Received: 20 May 2018 | Revised: 12 August 2018 | Accepted: 15 August 2018

DOI: 10.1002/cnr2.1135

ORIGINAL ARTICLE

WILEY Cancer Reports

Prospective analysis of 30-day mortality following palliative chemotherapy at a tertiary cancer centre

James A. McCracken[1] | Adrian Dabscheck[2] | Maria Coperchini[2] | Ilana Hornung[1] | Azim Jalali[1] | Georgina Akers[1] | Amalia Karahalios[3] | Fran Gore[4] | Lara Lipton[1]

[1] Department of Oncology, Western Health, Sunshine, Victoria, Australia

[2] Department of Palliative Care, Western Health, Sunshine, Victoria, Australia

[3] Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

[4] Mercy Palliative Care, Mercy Health, Sunshine, Victoria, Australia

Correspondence
Dr James A. McCracken, Department of Medical Oncology, Sunshine Hospital, Furlong Road, St. Albans, Victoria 3021, Australia.
Email: jmccracken2@gmail.com

Funding information
Western Central Melbourne Integrated Cancer Service (WCMICS)

Abstract

Background: Thirty-day mortality after chemotherapy has been suggested as a marker of quality in oncology care. Retrospective audits worldwide have put this figure at between 8.1% and 43%, with previous retrospective Australian audits putting this figure at between 3.4% and 18%. To date, there has not been a prospective cohort study of patients receiving palliative intent chemotherapy at an Australian chemotherapy day unit.

Aim: The aim of the study is to benchmark 30-day mortality for patients receiving palliative intent chemotherapy and identify associated factors at an Australian tertiary cancer centre.

Methods and results: A prospective cohort study of all patients with a diagnosis of malignancy referred for palliative intent intravenous chemotherapy to the Sunshine Hospital Chemotherapy Day Unit over a 12-month period. The primary outcome was death within 30 days of receiving palliative intent chemotherapy. Other outcome measures included place of death and whether the patient received an outpatient palliative care referral. A total of 314 patients were enrolled in the study, and 98 patients died within the audit period. Of these, 21 (6.6%) died within 30 days of commencing palliative intent chemotherapy, and 60 (18.8%) died more than 30 days after receiving chemotherapy. Of the 34 patients that were referred, but did not start chemotherapy, 18 (52%) died. Multivariable logistic regression found that patients who received an outpatient palliative care referral and received chemotherapy were more likely to die within 30 days, although these did not reach statistical significance.

Conclusion(s): This prospective cohort study demonstrated that 6.6% of patients died within 30 days of the administration of palliative intent chemotherapy; however, none of the prespecified factors were found to be statistically significantly associated with 30-day mortality.

KEYWORDS

ambulatory care, benchmarking, death, neoplasms, palliative care

1 | INTRODUCTION

Thirty-day mortality after palliative chemotherapy has been suggested as a marker of quality in oncology care.[1-4] Higher use of chemotherapy at the end of life in patients with advanced disease has been associated with lower use of inpatient and community palliative care services, increased use of emergency and acute inpatient services, lower opiate use, and lower rates of death at home.[5,6] Other factors associated with higher use of chemotherapy at the end of life include poor communication between the treating team and the patient, lack of referral or access

to palliative care, younger age, male sex, and low Eastern Cooperative Oncology Group (ECOG) performance status.[5-7]

In the United Kingdom, a 2008 report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) provided a large-scale benchmarking of issues around death in cancer patients having palliative chemotherapy within the last 30 days of life.[8] This investigation found that of 47 000 patients treated with palliative intent, 2% died within 30 days. It also identified that 49% of patients dying within 30 days of palliative chemotherapy may have had suboptimal care. Key recommendations of this audit included limiting the prescription of palliative chemotherapy to experienced oncology staff, to patients with ECOG performance status 0 to 2 and to centres with specialist expertise in caring for toxicities.[8] Early implementation of palliative care and advance care directives was also recommended.

The NCEPOD report has subsequently inspired a number of global and local audits of 30-day mortality, with rates ranging from 8.1% to 43%.[6,7,9-15] However, comparison across studies is limited by differing study designs, differing populations, and tumour types. Some of these studies are of a single tumour stream,[11,13] and include adjuvant treatment.[1,3] Also, the geographic and subsequent cultural variation in oncology practice, and in the access to and uptake of palliative care services, limits the ability to generalise from these results.

Three Australian studies have explored the 30-day mortality benchmark.[3,4,7] In a retrospective audit of patients within a regional Australian cancer centre, Zdenkowski and colleagues found that 12% of oncology patients treated with palliative intent chemotherapy died within 30 days of treatment.[4] The authors found that shorter duration of palliative care involvement and male sex were predictive of 30-day mortality. Yoong and colleagues also performed a retrospective audit of all patients receiving (curative and palliative intent) chemotherapy at a regional Australian cancer centre.[3] This study found a 30-day mortality rate of 3.4%. However, 23% of deaths within their cohort were treatment related.[3]

In a review of 747 deceased oncology patients at 2 cancer centres in Sydney, Kao and colleagues found that 18% of patients had received chemotherapy within their last 30 days of life, with 8% receiving it in the last fortnight. These patients were significantly more likely to be young, of a specific tumour stream (central nervous system), and deemed to have a chemotherapy sensitive tumour.[7]

The current study is the first prospective, cohort study of patients referred to a Melbourne tertiary cancer centre for palliative intent chemotherapy. The aim of this study was to benchmark an Australian tertiary cancer centre, and to identify factors that are associated with 30-day mortality after receiving palliative intent chemotherapy. We also performed an exploratory analysis of the potential differences amongst the cohort, including patterns of referral to palliative care, exploring reasons for patients who were referred but did not receive chemotherapy, reason for discontinuing treatment, and place of death within the cohort.

2 | METHODS

This study was a prospective cohort study of all patients referred for palliative intent chemotherapy, to the Sunshine Hospital Chemotherapy Day Unit from December 8, 2014 to December 8, 2015. The Chemotherapy Day Unit referral form mandated that the referring clinician identify the chemotherapy intent as curative or palliative, and document the ECOG performance status at the time of referral. All chemotherapies were administered as per eviQ protocols.[16]

Patients were eligible if they were referred for intravenous chemotherapy and if the intent of their treatment was marked as "palliative" on their referral form. Patients for single-agent antibody treatment or oral chemotherapy were excluded. Patients who had prior adjuvant or palliative chemotherapy were not excluded.

Deidentified patient data were stored in a secure access database for collection across prespecified data points. The last patient was enrolled on December 8, 2015, and all data were collected for 30 days beyond this point. Data collection ceased on February 21, 2016. As these data are collected as standard of care by our day oncology unit, informed patient consent was not sought. The project, including a waiver of consent, was approved by both Western Health (QA2014.90) and Mercy Health (R14-30P) Ethics Committees. The project was funded by a grant from the Western and Central Melbourne Integrated Cancer Service.

3 | STATISTICAL METHODS

For patients who started chemotherapy, we fitted logistic regression models to estimate the univariate associations between those who did and did not die within 30 days of starting chemotherapy and the following risk factors: age (years), sex, any symptom(s) (yes/no), number of lines of chemotherapy (0 or $\geq$1), ECOG score (0/1 or 2/3), and whether the patient was referred to outpatient palliative care (no/yes). Next, a multivariable logistic regression model was fitted, which included all of the above risk factors. In addition to the regression models, a descriptive exploratory analysis was performed to assess why patients who were referred chemotherapy did not commence chemotherapy, location of patient deaths for those who died, reasons for discontinuing chemotherapy, and involvement of palliative care.

4 | RESULTS

A total of 319 patients were enrolled in the study, with an average age of 63 years (standard deviation = 13.1), and 45.4% of patients were female. Of note, 59.2% of our cohort were born outside Australia (compared to an Australian average of 28%), and 79% of our cohort named English as their primary spoken language. Demographic data are displayed in Table 1.

Of the 319 patients enrolled in the study, 21 (6.6%) patients died within 30 days of receiving chemotherapy, 60 (18.8%) died more than 30 days after receiving chemotherapy, and 204 (63.9%) who started chemotherapy were alive at the end of the study. Of the 34 patients that did not commence chemotherapy, 18 patients within this group died within the study period.

The most common malignancies in patients referred for chemotherapy were lung (29.8%) and colorectal cancer (20.1%) (Table 1).

TABLE 1 Demographic data for the 319 patients enrolled in the study

	Number (%)
Age (years)[a]	63 (SD = 13.1)
Sex	
Male	174 (54.5)
Female	145 (45.5)
Country of birth	
Australia	130 (40.8)
Elsewhere	189 (59.2)
Primary language	
English	252 (79.0)
Other	67 (21.0)
Lives alone	
Yes	42 (13.2)
No	277 (86.8)
Accommodation	
Independent living	317 (99.4)
Residential aged care	1 (0.3)
Supported accommodation	1 (0.3)
Tumour	
Breast	27 (8.5)
Colorectal	64 (20.1)
Genitourinary	16 (5.0)
Gynaecology	18 (5.6)
Haematology	28 (8.8)
Lung	95 (29.8)
Other[b]	11 (3.4)
Upper GI	60 (18.8)
Lines of chemotherapy	
0	203 (63.6)
1	80 (25.1)
2	27 (8.5)
3	6 (1.9)
4	3 (0.9)
ECOG[c]	
0	77 (24.2)
1	185 (58.2)
2	52 (16.4)
3	4 (1.3)
Charlson comorbidity index (CCI—age adjusted)	
0	195 (61.1)
1	67 (21.0)
2	46 (14.4)
3	6 (1.9)
4	4 (1.3)
5	1 (0.3)
Referred to outpatient palliative care	
No	167 (52.4)
Yes	152 (47.6)
Place of death[e]	
Other	73 (22.9)
Home	25 (7.8)
m Patient alive	221 (69.3)
Patient status[f]	
Did not start chemotherapy	34 (10.7)
Started chemotherapy and died more than 30 days after last chemotherapy	60 (18.8)
Started chemotherapy and died within 30 days of last chemotherapy	21 (6.6)
Started chemotherapy and alive	204 (63.9)

[a]Mean (standard deviation).

[b]Other: 5 unknown primary, 5 neuroendocrine, 1 primary peritoneal.

[c]One person missing ECOG score.

[d]One person missing date of last chemotherapy.

[e]This is elaborated upon in Table 4.

[f]Eighteen people from this group died during the audit period.

Most patients were chemotherapy naïve (63.6%), with 25.1% having had 1 prior line of treatment. The majority of patients had an ECOG performance status 0 or 1 (82.4%).

Table 2 shows the results from the univariate and multivariable analysis. Age, sex, lines of chemotherapy, and ECOG performance status were not associated with death within 30 days of chemotherapy. Patients who were referred for outpatient palliative care had higher odds of dying within 30 days of their last chemotherapy compared to patients who were not referred to outpatient palliative care (OR 2.37, 95% CI 0.89-6.34), although this did not reach statistical significance. A similar association was seen in the multivariable analysis (OR 2.29, 95% CI 0.90-5.86), although this also failed to reach statistical significance.

4.1 | Exploratory analysis

Of the 319 patients referred for chemotherapy, 34 (10%) did not commence treatment, as shown in Table 3.

The main reason for not starting planned chemotherapy treatment was deterioration of patient condition (50%). Twenty-one percent of patients elected not to proceed with treatment, whilst in 15% of patients, a clinical decision was made not to commence treatment. Of those that did not commence chemotherapy, 52% (18) died during the audit period, and were more likely to die at home (50%), as shown in Table 4. The location of death, for those who did have chemotherapy, is also shown in Table 4.

Of the patients that did not commence chemotherapy, 26 (76%) were known to a palliative care service (11 referred prior to study enrolment, 15 during the study period) and 8 were not.

4.2 | Reason for ceasing chemotherapy

A total of 199 patients ceased treatment during the study (70%). The main reasons for patients ceasing an individual line of chemotherapy were progression of disease (39%) or treatment-related toxicity (30%). Twenty-two percent of patients completed a planned course of treatment, as shown in Table 5.

TABLE 2 Results of logistic regression analysis comparing patients who started chemotherapy and died within 30 days with those who did not die within 30 days

Risk Factor	Died Within 30 days of Chemotherapy	Alive 30+ days Postchemotherapy	Univariable Model		Multivariable Model[a]	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Deaths in total	21	264	0.99 (0.95, 1.03)	.592	0.99 (0.95, 1.03)	.507
Age (years)	62.9	63.1				
Sex						
Male	12	142	Ref	-	Ref	-
Female	9	122	0.87 (0.36, 2.14)	.767	0.79 (0.31, 1.98)	.607
Any symptom(s)						
No	5	79	Ref	-	Ref	-
Yes	16	185	1.37 (0.48, 3.86)	.556	1.15 (0.39, 3.38)	.794
Lines of chemotherapy						
0	14	170	Ref	-	Ref	-
≥1	7	94	0.90 (0.35, 2.32)	.834	0.82 (0.31, 2.13)	.677
ECOG score						
0/1	17	218	Ref	-	Ref	-
2/3	4	46	1.12 (0.36, 3.47)	.851	0.88 (0.27, 2.84)	.825
Referred to outpatient palliative care						
No	7	141	Ref	-	Ref	-
Yes	14	123	2.29 (0.90, 5.86)	.083	2.37 (0.89, 6.34)	.085

Excluding 34 patients who did not start chemotherapy.

[a]Multivariable model includes the following potential confounding factors: age (years), sex, any symptoms, lines of chemotherapy (0 or ≥1), ECOG group (0/1 or 2/3), and whether the patient was referred to outpatient palliative chemotherapy.

TABLE 3 Reasons for not commencing chemotherapy

Reason	N	%
Patient too unwell	17	50
Patient decision	7	21
Clinical decision	5	15
Clinical trial referral	2	6
Transferred care	2	6
Pilot completion	1	3

TABLE 5 Reasons for ceasing chemotherapy

Reason	N	%
Treatment progression—radiological or clinical	78	39
Toxicity	60	30
Completed planned course of treatment	44	22
Patient decision	16	8
Change in treatment (transfer/surgery/radiotherapy)	4	2
Not specified	2	1

TABLE 4 Place of death for patients who had and did not have chemotherapy

Place of Death	No Chemo		Yes Chemo	
	N	%	N	%
Home	9	50	13	22
Inpatient palliative care	5	28	25	42
Intensive care unit	2	11	0	0
Emergency department	1	6	2	3
Acute inpatient	1	6	19	32
Not specified	0	0	1	2

5 | DISCUSSION

This prospective cohort study demonstrated that 6.6% of patients died within 30 days of administration of palliative intent chemotherapy in this particular Australian tertiary cancer centre. Multivariable analysis did not identify any prespecified variables that were associated with 30-day mortality. In our study, the strongest predictor was referral to outpatient palliative care; however, this failed to reach statistical significance. Previous research has identified male patients, and patients known to palliative care for less than 30 days to be factors statistically significantly predictive of 30-day mortality.[4]

The current study demonstrated a 30-day mortality for patients receiving palliative intent chemotherapy of 6.6%. Previous research in Australian cancer centres demonstrated mortality rates of between 3.4% and 18%, for patients within 30 days of last receiving chemotherapy.[3,4,7] International studies have demonstrated mortality rates ranging from 8.1% to 38%.[6,7,9-15] Our data did not capture treatment-related deaths; however, others have estimated this to be between 4% and 25% of deaths with 30 days of treatment.[1,3,17]

This was the first prospective observational study that aimed to identify factors associated with mortality after administration of palliative chemotherapy. Although our study recruited patients for a complete calendar year, we had a small number of patient deaths in our cohort. Whilst our results compare favourably to other Australian

centres, Yoong and colleagues had a mortality rate of 3.4% amongst all patients; however, these results included patients receiving adjuvant treatment.[3] Whilst in a review of deceased oncology patients, Kao and colleagues demonstrated that 18% of patients received chemotherapy within the last 4 weeks of life.[7] Mortality rates in Australian studies in patients treated with palliative have intent, have ranged from 12% to 18%, though the differences in methodology may account for some of the variation within these figures.[4,7] The low mortality rate in our study limits the statistical analysis and subsequent associations. To enable a more robust comparison of factors that are associated with mortality in this population, a large multicentre study is needed, that should include more objective measures, such as serum albumin and those requiring inpatient admissions during active treatment.

This study also explored reasons for patients discontinuing chemotherapy. The most common reason for discontinuing chemotherapy was disease progression in 39% of cases, with treatment-related toxicity being the next most common reason in 30% of cases. Of our cohort, 10.7% of patients who were referred for chemotherapy did not commence treatment, with the most common reason being clinical deterioration. Patients also elected to self-terminate treatment in 8% of cases. Previous studies have shown that disease progression is the most common cause of death within 30 days of ceasing chemotherapy.[1,3] O'Brien and colleagues identified that those receiving third or subsequent lines of chemotherapy were those most at risk of dying.[1,18] This is likely due to these patients being less likely to respond to treatment. Subsequently, early integration of palliative care has been demonstrated to reduce the use of chemotherapy within this period.[19] Whilst the NCEPOD guidelines recommended the early implementation of palliative care, those being referred for a second line and beyond, or with a poor performance status, should be prioritised.

Whilst our results show that there was a higher rate of death within the acute inpatient setting in those that received chemotherapy, in comparison to those who did not, most patients in our study died at home, or within an inpatient palliative care facility. The majority of patients who died within 30 days of study enrolment were most likely to die at home, or within an inpatient palliative care facility. This may be reflective of early palliative care involvement. Greer and colleagues demonstrated in a randomised control trial of 151 patients with metastatic nonsmall cell lung cancer that those randomised to receive early integrated palliative care had a significantly higher enrolment in hospice care.[5] Our data support this, and also support the early integration of palliative care for those patients receiving palliative intent chemotherapy, in order to avoid unnecessary hospital admissions, and inappropriate treatment. Our results also suggest that of patients who received chemotherapy, those that were referred to palliative care were more likely to die within 30 days of receiving chemotherapy, than those who were not referred. This may reflect a higher symptom burden in these patients that subsequently triggered a referral from their treating oncologist.

Limitations to acceptance of palliative care may be reflected in cultural variation with 59% of patients being born overseas and 21% of being non-English speaking. This may potentially cause limitations in discussions regarding palliative care. However, our data showed that less than 50% of patients were referred to palliative care. This may be due to an underuse of interpreters, whereby previous studies have shown this to compromise care, lead to a poorer understanding of their disease and prognosis, as well as poorer management of symptoms at end of life.[20,21]

In conclusion, our prospective cohort study of 30-day mortality in a tertiary cancer centre shows 30-day mortality of 6.6% for those receiving palliative intent chemotherapy. Regular assessment of mortality rates should be an ongoing quality assurance exercise to ensure that chemotherapy is appropriately prescribed, and cancer patients appropriately treated. Auditing palliative care referral practices and places of death should also form a part of this audit process. The acceptable level of 30-day mortality following the administration of palliative chemotherapy is not standardised. We would suggest that this is an area of discussion in multidisciplinary oncology forums and that these data may become a useful part of this debate.

ACKNOWLEDGEMENTS

Western Central Melbourne Integrated Cancer Service (WCMICS) for development and support of ACCESS database. Mr Brian Pound (consumer representative).

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHORS' CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and he accuracy of the data analysis. *Conceptualization*, L.R.L., M.L.C., G.E.A., I.H., A.D., F.G.; *Methodology*, L.R.L., M.L.C., A.K., G.E.A., I.H.; *Investigation*, L.R.L., M.L.C., G.E.A.; *Formal Analysis*, L.R.L., M.L.C., A.K., G.E.A., I.H., J.A.M.; *Resources*, L.R.L., M.L.C., G.E.A., F.G.; *Writing – Original Draft*, L.R.L., M.L.C., G.E.A., A.D., A.J., J.A.M.; *Writing – Review & Editing*, L.R.L., A.K., M.L.C., G.E.A., A.D., A.J., J.A.M.; *Visualisation*, L.R.L., G.E.A., M.L.C., J.A.M.; *Supervision*, L.R.L., M.L.C., J.A.M.; *Funding Acquisition*, L.R.L., G.E.A., I.H.

ORCID

James A. McCracken http://orcid.org/0000-0003-0066-7705

REFERENCES

1. O'Brien MER, Borthwick A, Rigg A, et al. Mortality within 30 days of chemotherapy: a clinical governance benchmarking issue for oncology patients. *Br J Cancer*. 2006;95(12):1632-1636.

2. Banner R. Benchmark 30-day mortality rate needed. *Clin Oncol*. 2009;21(9):733-734.

3. Yoong J, Seah J, Hamilton K, Teo LN, Chong G. Mortality within 30 days of receiving systemic anti-cancer therapy at a regional oncology unit: what have we learned? *Asia Pac J Clin Oncol*. 2012;8(4):325-329.

4. Zdenkowski N, Cavenagh J, Ku YC, Bisquera A, Bonaventura A. Administration of chemotherapy with palliative intent in the last 30 days of life: the balance between palliation and chemotherapy. *Intern Med J*. 2013;43(11):1191-1198.

5. Greer JA, Prl WF, Jackson VA, et al. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol*. 2012;30(4):394-400.
6. Nappa U, Lindqvist O, Rasmussen BH, Axelsson B. Palliative chemotherapy during the last month of life. *Ann Oncol*. 2011;22(11):2375-2380.
7. Kao S, Shafiq J, Vardy J, Adams D. Use of chemotherapy at end of life in oncology patients. *Ann Oncol*. 2009;22:2375-2380.
8. Mort DLM, Smith N, Protopapa K, Mason M. A review of patients who died within 30 days of receiving systemic anti-cancer therapy. National confidential enquiry into patient outcome and death. In: Kingdom DoHU, editor. 2008.
9. Emanuel EJ, Young-Xu Y, Levinsky NG, Gazelle G, Saynina G, Ash AS. Chemotherapy use among medicare beneficiaries at the end of life. *Ann Intern Med*. 2003;138(8):639-643.
10. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol*. 2004;22(2):315-321.
11. Asola R, Huhtala H, Holli K. Intesity of diagnostic and treatment activities during the end of life of patients with advanced breast cancer. *Breast Cancer Res Treat*. 2006;22:12-17.
12. Barbera L, Paszat L, Chartier C. Indicators of poor quality end of life cancer care in Ontario. *J Palliat Care*. 2006;22(1):12-17.
13. Murillo JR, Koeller J. Chemotherapy given near the end of life by community oncologists for advanced non-small cell lung cancer. *Oncologist*. 2006;11(10):1095-1099.
14. Earle CC, Landrum MB, Souza JM, Neville B, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of care issue? *J Clin Oncol*. 2008;26(23):3860-3866.
15. Dasch B, Kalies H, Feddersen B, Ruderer C, Hiddemann W, Bausewein C. Care of cancer patients at the end of life in a German university hospital: a retrospective observational study from 2014. *PLoS One*. 2017;12(4):e0175124.
16. NSW. CI. eviQ Cancer Treatments Online http://www.eviq.org.au2017 [Available from: http://www.eviq.org.au.
17. Bradshaw A, Lyons J, Logue JP, Choudhury A. Thirty-day mortality for patients with genitourinary malignancies being treated with chemotherapy. *Clin Oncol*. 2009;21(9):730.
18. Wallingoton M, Saxon EB, Bomb M, et al. 30-day mortality after systemic anticancer treatment for breast and lung cancer in England: a population-based observational study. *Lancet Oncol*. 2016;17(9):1203-1216.
19. Magarotto R, Lunardi G, Coati F, et al. Reduced use of chemotherapy at the end of life in an integrated-care model of oncology and palliative care. *Tumori*. 2011;97(5):573-577.
20. Flores G. Language barriers to health care in the United States. *N Engl J Med*. 2006;355(3):229-231.
21. Silva M, Genoff M, Zabal A, Stabler SM, Gany F, Diamond L. Interpreting in palliative care: a systematic review of the impact of interpreters on the delivery of palliative care services to cancer patients with limited English proficiency. *J Clin Oncol*. 2014;32(31_supp):123.

How to cite this article: McCracken JA, Dabscheck A, Coperchini M, et al. Prospective analysis of 30-day mortality following palliative chemotherapy at a tertiary cancer centre. *Cancer Reports*. 2018;1:e1135. https://doi.org/10.1002/cnr2.1135