Characteristics of critically ill cancer patients in the Netherlands

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LOW COMPLICATION RATES IN THE USE OF PORT-A-CATHS IN ONCOLOGY PATIENTS

CHAPTER 7

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Abstract

Background: Port-A-Caths (PACs) represent an important component of the care of cancer patients, in particular for administration of chemotherapy. We here sought to analyse the longevity and complications of PACs in cancer patients in a large community hospital.
Methods: We retrospectively analysed the indications, duration of use, complications and reasons for removal of PACs in cancer patients treated in our centre from January 2005 to December 2010, and compared these with findings in patients who received a PAC in the same period for reasons not related to cancer.
Results: During the study period 152 cancer patients received a total of 170 PACs; in the same period, 21 patients received a total of 35 PACs for reasons unrelated to cancer. The total analysis comprised 70.919 days of PAC use. Most cancer patients had a solid tumour (97%). PACs were removed because of a complication in 25 cases in cancer patients (14.7%) versus 15 cases in non-cancer patients (42.9%, $P < 0.01$). Culture proven infection was the reason for PAC removal in 16 cases in cancer patients (23.5%) versus 8 cases in non-cancer patients (42.1%; P =ns). The total number of PAC associated infections was 20 in cancer patients (0.35 infections per 1,000 PAC days) versus 19 in non-cancer patients (1.43 infections per 1,000 PAC days; $P <0.01$). No PAC associated thrombosis was found.
Conclusion: In clinical practice the use of PACs in cancer patients is safe with lower complication rates when compared with PAC use in patients without malignancy.

Introduction

Venous access is problematic for oncology patients receiving repeated courses of cytotoxic therapy. Totally implantable ports connected with a central venous catheter were first introduced in 1982 and soon replaced subcutaneously tunnelled catheters such as Hickman, Groshong and Broviac lines [1, 2]. These totally implantable venous access ports (TIVAPs), among which Port-A-Caths (PACs), now represent an important component of the regular care of cancer patients by providing a simple way of accessing the venous system for administration of chemotherapy, antibiotics, analgesics, blood products and fluids, and for the collection of blood. Although in general these devices are safe, their use can be associated with significant complications, most notably infection and thrombosis.

Previous studies have examined complication rates of PAC use in cancer patients [3-11]. Such knowledge is significant considering the importance of PACs for the clinical care of cancer patients and for guiding preventive measures. This in particular holds true for the main complications described in literature, infection and thrombosis. In the current study we retrospectively analysed the indications, duration of use, complications and reasons for removal of PACs in patients with malignancies treated in our centre (a large community hospital in the Netherlands) from January 2005 to December 2010. In addition, we analysed the microbial causes of PAC associated infections in these patients and their impact on PAC use and removal. In order to obtain insight into complications that may relate to cancer specifically, we compared findings in cancer patients with those in patients who received a PAC in the same period for reasons not related to cancer.

Materials and Methods

Patients

We performed a retrospective analysis of 173 adult patients (> 18 years of age) who received a total of 205 PACs between January 2005 and December 2010 in the Reinier de Graaf Hospital in Delft, the Netherlands. The analysis was approved by the institutional medical ethics committee.

Study design

Porth-A-Cath removals within two days after implantation were excluded since these were considered related to the surgical procedure. A single type of PAC was used (Deltec™, Smiths Medical). The PACs were placed by surgeons from the Department of Vascular Surgery in the operation room under general or local anaesthesia using a standardized surgical technique. The access route was chosen according to the patient's anatomy, preferably the right subclavian or external jugular vein. Prophylactic antibiotics were not routinely administered. The PACs were accessed and cared for by trained nursing staff. Lock with heparin solution was done after every PAC access and every four weeks if the PAC was not in use. Patients did not receive routine anticoagulant therapy. PAC associated infection was defined as (1) a positive culture of blood obtained from either a peripheral vein or from the port and (2) clinical suspicion of PAC infection as reflected by local symptoms or absence of another infectious source [12]. For the analysis of PAC associated infections, multiple positive blood cultures with a single pathogen in one clinical episode were counted as one PAC associated infection with this pathogen [12]. The

occurrence of a PAC associated infection was defined as a complication; other non-infection related complications were analysed by studying reasons for PAC removal making use of patient hospital records. Diagnostic procedures were done as ordered by the physician; systematic venographies were not done. Minor complications such as local pain, skin irritation and/or transient inability to draw blood from the PAC were not analysed.

Statistical analysis

Data are expressed as means, medians, interquartile range and ranges as indicated. Differences between cancer patients and non-cancer patients were analysed by Mann-Whitney U test, Chi square test or Log Rank test. A p value below 0.05 was considered to be statistically significant.

Results

Patients

From January 2005 to December 2010 152 patients with a malignancy received a total of 170 PACs; in the same period, 21 patients received a total of 35 PACs for reasons unrelated to cancer (Table 1). In both groups, more women than men received a PAC (73.7% amongst cancer patients and 61.9% amongst non-cancer patients). The vast majority of patients with a malignancy suffered from a solid tumour, with breast and colorectal cancer as the predominant diagnoses (47.4% and 32.9% respectively). In non-cancer patients neuromuscular disease was the most frequent diagnosis (57.1%). The total analysis comprised 70,919 days of PAC use, of which 57,642 days in cancer patients and 13,277 days in non-cancer patients. In cancer patients all PACs were used for administration of chemotherapy. In 14 cases (9.2%) it was also used for immunotherapy. In non-cancer patients 10 PACs (47.6%) were placed for immunotherapy and 8 PACs (38.1%) for chronic treatment with dopamine for heart failure (table 1).

Longevity of PACs

Table 2 shows the longevity and reasons for removal of the inserted PACs. Twenty percent of PACs in cancer patients were in use at the end of follow-up, compared with 31.4% in non-cancer patients (p=ns). Figure 1 is a Kaplan Meier plot showing that the average survival of the PACs was similar in cancer and non-cancer patients (mean time to removal 927 days vs. 899 days, p=0.9 by log rank test). The percentage of PACs removed during the follow-up period was 40% in cancer patients and 51.5% in non-cancer patients (p=ns). The mean number of days a PAC was in situ at the time of removal was 309 days and 500 days in cancer and non-cancer patients respectively, p=ns). In cancer patients, most PACs were removed because therapy was completed (63.2% vs. 15.8% in non-cancer patients, p<0.01). Twenty-five (14.7%) and 15 (42.9%) of PACs were removed for complications (infectious or non-infectious) in cancer and non-cancer patients respectively (p<0.01).

PAC associated infections

PAC associated blood stream infection occurred in 25 of 173 patients (14.4%) (Table 3). Amongst cancer patients, 18 (11.8%) were diagnosed with PAC associated infection during the study period, versus 7 (33.3%) non-cancer patients (P = 0.02). The total number of PAC associated infections was 21 in cancer patients (0.36 infections per 1,000 PAC days) versus 18 in non-cancer patients (1.4 infections per 1,000 PAC days; P < 0.01 versus cancer patients); Of interest,

Table 1: Patient characteristics and indications for PAC placement

	Total	Cancer patients		Non-cancer patients	
Number of PACs (%)	205	170 (82.9)		35 (17.1)	
Number of patients (%)	173	152 (87.9)		21 (12.1)	
Female (%)	125 (72.3)	112 (73.7)		13 (61.9)	
Male (%)	48 (27.7)	40 (26.3)		8 (38.1)	
Mean age (range) at time of PAC placement	51.8 (18-80)	51.7 (26-77)		53.5 (18-80)	
Diagnosis (%)					
		Breast cancer	72 (47.4)	Neuromuscular disease[1]	12 (57.1)
		Colorectal cancer	50 (32.9)	Congestive heart failure	8 (38.1)
		Upper GI cancer	9 (5.9)	CIVD[2]	1 (4.8)
		Ovarian cancer	11 (7.3)		
		Lymphoma	4 (2.6)		
		Other	6 (3.9)		
Indication					
- Chemotherapy		152 (100)		-	
- Immunotherapy[3]		14 (9.2)		10 (47.6)	
- Analgesics		-		2 (9.5)	
- Dopamine		-		8 (38.1)	
- Biphosponate (APD)		-		1 (4.8)	
Mean (range) number of days in situ					
- Total	70,919	57,642		13,277	
- Per PAC	346 (9 - 2,064)	339 (9 - 2,064)		379 (13 - 1,839)	

[1] Dystrophia (N=4), Chronic inflammatory demyelinating polyneuropathy (N=6) and multiple sclerosis (N=2).
[2] Common variable immunodeficiency.
[3] Refers to monoclonal antibodies: in cancer patients trastuzumb (Herceptin®, antibody directed against epidermal growth factor receptor-2) or bevacizumab (Avastin®, antibody directed against the vascular endothelial growth factor receptor), in non-cancer patients gammaglobuline (Gammagard®).

the median time that a PAC was in situ before a blood stream infection occurred was shorter in cancer patients than in non-cancer patients (100 versus 414 days respectively, P = 0.01). The cumulative proportion of PACs removed for an infectious complication is shown in figure 2. Causative organisms did not differ between cancer and non-cancer patients (Table 3). In both groups, gram-positive pathogens, in particular *Staphylococcus aureus* and coagulase negative staphylococci, were most prevalent (more than two thirds of all blood stream infections).

Discussion

In the last decades, much attention has been given to the achievement of an adequate means of venous access in cancer patients that is suitable for long-term use, in particular for repeated administration of chemotherapy and blood draw for testing. Totally implantable venous access

Table 2: Number and reasons for PAC removal

PACs	Total (n = 205)	Cancer (n = 170)	Non-cancer (n = 35)
Number of PACs in situ at closure of data collection (%)	45 (22.0)	34 (20.0)	11 (31.4)
Number of PACs removed (%)	86 (41.9)	68 (40.0)	18 (51.5)
Number of days in situ[1]			
- Mean	353	312	500
- Median	224	215	247
- Range	6-2,064	6-2,064	24 -1,809
Number of patients with PAC removed	77	64	13
- Female	60	51	9
- Male	17	13	4
Reason for removal (% of total removed)			
- Treatment completed	46 (53.5)	43 (63.2)	3 (15.8)
- PAC infection[2]	24 (27.9)	16 (23.5)	8 (42.1)
- Occlusion[3]	4 (4.7)	2 (3.0)	2 (10.5)
- Malfunction[4]	9 (10.5)	4 (5.9)	5 (26.3)
- Other[5]	3 (3.5)	3 (4.5)	0

[1] p=ns for difference between patients with cancer and non-cancer patients

[2] PAC infection is defined as positive culture from blood obtained from the port or a peripheral vein and clinically suspicion of PAC as defined by symptoms or ruling out other foci.

[3] Defined as inability to infuse fluids into the PAC system, confirmed by administration of radiological contrast fluid into the Port.

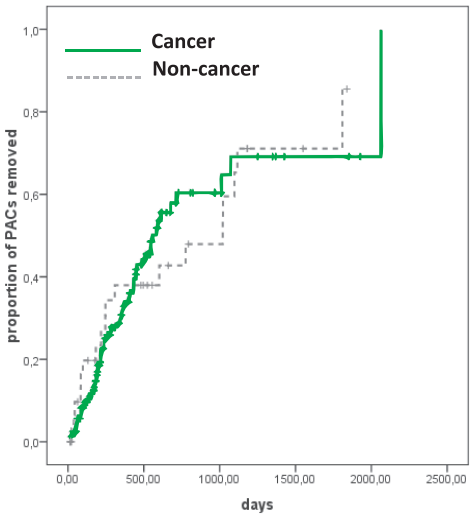
[4] For example nicking of the line, Port moved away into deeper (breast-) tissue, Port turned away.

[5] Due to progressive disease in the chest-wall covering the port, necessity to insert a Levine shunt, fat necrosis around the PAC.

ports, such as PACs are preferred to other approaches for many different reasons, including a reduced risk for infection and thrombosis, less visibility and fewer restrictions on daily activity [13]. We here report on our experience with PACs in a large community hospital in the Netherlands during a six-year period (January 2005 – December 2010), comparing indications, duration of use, complications and reasons for removal in 170 cancer patients and 35 patients without malignancy, comprising more than 70,000 days (which is almost 200 patient years) of PAC use.

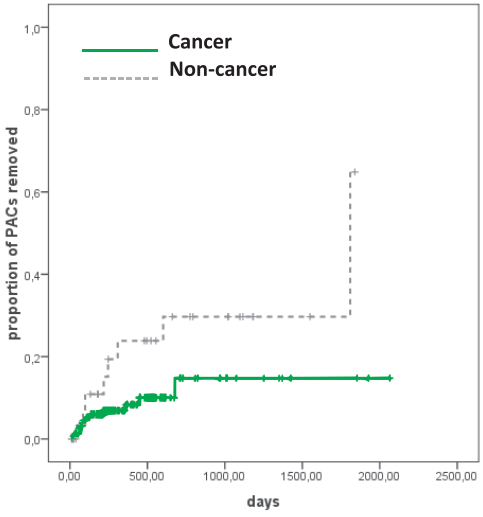
The complication rate of PACs in cancer patients in part depends on the type of malignant disease (solid tumour or haematological malignancy) and neutrophil counts in peripheral blood [13]. In the current analysis the vast majority of oncology patients had solid tumours, in particular breast and colorectal cancer (table 1) and only three patients had leucocytopenia at the time of PAC associated infection (data not shown). Hence, our results predominantly apply to patients with solid tumours and normal leucocyte counts. The current study excluded early complications of PAC placements, such as pneumothorax, primary malposition and arterial

Figure 1: Cumulative proportion of Porth-A-Caths (PACs) removed for any reason



Cases were censored at death or end of follow-up. Cancer patients are in green, non-cancer patients in dotted line. P=ns by log rank test for difference between PACs in patients with cancer and PACs in other patients.

Figure 2: Proportion of Porth-a-Caths (PACs) removed for infectious complications



Cancer patients are in green, non-cancer patients in dotted line. P=0.03 by log rank test for difference between PACs in patients with cancer and PACs in other patients.

Table 3: Porth-a-Caths (PACs) of patients with blood stream infections (BSI) and causative organisms

	All PACs	Cancer	Non-cancer	*p*
Number of PACs inserted	205	170	35	
Number of patients with PAC and BSI (%)	25 (14.4)	18 (11.8)	7 (33.3)	*0.02*
Number PACs with BSI (% of total)	30 (14.6)	18 (10.6)	12 (34.3)	*< 0.01*
Number of episodes of positive blood cultures[1]	39	21	18	*< 0.01*
Number of different organism in these cultures	43	21	22	
Number of days PAC in situ prior to positive blood culture				*0.01*
Median	167	100	414	
IQR	55-553	36-234	125-902	
Causative organisms				
Gram-positive	**29**	**14**	**15**	***ns***
- *Staphylococcus aureus*	10	5	5	
- Coagulase negative staphylococci	16	7	9	
- *Enterococcus*	1	-	1	
- *Streptococcus pneumoniae*	1	1	-	
- Other streptococci	1	1	-	
Gram-negative	**13**	**6**	**7**	***ns***
- *Escherichia coli*	2	1	1	
- *Pseudomonas aeruginosa*	2	-	2	
- *Klebsiella oxytoca*	1	-	1	
- *Klebsiella pneumoniae*	1	1	-	
- *Serratia marcescens*	1	1	-	
- *Rhizobacteria*	1	-	1	
- *Stenotrophomonas maltophilia*	1	-	1	
- *Enterobacter*	2	1	1	
- *Acinetobacter*	1	1	-	
- *Aeromonas hydrophilia*	1	1	-	
Yeasts	**1**	**1**	**-**	**-**
Candida glabratum	1	1	-	

[1] *One blood culture per episode (i.e. if four blood cultures were positive for a particular pathogen during the same infection, only one culture was counted).*

perforation, since these are related to the surgical procedure. The overall rate of removal of PACs for infectious or non-infectious complications was lower in cancer patients compared with non-cancer patients. Furthermore, the risk that a PAC will be removed for infectious reasons is lower in cancer patients than in non-cancer patients. Although a definitive explanation for this difference is lacking, it may be related to a higher experience amongst oncology nurses in the management of PACs and/or differences in underlying diseases. For example insufficient hygienic precautions, inadequate flushing of the system after the introduction of fluids or a too

long interval between usages of the Port make the system at risk for irreversible complications. Insufficient dosing of positive pressure leading to narrowing the lumen of the catheter due to deposits of fibrin or other substances will eventually obstruct the PAC [6]. Different infection rates in cancer and non-cancer patients could have been caused by differences in susceptibility for infection due to the underlying disease. However, although the most important indication for PAC use in non-cancer patients was immunotherapy in the form of infusion of gammaglobulin, this therapy was provided for neuromuscular disease in all but one patient (who had a common variable immunodeficiency). As such, infection rates in non-cancer patients are not biased due to a large number of patients with primary immunodeficiency.

Although PACs are associated with much fewer infectious complications than other approaches to obtain prolonged access to the venous circulation, infection remains an issue of concern [7, 13]. In clinical practice, the diagnosis of PAC associated infection can be made with or without bacteriological confirmation [14, 15]. In the present analysis we only included culture proven infection: PAC associated infection was defined as a positive culture of blood obtained from either a peripheral vein or the port and clinical suspicion of PAC infection as reflected by local symptoms or absence of another infectious source [12]. The incidence of PAC associated infection amongst cancer patients found here (11.8%) is within the same range as that reported in previous studies: positive blood cultures associated with PACs have been reported to occur in 2.4–16.0% of patients [3, 4, 11], representing a major cause of hospital-acquired bacteraemia and the most frequent reason for catheter removal [4, 16]. The vast majority of PAC associated infections were caused by coagulase negative staphylococci and *Staphylococcus aureus*, which is in accordance with earlier investigations [11, 13].

There are no standard criteria for catheter removal in PACs [12, 13]. In the presence of uncomplicated infection due to coagulase-negative staphylococci, the PAC may be retained if there is no evidence of persisting or relapsing bacteraemia. For PAC associated infection caused by pathogens other than coagulase-negative staphylococci, some physicians would retain the port, partially depending on the patient's clinical status. In our analysis, most PAC associated infections resulted in PAC removal in cancer patients (80% of cases), but not in patients without cancer (42%). This difference was not related to a clear difference in causative pathogens. It is conceivable that medical oncologists are reluctant to continue chemotherapy through a PAC that has been infected and that as a consequence thereof PAC associated infection more often leads to PAC removal in cancer patients.

The reported incidence of venous thrombosis as a PAC associated complication varies between zero and 10% [13]. In our centre, thrombosis was never the cause of PAC removal during the six-year study period. Notably, since most cases of catheter-related thrombosis are asymptomatic [13], this does not exclude that thrombosis did occur in our population. Data on prophylactic anti-coagulant therapy are not available for the studied population, but this is not a routine policy in our hospital.

Several earlier investigations examined the complication rate of PACs in a single centre setting. No device related deaths were observed and complications as infection and thrombosis were rare for all type of patients [5, 9, 11] In a Dutch retrospective analysis encompassing a period of 7,5 years (1992 – 1999) involving 38 PACs, the most prevalent complications were infection (two cases or 5.3%) and thrombosis (three cases or 7.9%) [5]. Although the number of PACs studied was relatively low, these data suggest that the incidence of PAC associated thrombosis may have decreased in more recent years, probably at least in part as a result of

better preventive care by the nursing staff.

Our study has several limitations. Firstly, the study has a low sample size relative to the low incidence of PAC related problems, which in particular is true for thrombosis. Secondly, the study groups were not comparable with respect to baseline and prognostic variables, which may hamper appropriate comparisons.

The use of PACs is widely implemented in the clinical care of patients with cancer. These devices have a high acceptance among patients, nurses and doctors. The current analysis illustrates the low rate of complications associated with the use of PACs in the setting of a large community hospital in the Netherlands.

References

1. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E: Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery 1982, 92(4):706-712.
2. Nanninga AG, de Vries EG, Willemse PH, Oosterhuis BE, Sleijfer DT, Hoekstra HJ, Mulder NH: Continuous infusion of chemotherapy on an outpatient basis via a totally implanted venous access port. Eur J Cancer 1991, 27(2):147-149.
3. Biffi R, de Braud F, Orsi F, Pozzi S, Mauri S, Goldhirsch A, Nole F, Andreoni B: Totally implantable central venous access ports for long-term chemotherapy. A prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. Ann Oncol 1998, 9(7):767-773.
4. Silver DF, Hempling RE, Recio FO, Piver MS, Eltabbakh GH: Complications related to indwelling caval catheters on a gynecologic oncology service. Gynecol Oncol 1998, 70(3):329-333.
5. Koolen DA, van Laarhoven HW, Wobbes T, Punt CJ: Single-centre experience with tunnelled central venous catheters in 150 cancer patients. Neth J Med 2002, 60(10):397-401.
6. Yeste Sanchez L, Galbis Caravajal JM, Fuster Diana CA, Moledo Eiras E: Protocol for the implantation of a venous access device (Port-A-Cath System). The complications and solutions found in 560 cases. Clin Transl Oncol 2006, 8(10):735-741.
7. Maki DG, Kluger DM, Crnich CJ: The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc 2006, 81(9):1159-1171.
8. Liaw CC, Chen JS, Chang HK, Huang JS, Yang TS, Liau CT: Symptoms and signs of port-related infections in oncology patients related to the offending pathogens. Int J Clin Pract 2008, 62(8):1193-1198.
9. Samaras P, Dold S, Braun J, Kestenholz P, Breitenstein S, Imhof A, Renner C, Stenner-Liewen F, Pestalozzi BC: Infectious port complications are more frequent in younger patients with hematologic malignancies than in solid tumor patients. Oncology 2008, 74(3-4):237-244.
10. Nishinari K, Wolosker N, Bernardi CV, Yazbek G: Totally implantable ports connected to valved catheters for chemotherapy: experience from 350 Groshong devices. J Vasc Access 2010, 11(1):17-22.
11. Heibl C, Trommet V, Burgstaller S, Mayrbaeurl B, Baldinger C, Koplmuller R, Kuhr T, Wimmer L, Thaler J: Complications associated with the use of Port-a-Caths in patients with malignant or haematological disease: a single-centre prospective analysis. Eur J Cancer Care (Engl) 2010, 19(5):676-681.
12. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad, II, Rijnders BJ, Sherertz RJ, Warren DK: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009, 49(1):1-45.
13. Kurul S, Saip P, Aydin T: Totally implantable venous-access ports: local problems and extravasation injury. Lancet Oncol 2002, 3(11):684-692.
14. Wickham R, Purl S, Welker D: Long-term central venous catheters: issues for care. Semin Oncol Nurs 1992, 8(2):133-147.
15. Greene JN: Catheter-related complications of cancer therapy. Infect Dis Clin North Am 1996, 10(2):255-295.
16. Freytes CO: Indications and complications of intravenous devices for chemotherapy. Curr Opin Oncol 2000, 12(4):303-307.