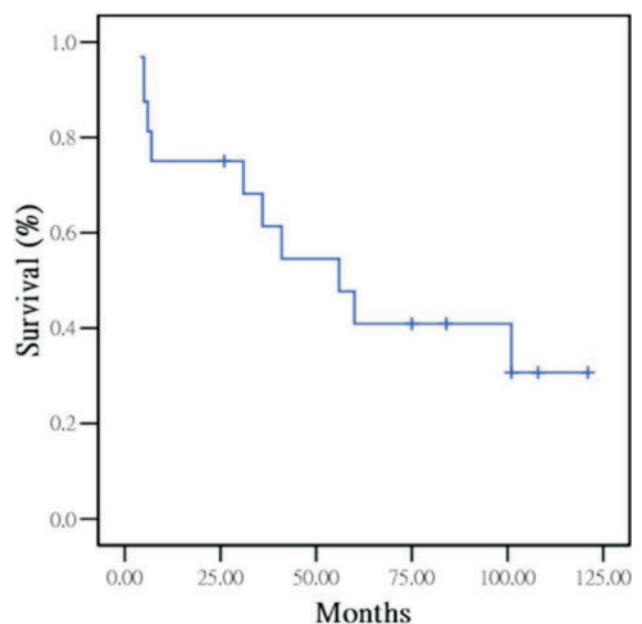


Fig. 1. Kaplan-Meier survival curve for all patients.

Table 2. Univariate analysis for survival predictors

Variables	Treatment success (n = 11)	Treatment failure (n = 5)	p-value
AJCC staging			> .99
I + II (n = 5)	3	2	
III + IV (n = 11)	7	4	
Histologic type			> .99
Mucinous-type (n = 13)	9	4	
Colonic-type (n = 3)	2	1	
Operation intent			0.08
With curative intent (n = 14)	11	3	
With palliative intent (n = 2)	0	2	
Operation type			> .99
Right hemicolectomy (n = 8)	5	3	
Appendectomy (n = 8)	6	2	
Pseudomyxoma peritonei			> .99
Present (n = 10)	7	3	
Absent (n = 6)	4	2	

Note. Treatment success is defined as patients who survived for over 3 years.

ence could be seen by the type of operation. Seven out of eleven stage IV patients received 5-FU based post-operative chemotherapy (Table 1) but no survival benefit could be seen. We arbitrarily grouped stage I/II lesions in AJCC staging as “earlier stage” and stage III/IV lesions as “later stage” for comparison. No survival difference could be seen between the two groups (Table 2).

When we compared fourteen patients who received surgery of curative intent, including either appendectomy or right hemicolectomy with debulking surgery or intraoperative hyperthermia therapy, a favorable survival trend could be seen ($p = 0.08$) (Table 2). Two patients received only palliative tumor resection due to advanced peritoneal carcinomatosis and neither survived for over 6 months. Besides, seven out of ten patients (Table 2) with pseudomyxoma peritonei received intra-operative hyperthermia therapy. A favorable survival trend could be seen ($p = 0.09$) for these patients, compared with those receiving no hyperthermia therapy.

In terms of post-operative complications, two patients (12.5%) had minor surgical wound infection. One patient (6.3%) had intra-abdominal abscess and delayed gastric emptying. One patient (6.3%) had small bowel and colon injury with subsequent ileus during re-debulking surgery. The over-all post-operative morbidity rate is 25%.

Discussion

When examining the 15-year experience at our hospital, no primary adenocarcinoma of the appendix can be diagnosed preoperatively, which is similar to those reported in the literature.⁶⁻⁸ Acute appendicitis and pelvic or ovarian tumors are still the most common clinical presentation. In our study, five patients present with acute appendicitis and six patients present with pelvic or ovarian tumors, which represents a total of 68.8% of our patients. One of the most common features of primary adenocarcinoma of the appendix is the tendency to perforate, which occurs in 12 (75%) of our patients (pseudomyxoma peritonei is assumed to be a perforated state). The reason for high incidence of perforation has been attributed historically to 1) thin muscular coat in this region of gastrointestinal tract, 2) terminal arterial supply, as opposed to branching arcades of the intestine, and 3) small appendiceal lumen, making it easy to perforate by tumor growth and copious mucinous secretion.⁹ Pseudomyxoma peritonei originates from mucinous appendiceal adenocarcinoma and is characterized by mucinous ascites. Initially, the neoplasm obstructs appendiceal lumen. Subsequently, appendiceal perforation causes tumor cells to spread into the whole peritoneal cavity. The diffusely scattered tumor cells in this condition

make it a deadly disease if left untreated. Patients eventually die from massive tumor load, terminal starvation, or surgical complications from repeated debulking surgery.¹⁰

The significance of tumor histological type remains controversial. Some studies conclude that colonic-type adenocarcinoma has poorer prognosis^{8,11} but another study done by Ito et al.¹² claims that mucinous-type adenocarcinoma has poorer outcome. The study done by Hwang reveals that patients with mucinous appendiceal adenocarcinoma who receive non-curative resection even have a significantly longer median survival compared to those with colonic-type adenocarcinoma,¹ suggesting that mucinous-type adenocarcinoma has better outcome. Our study shows no survival difference between these two groups (Table 2). However, all these studies share the same problem of small patient numbers so a large multicenter study is still needed for elucidation.

For colonic-type adenocarcinoma, right hemicolectomy was performed on all our three patients and achieved two disease-free survival of more than 2 years. When reviewing the literature, studies have shown that right hemicolectomy can double the survival achieved by appendectomy only.^{13,14} That is because colonic-type adenocarcinoma can metastasize through lymphatic drainage and a formal right hemicolectomy will solve this problem. For mucinous-type adenocarcinoma with pseudomyxoma peritonei, right hemicolectomy used to be the preferred procedure.¹¹ In a retrospective review of 501 patients who received right hemicolectomy in the absence of intraperitoneal chemotherapy, Sugarbaker found that those patients actually had a survival disadvantage.¹⁵ Our study shows no survival advantage for these patients. However, our sample size is too small to make this conclusion.

Mucinous-type appendiceal adenocarcinoma with pseudomyxoma peritonei is a special disease entity. The diffusely scattered tumor cells in the peritoneal cavity usually stay on the peritoneal surface and grow slowly. In earlier years, surgeons tried to combat this disease with repeated debulking surgery and intravenous chemotherapy but the results are discouraging.^{7,16} In recent years, Sugarbaker has developed a definitive cytoreductive surgery with hyperthermic

intraoperative intraperitoneal chemotherapy and has performed on these patients with gratifying results.^{2,3} Nowadays, this concept has gradually become accepted as a feasible option. With traditional debulking surgery, the over-all five year survival rates is about 30-50% according to the literature, which is similar to our result. However, when cytoreductive surgery and hyperthermia intraoperative intraperitoneal chemotherapy is performed, five year survival rate can be improved to 52-96% by authors around the world.^{14,16,17} In 2010, twenty-three institutions in France have also demonstrated that this technique can be used for colonic-type appendiceal adenocarcinoma with peritoneal carcinomatosis to improve patient survival.¹⁸ From the viewpoint of operation with curative intent, our data also support that as long as tumor can be resected radically grossly, there will be survival advantage (Table 2).

The rationale of this comprehensive cytoreductive surgery is to remove all visible tumors and perform lysis of adhesion between bowel loops. This allows intraperitoneal chemotherapy to gain direct contact with any residual tumor cells. Intraperitoneal chemotherapy gives high response rates to residual tumors in the peritoneal cavity because the "peritoneal plasma barrier" provides dose intensive therapy.^{14,17} In other words, chemotherapeutic effect can be obtained best through intraperitoneal route, instead of intravenous route. After complete cytoreductive surgery, the 5 day perioperative intraperitoneal chemotherapy can exert best contact to residual tumors smaller than 2.5 mm and gain best locoregional control.¹⁷ Our study also shows that post-operative intravenous chemotherapy gains no survival advantage for stage IV patients. The discouraging result of intravenous chemotherapy is matched with that published by the Memorial Sloan-Kettering Cancer Center in 1992 and 2005.^{7,21}

Heat is part of the optimizing process in the operation and is used to bring as much dose intensity to the abdominal and pelvic surfaces as possible. Theoretically, heat by itself has more toxicity for cancerous tissue than for normal tissue. In our hospital, seven out of ten pseudomyxoma peritonei patients received 46 °C intraoperative and postoperative intraperitoneal hyperthermia therapy done by a single surgeon. No intraperitoneal chemotherapy was used. Associated

morbidity rate was 12.5% and no mortality was reported. The estimated 1-, 3-, and 5-year survival rates were 100%, 88%, and 49%, respectively.¹⁹ Our data showed a favorable survival trend in patients who received hyperthermia therapy for pseudomyxoma peritonei. Though it is currently not mainstream treatment protocol, the low morbidity and mortality rate makes it a suitable choice for patients with severe medical comorbidities.

To treat primary adenocarcinoma of the appendix, many medical centers around the world begin to practice the procedure proposed by Sugarbaker team but many of these centers fail to replicate the safety and survival benefits shown during their initial experience. Morbidity rate as high as 27% can still be seen by the experienced team of Sugarbaker. Other institutions report even higher morbidity rate as 33-56%.^{5,21-23} In our report, we have a low surgical morbidity rate of 25% and we think that the extensive procedure of peritonectomy is responsible for the high morbidity rate. Clearly, numerous years of experience is required to overcome the initial learning curve before surgeons can appropriately select patients for treatment, perform the procedure safely, and manage the postoperative complications wisely. In other words, the best result can only be achieved in experienced hands. As a starter of this procedure, reported from Australia, morbidity as high as 40% and mortality as high as 6% can actually incur severe criticism in the surgical community.⁵ From the experience of many referral centers in the world, cytoreductive surgery with hyperthermic intraoperative intraperitoneal chemotherapy cannot be mastered until more than fifty cases of experience.^{5,24} An inexperienced surgeon can actually do more harm than good to a patient in terms of disease control and postoperative quality of life. That is the reason why referral centers should be established in the surgical society in Taiwan to treat this kind of cancer. If early referral can be achieved, appropriate actions will be taken quickly and operative morbidity and mortality will be reduced. The patient's over-all quality of life will be enhanced undoubtedly.⁴ Only through this approach can surgeons in the referral centers gain enough experience in Taiwan to fully master the technique, and to give best results to the patients.

Conclusion

Current operative trend for appendiceal cancer, either of mucinous or colonic type, is right hemicolectomy. If pseudomyxoma peritonei is noted during the operation, cytoreductive surgery plus intraperitoneal chemotherapy with or without hyperthermia therapy should be done. According to our limited case analysis, post-operative adjuvant intravenous chemotherapy for stage IV patients shows no survival benefit.

References

- Hsu JT, Chen HM, Liao CH, Yeh CN, Yeh TS, Hwang TL, Jan YY, Chen MF. Clinicopathologic features and predictors for survival of mucinous and nonmucinous appendiceal adenocarcinoma. *Dig Surg* 2008;25:369-75.
- Sugarbaker PH, Kern K, Lack E. Malignant pseudomyxoma peritonei of colonic origin. Natural history and presentation of a curative approach to treatment. *Dis Colon Rectum* 1987;30:772-9.
- Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; 221:29-42.
- Sugarbaker PH. Twenty-three years of progress in the management of a rare disease. *Dis Colon Rectum* 2011; 54:265-6.
- Chua TC, Liauw W, Saxena A, Al-Mohaimeed K, Fransi S, Zhao J, Morris DL. Evolution of locoregional treatment for peritoneal carcinomatosis: single-center experience of 308 procedures of cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Am J Surg* 2011;201:149-56.
- Gough DB, Donohue JH, Schutt AJ, Gonchoroff N, Goellner JR, Wilson TO, Naessens JM, O'Brien PC, van Heerden JA. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. *Ann Surg* 1994;219:112-9.
- Smith JW, Kemeny N, Caldwell C, Banner P, Sigurdson E, Huvos A. Pseudomyxoma peritonei of appendiceal origin. The Memorial Sloan-Kettering Cancer Center experience. *Cancer* 1992;70:396-401.
- Cortina R, McCormick J, Kolm P, Perry RR. Management and prognosis of adenocarcinoma of the appendix. *Dis Colon Rectum* 1995;38:848-52.
- Cerame MA. A 25-year review of adenocarcinoma of the appendix. A frequently perforating carcinoma. *Dis Colon Rectum* 1988;31:145-50.
- Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. *Ann Surg Oncol* 2007;14:484-92.
- Nitecki SS, Wolff BG, Schlunkert R, Sarr MG. The natural

- history of surgically treated primary adenocarcinoma of the appendix. *Ann Surg* 1994;219:51-7.
12. Ito H, Osteen RT, Bleday R, Zinner MJ, Ashley SW, Whang EE. Appendiceal adenocarcinoma: long-term outcomes after surgical therapy. *Dis Colon Rectum* 2004;47:474-80.
 13. Hesketh KT. The management of primary adenocarcinoma of the vermiform appendix. *Gut* 1963;4:158-68.
 14. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 2006;7:69-76.
 15. González-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. *Br J Surg* 2004;91:304-11.
 16. Youssef H, Newman C, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin. *Dis Colon Rectum* 2011;54:293-9.
 17. Sugarbaker PH. Surgical responsibilities in the management of peritoneal carcinomatosis. *J Surg Oncol* 2010;101:712-24.
 18. Elias D, Glehen O, Pocard M, Quenet F, Goéré D, Arvieux C, Rat P, Gilly F; Association Française de Chirurgie. A comparative study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. *Ann Surg* 2010;251:896-901.
 19. Hsu KH, Chou CY, Chang YC. Intraperitoneal hyperthermia in the management of pseudomyxoma peritonei. *Hepatogastroenterology* 2007;54:47-52.
 20. Miner TJ, Shia J, Jaques DP, Klimstra DS, Brennan MF, Coit DG. Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. *Ann Surg* 2005;241:300-8.
 21. Sugarbaker PH. Are there curative options to peritoneal carcinomatosis? *Ann Surg* 2005;242:748-50.
 22. Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, Chang D. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. *Ann Surg Oncol* 2006;13:635-44.
 23. Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. *Br J Surg* 2007;94:1408-14.
 24. Yan TD, Links M, Fransi S, Jacques T, Black D, Saunders V, Morris DL. Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy — a journey to becoming a nationally funded peritonectomy center. *Ann Surg Oncol* 2007;14:2270-80.

病例分析

源自於闌尾的腺癌

陳柏全¹ 林劭潔¹ 李政昌¹ 賴昭翰² 林博文¹

國立成功大學附設醫院 ¹大腸直腸外科 ²心臟血管外科

目的 源自於闌尾的腺癌是個很罕見的疾病，世界上，愈來愈多機構試圖找尋針對此疾病最好的治療方針。為此，我們進行院內的病歷回顧，並比較我們與世界各機構的治療結果。

方法 我們總共分析了 16 個病人。包括比較病人的疾病表現、手術相關的資料、及總存活天數。

結果 病患若接受腫瘤根除手術加上廣泛腹內腫瘤清除手術或術中高溫水療，則有較好的存活趨勢。

結論 本院在治療闌尾腺癌上，結果與世界其他報告相符。但是在腫瘤細胞根除手術及術中高溫化學治療這方面，尚未達成現今世界上的治療趨勢。我們建議在台灣應該成立專責的治療機構，才能提供病人最好的照顧。

關鍵詞 腹腔假黏液癌、闌尾癌、闌尾腺癌、術中高溫化學治療。