Journal of Gastrointestinal & Digestive System

Porpiglia et al., J Gastrointest Dig Syst 2016, 6:5
DOI: 10.4172/2161-069X.1000477

Review Article OMICS International

The Role of Heated Intraperitoneal Chemotherapy (HIPEC) in Low-Grade Appendiceal Neoplasm: Friend or Foe?

Andrea Porpiglia, Duy Nguyen, Jeffrey Farma and Sanjay S Reddy*

Fox Chase Cancer Center, Philadelphia, PA, USA

***Corresponding author:** Sanjay S Reddy, Fox Chase Cancer Center, Philadelphia, PA, USA, Tel: 1 215-728-2570; E-mail: sanjay.reddy@fccc.edu

Received date: October 13, 2015; **Accepted date:** November 2, 2016; **Published date:** November 9, 2016

Copyright: © 2016 Porpiglia A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Low-grade mucinous appendiceal neoplasms are rare tumors. There is limited data on the treatment for pseudomyxoma peritonei with low-grade appendiceal histology. Classifications of appendiceal neoplasms include low-grade appendiceal mucinous neoplasm (LAMN), diffuse peritoneal adenomucinosis (DPAM), and peritoneal mucinous carcinomatosis (PMCA). Studies have demonstrated patients with low-grade appendiceal neoplasms have improved overall survival compared to patients with high-grade appendiceal neoplasms. Since low-grade tumors have better prognosis some retrospective trials have suggested observation in patients with these types of tumors. Another option includes cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). We have done an extensive literature search exploring the various methods in which to treat patients with this disease.

Keywords: Intraperitoneal chemotherapy; Appendiceal; Diffuse peritoneal adenomucinosis

Introduction

Cancers of the appendix are rare and complex tumors. The incidence of all appendiceal malignancies is 0.12 cases per 1,000,000 per year [1]. In 1940, Woodruff and McDonald first described cystic mucinous tumors of the appendix [2]. Further classification of appendiceal neoplasms include low-grade appendiceal mucinous neoplasm (LAMN), for all low-grade mucinous tumors of the appendix that lack invasion of the appendiceal wall [3]. Other groups include diffuse peritoneal adenomucinosis (DPAM), and peritoneal mucinous carcinomatosis (PMCA), which the latter is on the spectrum of high-grade disease [3].

Pseudomyxoma peritonei syndrome is characterized by neoplastic mucoceles and epithelial cells present in the mucus outside the appendix [4]. Misdraji et al. at the Massachusetts General Hospital reported 49 cases of low-grade mucinous neoplasms, and those with an intact appendix had a more indolent course, and no recurrence was seen within a six-year follow-up. The same low-grade tumor with a ruptured appendix, and extra-appendiceal spread, had only a 45% 5-year survival [5]. Varrisco et al. performed a retrospective chart review and meta-analysis for appendiceal neoplasms. Their data supported the use of appendectomy alone in localized cases of low-grade adenocarcinoid of the appendix, provided there was no cecal involvement [6]. However, there is no standard established in the decision making in those with pseudomyxoma peritonei from low-grade appendiceal neoplasms.

In this review we consider the benefits of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of low-grade appendiceal neoplasms, diffuse-peritoneal adenomucinosis (DPAM) disease, and pseudomyxoma peritonei. There remains much debate on whether an optimal cytoreduction is all that is needed in this subset of patients. Sugarbaker et al. have popularized the use of not only cytoreduction, but heated intraperitoneal chemotherapy in the treatment algorithm [4]. We have done a retrospective review of the literature on patients with low-grade appendiceal disease to evaluate treatment with cytoreduction alone versus cytoreduction with the addition of hyperthermic intraperitoneal chemotherapy.

Methods

A comprehensive literature search was performed using PubMed. The keywords used to perform the search include: hyperthermic intraperitoneal chemotherapy, low-grade appendiceal neoplasms, diffuse peritoneal adenomucinosis disease, pseudomyxoma peritonei, and cytoreductive surgery. The search was limited to articles published in English, as well as those published in the last 20 years. The articles were read in full by the authors and were included based on the relevance to the article topic. The articles included specifically discussed low-grade appendiceal neoplasms. There were 18 studies that were retrospective reviews, 1 meta-analysis, 1 prospective trial and 2 prospective reviews.

Results

Historically, pseudomyxoma peritonei was a disease treated with repeat debulking surgeries, and rates of recurrence were reported to be as high as 76%. There was no difference in those patients who had curative resections or subtotal debulking [7,8]. Cytoreductive surgery includes removal of the primary tumor, an omentectomy, and removal of tumor implants, with the goal to remove all macroscopic disease. Ball tip cautery is often used to destroy tumor on intra-abdominal structures [9]. A scoring system has been adapted to determine the extent of cytoreduction, and is referred to as the completeness of cytoreduction score (CCR). A score of 0 indicates that no tumor remains, a 1 indicates nodules <2.5 mm in diameter, a 2 when disease measures 2.5 mm to 2.5 cm, and finally a CCR of 3 is when residual tumor deposits measure greater than 2.5 cm [10]. Sugarbaker has shown those patients who had scores of 0 and 1 had improved overall survival [10]. Youseff et al. reported their experience of 456 patients

with pseudomyxoma peritonei from an appendiceal primary [11]. They compared patients who underwent complete cytoreduction to those who had sub-optimal debulking surgery secondary to intra-abdominal burden of disease. Both groups received HIPEC at the time of surgery. In those patients who had complete cytoreduction versus sub-optimal debulking, the 5 year overall survival was 87% versus 34%, respectively.

Critics of cytoreduction and heated intraperitoneal chemotherapy in those with low-grade disease often argue that the natural history of the indolent tumor biology may in fact play the largest role of all in determining outcomes. A common critique is why not simply observe these patients? McDonald et al. looked at 43 patients with LAMN, who had a low-risk of dissemination [12]. Those who were low risk for dissemination had low-grade cytological atypia, localized mucin deposition, and no radiographic evidence of peritoneal spread. When these patients were closely observed with serial imaging and tumor markers every six months, no patients showed progression of disease at 40-months of follow-up. Despite these findings, there is limited data on the role of observation for patients with low-grade appendiceal neoplasms (Table 1).

Some authors believe low-grade appendiceal neoplasms have an overall favorable prognosis, and optimal surgical debulking alone is all that is needed. Several studies have reviewed the role of cytoreductive surgery alone, and Memorial Sloan Kettering Cancer Center (MSKCC) reported their series of patients from 1980 to 2002 who underwent aggressive surgical debulking [13]. The median survival was 9.8 years, and those with low-grade neoplasms had median survival rates as high as 12.8 years. Despite these compelling numbers, 91% had disease recurrence. The authors argued similar survival rates to those patients from other studies that received HIPEC and cytoreductive surgery. The Mayo clinic reported their data on 29 patients who were treated with aggressive cytoreductive surgery [7]. The 5 year survival rate was 53% and 76% had some evidence for recurrence. However, the study included patients with appendiceal, ovarian, colon, endometrial, and pancreatic tumors. Therefore, extrapolating data from low-grade appendiceal neoplasms must be taken with caution. Another study evaluating the role of cytoreductive surgery in pseudomyxoma peritonei was from Jarvinen et al. [14]. They reviewed 33 patients with DPAM who had serial debulking surgeries totaling 113 operations. The overall 5 and 10 year survival rates were 67% and 31% respectively. Most of the above-mentioned studies are retrospective in nature, and there are no prospective randomized controlled trials comparing cytoreductive surgery to observation. However, Zih et al. compared those who had cytoreduction alone and those who were managed expectantly [15]. The expectant observation group had very limited disease (1 or 2 quadrants of disease) and low-grade tumors. The 5 year overall survival in the cytoreductive surgery alone group was 74%, and in the expectant observation group was 95%. The majority of these patients in the study had low-grade disease, 46% in the surgery alone group, and 29% in the expectant observation group. This study demonstrates that low-grade tumors can be treated with cytoreductive surgery alone or possibly even observation.

Despite the improved 5 year survival rates in those undergoing optimal cytoreduction, the introduction of HIPEC was used as a way to potentially maximize both overall and disease-free survival. This strategy was first introduced in the treatment of patients with pseudomyxoma peritonei, and was published by Spratt et al. in 1980 [16]. Marcotte et al. performed a prospective study analyzing patients with peritoneal dissemination from appendiceal origin [17]. The patients underwent optimal cytoreduction followed by HIPEC with Oxaliplatin. This study specifically looked at patients with low-grade tumors (DPAM), as opposed to high-grade tumors (PMCA). The findings suggest that of these patients with low-grade disease, no recurrences were noted. Sugarbaker et al. have reported extensively on the use of HIPEC in appendiceal peritoneal dissemination. In 1999 he reported his series of 385 patients, the results of which demonstrated improved survival in the group that underwent optimal cytoreduction and HIPEC, versus those with sub-optimal reduction and HIPEC [18]. Also noted was better survival in those with adenomucinosis, compared to those with mucinous adenocarcinoma, a higher-grade variant.

					Overall survival		Disease Free Survival	
Chief Investigator	**n**	**Tumor classification**	**Treatment**	**Median follow-up**	**3 year**	**5 year**	**3 year**	**5 year**
Marcotte [17]	7	DPAM	n=5 HIPEC, n=2 negative second look	22.6 months	71.60%	N/A	100%	N/A
	24	PMCA-intermediate	n=17 HIPEC, n=2 negative second look, n=5 unresectable			N/A	30.80%	N/A
	7	PMCA	n=1 HIPEC, n=1 negative second look, n=5 unresectable			N/A	N/A	N/A
Sideris [27]	5	DPAM	cytoreduction early postoperative intraperitoneal chemotherapy, HIPEC	23 months	N/A	100%	N/A	N/A
	12	intermediate			N/A	87%	N/A	N/A
	7	PMCA			N/A	0%	N/A	N/A
Bradley [19]	58	DPAM	cytoreductive surgery+IPC	2.1 year	N/A	62%	N/A	N/A
	20	PMCA-intermediate		3.6 year	N/A	68%	N/A	N/A
	23	PMCA		3.1 year	N/A	37.7%	N/A	N/A

Chua [21]	1419	DPAM	cytoreductive surgery+IPC (mitomycin C)	36 months	N/A	81%	N/A	N/A
	140	Hybrid			N/A	78%	N/A	N/A
	700	PMCA			N/A	59%	N/A	N/A
	39	unknown			N/A	N/A	N/A	N/A
Zih [15]	75	low grade	cytoredutive surgery or expectant observation	38 months	N/A	74%, 95%	N/A	N/A
	5	intermediate/high			N/A		N/A	N/A
	1	unknown			N/A		N/A	N/A
Stewart [23]	55	DPAM	cytoreductive surgery+IPC (mitomycin C)	34.8 months	59%	53%	N/A	N/A
	18	intermediate					N/A	N/A
	29	PMCA					N/A	N/A
	8	high grade					N/A	N/A
Deraco [22]	28	DPAM	cytoreduction+IPC (cisplatin/mitomycin C)	28.6 months	N/A	96%	N/A	43% (5 year)
	5	intermediate			N/A		N/A	
Omohwo [28]	22	DPAM	cytoreductive surgery+IPC (mitomycin C)	23 months	80%	N/A	N/A	N/A
	34	PMCA			52%	N/A	N/A	N/A
Ronnett [29]	65	DPAM	cytoreductive surgery+IPC (mitomycin C)	N/A	N/A	84%	N/A	N/A
	14	intermediate			N/A	37.60%	N/A	N/A
	30	PMCA			N/A	6.70%	N/A	N/A
Andreasson [30]	69	low grade	debulking or cytoreductive surgery+IPC	40 months	N/A	88%	N/A	67%
	81	high grade			N/A	60%		
Elias [31]	50	low grade	Cytoreduction+		N/A	80%	N/A	68.50%
	37	intermediate grade	HIPEC (mitomycin C	48 months				
	18	high grade	or oxaliplatin/irinotecan)					
Murphy [26]	67	low grade	cytoreductive surgery+IPC (mitomycin C)	27 months	N/A	75%	N/A	80%
	16	high grade			N/A		N/A	65%

Table 1: Observation for patients with low-grade appendiceal neoplasms.

Bradley et al. reviewed 101 patients treated with cytoreductive surgery and HIPEC. When low-grade and high-grade disease was compared, those with DPAM had a 61.8% 5 year overall survival, compared to 37.7% with PMCA [19]. Jarvinen et al. compared patients who underwent serial debulking, versus those who had cytoreductive surgery and HIPEC [20]. In those with low-grade disease, the 5 year overall survival was 67% in the debulking group, and 98% in those who received HIPEC. One of the largest reviews of patients with appendiceal pseudomyxoma peritonei from Chua et al. reviewed 2,298 patients [21]. The 5 year overall survival for DPAM was 81%, versus 59% for PMCA. All these studies suggest improved survival in those with low-grade disease, but whether or not the addition of HIPEC also plays a role is difficult to know without randomized control trials. Although we see a potential benefit with the use of HIPEC in selected patients, the risks and benefits of using this need to be adjusted for Deraco et al. conducted a phase II study by evaluating cytoreductive surgery and HIPEC using Mitomycin-C and Cisplatin [22]. They had 33 patients with pseudomyxoma peritonei, the majority of which had DPAM. There was a 96% and 43% 5 year overall survival and progression-free survival, respectively. Grade 2 or 3 complications occurred 33% of the time, and this is keeping with the literature, which reports a morbidity rate of 24-45% [10,17,21,23,24] and mortality rates of 1.6-5% [11,21,23,25,26]. Again demonstrating prolonged survival with combination of cytoreductive surgery and HIPEC.

Discussion

Appendiceal neoplasms are rare, and treatment of this disease remains controversial. There are proponents that believe surgical debulking alone is sufficient to treat appendiceal neoplasms with peritoneal dissemination. However, others believe there is a risk of local recurrence, and cytoreductive surgery plus HIPEC is necessary.

Studies suggest that patients with low-grade appendiceal tumors have improved overall survival when compared to high-grade appendiceal tumors, or even those with metastatic colorectal cancer, when treated with HIPEC and cytoreduction [10,25].

Conclusion

Treatment of low-grade appendiceal neoplasms remains a controversial topic for debate. Many studies show 5-year overall survival rates that are improved with cytoreductive surgery and HIPEC, when compared to cytoreductive surgery alone, 53-100% versus 53-75%, respectively [7,9,15,17,19,21-23,26-31]. Despite these results, there have been no randomized controlled trials comparing cytoreductive surgery and cytoreductive surgery with HIPEC in patients with low-grade appendiceal neoplasms. Further studies in a prospective and randomized setting need to be conducted.

References

1. McCusker ME, Coté TR, Clegg LX, Sobin LH (2002) Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program. 1973-1998. Cancer 94: 3307-3312.
2. Woodruff R, McDonald JR (1940) Benign and cystic tumors of the appendix. Surg Gynecol Obstet 71: 750-755.
3. Misdraji J (2010) Appendiceal mucinous neoplasms: controversial issues. Arch Pathol Lab Med 134: 864-870.
4. Sugarbaker PH (2009) Epithelial appendiceal neoplasms. Cancer J 15: 225-235.
5. Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH (2003) Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol 27: 1089-1103.
6. Varisco B, McAlvin B, Dias J, Franga D (2004) Adenocarcinoid of the appendix: is right hemicolectomy necessary? A meta-analysis of retrospective chart reviews. Am Surg 70: 593-599.
7. Gough DB, Donohue JH, Schutt AJ, Gonchoroff N, Goellner JR, et al. (1994) Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. Ann Surg 219: 112-119.
8. Fernandez RN, Daly JM (1980) Pseudomyxoma peritonei. Arch Surg 115: 409-414.
9. Smith JW, Kemeny N, Caldwell C, Banner P, Sigurdson E, et al. (1992) Pseudomyxoma peritonei of appendiceal origin. The Memorial Sloan-Kettering Cancer Center experience. Cancer 70: 396-401.
10. Sugarbaker PH, Jablonski KA (1995) Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg 221: 124-132.
11. Youssef H, Newman C, Chandrakumaran K, Mohamed F, Cecil TD, et al. (2011) Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin. Dis Colon Rectum 54: 293-299.
12. McDonald JR, O'Dwyer ST, Rout S, Chakrabarty B, Sikand K, et al. (2012) Classification of and cytoreductive surgery for low-grade appendiceal mucinous neoplasms. Br J Surg 99: 987-992.
13. Miner TJ, Shia J, Jaques DP, Klimstra DS, Brennan MF, et al. (2005) Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. Ann Surg 241: 300-308.
14. Jarvinen P, Jarvinen HJ, Lepisto A (2010) Survival of patients with pseudomyxoma peritonei treated by serial debulking. Colorectal Dis 12: 868-872.
15. Zih FS, Wong-Chong N, Hummel C, Petronis J, Panzarella T, et al. (2014) Mucinous tumor of the appendix with limited peritoneal spread: is there a role for expectant observation? Ann Surg Oncol 21: 225-231.
16. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J (1980) Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 40: 256-260.
17. Marcotte E, Sideris L, Drolet P, Mitchell A, Frenette S, et al. (2008) Hyperthermic intraperitoneal chemotherapy with oxaliplatin for peritoneal carcinomatosis arising from appendix: preliminary results of a survival analysis. Ann Surg Oncol 15: 2701-2708.
18. Sugarbaker PH, Chang D (1999) Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 6: 727-731.
19. Bradley RF, Stewart JH, Russell GB, Levine EA, Geisinger KR (2006) Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol 30: 551-559.
20. Järvinen P, Ristimäki A, Kantonen J, Aronen M, Huuhtanen R, et al. (2014) Comparison of serial debulking and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei of appendiceal origin. Int J Colorectal Dis 29: 999-1007.
21. Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, et al. (2012) Early-and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 30: 2449-2456.
22. Deraco M, Baratti D, Inglese MG, Allaria B, Andreola S, et al. (2004) Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. Ann Surg Oncol 11: 393-398.
23. Stewart JH, Shen P, Russell GB, Bradley RF, Hundley JC, et al. (2006) Appendiceal neoplasms with peritoneal dissemination: outcomes after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. Ann Surg Oncol 13: 624-634.
24. Vaira M, Cioppa T, DE Marco G, Bing C, D'Amico S, et al. (2009) Management of pseudomyxoma peritonei by cytoreduction+HIPEC (hyperthermic intraperitoneal chemotherapy): results analysis of a twelve-year experience. In Vivo 23: 639-644.
25. Gusani NJ, Cho SW, Colovos C, Seo S, Franko J, et al. (2008) Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol 15: 754-763.
26. Murphy EM, Sexton R, Moran BJ (2007) Early results of surgery in 123 patients with pseudomyxoma peritonei from a perforated appendiceal neoplasm. Dis Colon Rectum 50: 37-42.
27. Sideris L, Mitchell A, Drolet P, Leblanc G, Leclerc YE, et al. (2009) Surgical cytoreduction and intraperitoneal chemotherapy for peritoneal carcinomatosis arising from the appendix. Can J Surg 52: 135-141.
28. Omohwo C, Nieroda CA, Studeman KD, Thieme H, Kostuik P, et al. (2009) Complete cytoreduction offers longterm survival in patients with peritoneal carcinomatosis from appendiceal tumors of unfavorable histology. J Am Coll Surg 209: 308-312.
29. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, et al. (1995) Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol 19: 1390-1408.
30. Andréasson H, Graf W, Nygren P, Glimelius B, Mahteme H, et al. (2012) Outcome differences between debulking surgery and cytoreductive surgery in patients with Pseudomyxoma peritonei. Eur J Surg Oncol 38: 962-968.
31. Elias D, Honoré C, Ciuchendéa R, Billard V, Raynard B, et al. (2008) Peritoneal pseudomyxoma: results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Br J Surg 95: 1164-1171.