Chemotherapy in patients with unresected pancreatic cancer in Australia: a population-based study of uptake and survival

Monica I Dumbrava FRACP[1, 2]*, Elizabeth A Burmeister PhD[1, 3]*, David Wyld FRACP[2, 3], David Goldstein FRACP [4, 5], Dianne L O'Connell PhD[6, 7, 8], Vanessa L Beesley PhD[1], Helen M Gooden PhD[8], Monika Janda PhD[9], Susan J Jordan PhD[1], Neil D Merrett FRACS[10], Madeleine E Payne BSc[1], Mary A Waterhouse PhD[1,] Rachel E Neale, PhD[1]

[1]QIMR Berghofer Medical Research Institute, Brisbane, Australia

[2]Royal Brisbane and Women's Hospital, Brisbane, Australia

[3]The University of Queensland, Brisbane, Queensland, Australia

[4] University of New South Wales, New South Wales, Australia

[5] Prince of Wales Hospital, New South Wales, Australia

[6]Cancer Council New South Wales, Sydney, Australia

[7]University of Newcastle, New South Wales, Australia

[8]University of Sydney, New South Wales, Australia

[9] Queensland University of Technology, Brisbane, Australia

[10]University of Western Sydney, NSW, Australia

* Joint first authors

Corresponding author and requests for reprints: Rachel Neale PhD, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston, Brisbane, Queensland 4006, Australia. Email: rachel.neale@qimrberghofer.edu.au. Phone: (61) 7 3845 3598, Fax: (61) 7 3845 3502.

Abstract

Objectives

Clinical trials have demonstrated that palliative chemotherapy improves symptom control and prolongs survival in patients with unresectable pancreatic cancer, but there is a paucity of data describing its use and effectiveness in everyday practice. This study explored patterns of use of chemotherapy in patients with unresected pancreatic cancer in Australia and the impact of use on survival.

Methods

We reviewed the medical records of residents of New South Wales or Queensland, Australia, diagnosed with unresectable pancreatic adenocarcinoma between July 2009 and June 2011. Associations between receipt of chemotherapy and sociodemographic, clinical and health service factors were evaluated using logistic regression. We used Cox proportional hazards models to analyse associations between chemotherapy use and overall survival.

Results

During the study period, data were collected for 1173 eligible patients. Chemotherapy was received by 44% (n=184/414) of patients with localised pancreatic cancer and 53% (n=406/759) of patients with metastases. Chemotherapy receipt depended on clinical factors such as performance status and co-morbidity burden, and non-clinical factors such as age, place of residence, multi-disciplinary team review and the type of specialist first encountered. Consultation with an oncologist mitigated most of the socio-demographic and service-related disparities in chemotherapy use. The receipt of chemotherapy was associated with prolonged survival in patients with inoperable pancreatic cancer, including after adjusting for common prognostic factors.

Conclusions

To improve survival for patients diagnosed with pancreatic cancer it is important that all patients are offered the opportunity to discuss chemotherapy options with specialist oncologists. These findings are particularly relevant for health care systems covering areas with a geographically dispersed population.

Introduction

Pancreatic cancer is the 10th most commonly diagnosed cancer in the developed world and is the fourth most common cause of cancer death,[1] with only 7% of patients surviving 5 years.[2,3] Current projections suggest that it will be the second leading cause of cancer death within 10 years.[4,5] In addition to short survival, patients often experience symptoms such as pain, jaundice, nausea and vomiting, weight-loss and lethargy.[6] Surgery provides the best opportunity for long-term survival[7] but is only feasible for approximately 15% of patients.[8,9] Among patients unsuitable for surgery, chemotherapy has been found to alleviate symptoms and to confer a survival benefit.[10-12]

Practice guidelines recommend chemotherapy for most patients with inoperable pancreatic cancers.[13-16] However, studies from Australia, the United States and Europe indicate that systemic therapy in patients with pancreatic cancer has been underutilised[17-19] and that its use may be influenced by socio-demographic factors.[18-22] For example, being older,[18-22] female,[20] of racial or ethnic minority background,[20] of lower socio-economic status,[18,20] and single[19] have been associated with non-receipt of chemotherapy.

To date, population-based studies in Australia on receipt of palliative chemotherapy for pancreatic cancer and its impact on survival are scarce[17] and there is limited evidence outside trials regarding the association between use of chemotherapy and survival. We have shown that only half of patients with unresected pancreatic cancer in the Australian states of Queensland (QLD) and New South Wales (NSW) received chemotherapy.[9] This study explores the factors associated with its use and its impact on survival in a large Australian cohort.

Methods

Study population

This analysis is nested within a population-based study of patterns of care for patients with pancreatic cancer in QLD and NSW. The study sample, ethics approval and data collection have been previously described.[9] Briefly, the study population included patients aged ≥ 18 years who were diagnosed with pancreatic ductal adenocarcinoma or pancreatic cancer of unknown morphological subtype (ICD-10 code C25) between 1 July 2009 and 30 June 2011 and notified to the QLD Cancer Registry, or between 1 July 2009 and 31

December 2010 and notified to the NSW Central Cancer Registry. We extracted demographic data and data related to the initial diagnosis from the cancer registries. Trained research nurses collected clinical data from medical records for the period from diagnosis to 12 months after diagnosis.

We restricted this analysis to patients who did not die within 30 days of diagnosis, who did not have a completed resection of their primary tumour, and who had complete records regarding consultation with a medical oncologist, receipt of chemotherapy and Charlson comorbidity index. As there were only 22 patients who received chemo-radiation, we included them in the much larger group of participants who received chemotherapy alone.

Variables potentially associated with receipt of chemotherapy

Variables examined included socio-demographic and clinical factors: age at diagnosis; sex; socio-economic status, estimated by the socioeconomic index for areas (SEIFA)[23] (assigned to Australian locations by the Australian Bureau of Statistics and categorised into state-level quintiles); rurality of residence, estimated by the Accessibility/Remoteness Index for Areas (ARIA)[24]; Charlson comorbidity index;[25] Eastern Cooperative Oncology Group (ECOG) performance status;[26] TNM stage (Union for International Cancer Control (UICC) 6th Edition);[27] and primary tumour site. Variables describing processes within health services were also explored including: review at a multidisciplinary team (MDT) meeting; the specialty of the first specialist encountered at diagnosis; and hospital volume, defined as the case load of patients in our cohort initially managed in the hospital each year which we categorised into three levels: high ($\geq$ 30); intermediate (10 to 29); and low ($<$ 10).

Outcomes

We first analysed whether or not chemotherapy was received during the first year following diagnosis. To further understand the reasons for non-receipt of chemotherapy we also analysed referral to a medical oncologist, and receipt of chemotherapy among those who were reviewed by a medical oncologist. Overall survival was defined as the number of months from diagnosis until death from any cause or, if the patient did not die, until the end of the study (20 February 2014).

Statistical analysis

We used logistic regression to estimate the association between receipt of chemotherapy and review by a medical oncologist. We adjusted all analyses for age, ECOG performance status, sex and Charlson co-morbidity index score. We also adjusted for place of residence when estimating the effects of health service factors. When analysing associations with hospital volume we used generalised estimating equations with an exchangeable correlation matrix to account for patient clustering.

Median survival was estimated and survival curves generated using Kaplan-Meier methods. Following assessment that the proportional hazard assumptions were valid, Cox proportional hazards models were used to estimate the hazard ratios, adjusted for age, sex, Charlson comorbidity score, ECOG performance status, rurality of residence, tumour stage, review by a multidisciplinary team, hospital volume and the first encountered. These confounders were also included in multivariable logistic regression models used to estimate the odds ratios of mortality at one year following diagnosis. We used SAS version 9.4 and Stata version 15 (Statacorp, Texas) software for all analyses.

Results

Of the 1863 patients diagnosed with pancreatic cancer who had medical records available for review, we excluded 279 patients with completed resection of their primary tumour (irrespective of margin status) and 259 who died within 30 days of diagnosis, resulting in 1325 eligible patients. After excluding 152 people with missing data, there were 1173 patients included in the analysis (Figure 1). Compared with the patients included in the analysis, patients with missing data were older (aged ≥ 75 years: 61% versus 41%, $p<0.001$).

The mean age of included participants was 71 years (range, 29-95) and 54% were men. Most lived in a major city (69%) and almost two thirds (65%) had metastatic disease. Tumour location was documented for 90% of patients, with the majority of tumours located in the head of the pancreas (62%). A greater percentage of older patients had localised disease (45% of patients aged ≥ 80 years compared to 22% of patients aged ≤ 60 years, $p<0.001$).

Half of the patients received chemotherapy or chemo-radiation (N=590; 50%). Of the 583 who did not receive chemotherapy, 32% (N=184) were not reviewed by a medical oncologist, 30% (N=172) were not

offered chemotherapy after oncology review, 26% (N=152) declined chemotherapy, and the remainder (N=75; 13%) became too unwell or died before starting treatment.

Socio-demographic and clinical factors associated with not receiving chemotherapy and not being referred to a medical oncologist

The majority (81%) of patients aged ≥ 80 years and almost half (49%) of patients aged 70-79 did not receive chemotherapy, compared with approximately a third in each of the younger age groups (Table 1). Older patients were less likely to be reviewed by a medical oncologist (>80 vs <60 years: adjusted odds ratio (AOR)=12.14; 95% CI 5.12 – 28.83). Compared to those aged under 80 years, those aged ≥ 80 years were significantly less likely to be offered palliative chemotherapy (60% versus 89%, p<0.001) and more likely to decline chemotherapy when it was offered (23% versus 14%, p=0.001). Increasing age was strongly associated with non-receipt of chemotherapy in those reviewed by a medical oncologist, even after adjustment for other socio-demographic and prognostic factors (p-trend<0.001) (Table 1).

As expected, poor performance status was strongly associated with non-receipt of chemotherapy (bedbound vs fully active: AOR=8.26; 95% CI 4.549-15.20). Patients with poor performance status were less likely to be referred to a medical oncologist and less likely to receive chemotherapy after consultation than fully active patients.

A higher percentage of women (56% versus men 44%), people with a high Charlson comorbidity index (56% versus low 44%), and those with non-metastatic disease (56% versus stage IV 47%) did not receive chemotherapy. These same subgroups of patients were less likely to see a medical oncologist but equally likely to be treated once referred.

Living further from a major city was associated with non-receipt of chemotherapy after adjustment (OR remote vs metropolitan 1.64; 95% CI 1.04-2.57). Patients from remote areas were more likely not to consult with a medical oncologist than those from major cities (AOR=2.64; 95% CI 1.47-4.676). Among those who had a medical oncology review, receipt of chemotherapy was not associated with place of residence. As people from the most disadvantaged socio-economic areas were less likely to live in a metropolitan area than those from the least disadvantaged areas (47% versus 95%) similar estimates were obtained for exposures of

remoteness of residence and socio-economic areas. Living in the most disadvantaged socio-economic areas was associated with non-receipt of chemotherapy (AOR 1.72; 95%CI 1.10 – 2.69), lack of referral to a medical oncologist (AOR 2.29; 95% CI 1.24 – 4.23) and lack of chemotherapy treatment even after oncology review (AOR 1.50; 95% CI 0.93 – 2.40), although this was not statistically significant.

Associations between health service factors and non-receipt of chemotherapy and non-referral to a medical oncologist

Evidence of an MDT review and the type of specialist encountered at diagnosis were associated with receipt of chemotherapy. Over half (53%) of the patients with no evidence of MDT review did not receive chemotherapy, compared with 43% of those who were reviewed (AOR=1.46; 95% CI 1.10-1.94). The association remained significant after adjustment for hospital volume but there was no association amongst those who were reviewed by a medical oncologist. More patients first seen by a general surgeon did not receive chemotherapy than those seen by a specialist hepatobiliary surgeon (55% versus 41%; AOR=1.77; 95% CI 1.25-2.52). The association was reduced and no longer significant after adjustment for hospital volume (AOR=1.33; 95% CI 0.86-2.06).

Associations between receipt of palliative chemotherapy and mortality and survival

The receipt of palliative chemotherapy was associated with reduced mortality at one year (AOR=0.37; 95% CI 0.24-0.56, p<0.001) (Table 2). The association was similar for patients with localised or metastatic disease.

The median survival time for all patients with unresected pancreatic cancer who received chemotherapy was 6.9 months (range 6.3 to 7.4 months) and in those who did not receive chemotherapy median survival was 3.2 months (range 3.0 to 3.5 months) (Figure 2). Although the median survival in those with localised disease was longer than in those with metastatic disease, the adjusted hazard ratios were similar (Table 2).

Discussion

We found that 44% of patients with localised inoperable pancreatic cancer and 53% of patients with metastatic pancreatic cancer received chemotherapy. In addition to expected clinical factors, such as ECOG

performance status and co-morbidity burden, our results suggest that the receipt of palliative chemotherapy is influenced by other factors such as age, place of residence, presence or absence of an MDT review and the type of specialist first encountered. Consultation with a medical oncologist mitigated most of the socio-demographic and service-related disparities in chemotherapy use, except for age and socio-economic status. The receipt of chemotherapy was associated with prolonged survival in patients with inoperable pancreatic cancer, even after adjusting for patient, demographic, tumour and health service factors.

Despite explicit guideline recommendations to consider chemotherapy in most patients with advanced pancreatic cancer,[15,16,28] and the fact that 84% of the patients in this cohort consulted with a medical oncologist, only half of the patients with unresected pancreatic cancer received chemotherapy. This study was performed at a time when Gemcitabine was the most frequently used chemotherapeutic agent in Australia. Since emerging in the late 1990s, the benefits of Gemcitabine have driven a steady increase in chemotherapy use.[29,30] Population-based studies carried out in the United States prior to the Gemcitabine era reported use of palliative chemotherapy in less than a third of patients with advanced pancreatic cancer,[18,31] which had gradually increased to more than half during the last decade.[20,32] Other developed countries such as Ireland,[19] Netherlands,[33] Japan[34] and Australia[17] followed this trend, although at a slower pace. Studies conducted in Europe when Gemcitabine was considered the standard of care[19,35,36] reported that approximately 20% of patients received palliative chemotherapy.

Consistent with other international studies, we found that advanced age was the factor most strongly associated with non-receipt of chemotherapy in patients with inoperable pancreatic cancer.[37-45] This was partly because fewer older patients were reviewed by medical oncologists compared with their younger counterparts. The persistence of the effect after oncology consultation and adjustment for clinical factors might suggest that oncologists are reluctant to prescribe chemotherapy for elderly patients, even to those who appear otherwise fit, despite compelling evidence that chemotherapy achieves a similar benefit in elderly patients to that in their younger peers.[43,46-48]

Comparable with international literature, we identified rurality and socio-economic status as barriers to chemotherapy access.[8,18,49,50] The geographic influence on chemotherapy receipt appears to be due to lack of

access to medical oncologists in regional areas, with no differences in treatment among those who consult with an oncologist. It is challenging to disentangle the effects of rurality and socio-economic status, but the association between socio-economic status and chemotherapy uptake remained significant even after consultation with an oncologist. The reason for this is unclear, particularly since we did not observe any difference in the proportion of people who declined chemotherapy across socio-economic strata. The results may be due to uncontrolled confounding by lifestyle or comorbidity.

We observed that MDT review is strongly associated with chemotherapy use, even after adjusting for hospital volume, but there was no association with receipt of chemotherapy among people who consulted with a medical oncologist Although the effect of MDT review on receipt of palliative chemotherapy has not been specifically studied, evidence suggests that treatment for patients with metastatic pancreatic cancer in a high-volume facility and multidisciplinary cancer conferences improve patient outcomes[35,51,52] and are considered the gold standard of care.[53,54] However, a national audit in Australia in 2006 found that two thirds of the 155 hospitals surveyed did not have MDT meetings,[55] and a recent report from Queensland found that only 18% of patients with hepatobiliary cancer were reviewed at an MDT. Further, there is lack of consensus over the types of specialists who should attend MDT meetings and which patients should be discussed, with a tendency to focus on patients who are potential surgical candidates.[56] We did not collect detailed information about MDT meetings so our findings need further investigation, but the correlation of MDT review and receipt of chemotherapy in our study may have implications for future implementation of MDTs.

Compared with patients first seen by a hepatobiliary surgeon, those who were first reviewed by a general surgeon or another type of specialist were less likely to receive chemotherapy. However, after adjusting for hospital volume the association was no longer significant, suggesting that in larger hospitals the referral pathways increase the likelihood of high-quality care, irrespective of the type of specialist first encountered.

Consistent with reports from clinical trials and population-based studies, we found that chemotherapy was associated with improved survival in patients in the general population with advanced pancreatic cancer.[19,30,57,58] We estimated a slightly longer median survival time for patients who received chemotherapy

than the survival reported by the pivotal trial of Gemcitabine for patients with advanced pancreatic cancer[29] (6.8 months versus 5.6 months), likely due to the higher proportion of patients in our cohort with disease confined to the pancreas (35% versus 26%). Observational studies conducted during the last decade in other developed countries reported median survival times ranging between 3.8 months and 8 months for all patients with unresected pancreatic cancers receiving palliative chemotherapy.[17,19,57] Survival was prolonged regardless of whether or not the disease was metastatic which, together with our estimates of median survival, may inform the discussion between oncologists and patients about the benefit of Gemcitabine chemotherapy in patients considered fit for chemotherapy.

Our study has several limitations. Firstly, we relied on data available in medical records, and the absence of information in the record does not necessarily mean that a particular type of care did not occur. It is plausible that a patient was reviewed by a medical oncologist but that this was not documented. Secondly, patient fitness is a strong determinant of chemotherapy uptake, but a significant number of patients were missing ECOG performance status and we did not have other measures of fitness, potentially resulting in uncontrolled confounding. This is particularly likely to have influenced the association with age. Thirdly, the study was conducted at a time when Gemcitabine monotherapy was the standard of care. It is possible that palliative chemotherapy uptake will have increased somewhat since diffusion into routine practice of more potent regimens including protein-bound paclitaxel and FOLFIRINOX (a combination of 4 different drugs), and their determinants of use may be different from those documented here. Finally, survival associated with Gemcitabine therapy may change if this regimen is reserved for patients where performance status precludes other more toxic therapies, so estimated survival time associated with Gemcitabine use may decrease.

Our study highlights the sociodemographic disparities in access to medical oncologists and subsequent palliative chemotherapy. This warrants implementation of validated referral pathways to ensure that all patients are offered the opportunity to discuss chemotherapeutic options with highly specialised physicians.

References

1. Ferlay J SI, Ervik M,. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11: GLOBOCAN 2012 v1.0, 2012.
2. Australian Institute of Health and Welfare (AIHW) 2016. Australian Cancer Incidence and Mortality (ACIM) books: Pancreatic Cancer. Canberra: AIHW.; 2016.
3. SEER. Cancer Statistics Factsheets: Pancreas Cancer. April 2013. http://seer.cancer.gov/statfacts/html/pancreas.html (accessed 14th February 2014).
4. Cancer Institute NSW. Cancer incidence and mortality: projections 2011 to 2021. Sydney: May 2011.
5. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**(11): 2913-21.
6. American Cancer Society. Pancreatic Cancer. 4/5/2016 2016 (accessed 4 May 2016).
7. Zijlstra M, Bernards N, de Hingh IH, et al. Does long-term survival exist in pancreatic adenocarcinoma? *Acta Oncol* 2016; **55**(3): 259-64.
8. Abraham A, Al-Refaie WB, Parsons HM, Dudeja V, Vickers SM, Habermann EB. Disparities in pancreas cancer care. *Ann Surg Oncol* 2013; **20**(6): 2078-87.
9. Burmeister EA, O'Connell DL, Beesley VL, et al. Describing Patterns of Care in Pancreatic Cancer: A Population-Based Study. *Pancreas* 2015; **44**(8): 1259-65.
10. Goldstein D, El-Maraghi RH, Hammel P, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst* 2015; **107**(2).
11. Gresham GK, Wells GA, Gill S, Cameron C, Jonker DJ. Chemotherapy regimens for advanced pancreatic cancer: a systematic review and network meta-analysis. *BMC Cancer* 2014; **14**: 471.
12. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**(18): 1691-703.
13. Balaban EP MP, Khorana AA, Shah MA, Mukherjee S, Crane CH, Javle MM, Eads JR, Allen P, Ko AH, Engebretson A, Herman JM, Strickler JH, Benson AB 3rd, Urba S, Yee NS. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology* 2016; **34**: 2654-68.
14. Sohal DP MP, Khorana AA, Shah MA, Philip PA, O'Reilly EM, Uronis HE, Ramanathan RK, Crane CH, Engebretson A, Ruggiero JT, Copur MS, Lau M, Urba S, Laheru D. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology* 2016; **34**: 2784-96.
15. NCCN. NCCN Practice Guidelines for Pancreatic Cancer. Version 1.2016. 2016 (accessed 6th April 2016).
16. eviQ Cancer Treatments Online. Cancer Institute NSW, viewed 26th June 2016. 11 Jan 2016 2016. https://www.eviq.org.au/Category/tabid/65/categoryid/372/Default.aspx.
17. Jefford M, Thursfield V, Torn-Broers Y, Leong T, Guerrieri M, Speer T. Use of chemotherapy and radiotherapy in patients with pancreatic cancer in Victoria (2002-2003): a retrospective cohort study. *Med J Aust* 2010; **192**(6): 323-7.
18. Krzyzanowska MK, Weeks JC, Earle CC. Treatment of locally advanced pancreatic cancer in the real world: population-based practices and effectiveness. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003; **21**(18): 3409-14.
19. Sharp L, Carsin AE, Cronin-Fenton DP, O'Driscoll D, Comber H. Is there under-treatment of pancreatic cancer? Evidence from a population-based study in Ireland. *Eur J Cancer* 2009; **45**(8): 1450-9.
20. Khanal N, Upadhyay S, Dahal S, Bhatt VR, Silberstein PT. Systemic therapy in stage IV pancreatic cancer: a population-based analysis using the National Cancer Data Base. *Ther Adv Med Oncol* 2015; **7**(4): 198-205.
21. Sehgal R, Alsharedi M, Larck C, Edwards P, Gress T. Pancreatic cancer survival in elderly patients treated with chemotherapy. *Pancreas* 2014; **43**(2): 306-10.
22. Haj Mohammad N, Bernards N, Besselink MG, et al. Volume matters in the systemic treatment of metastatic pancreatic cancer: a population-based study in the Netherlands. *J Cancer Res Clin Oncol* 2016; **142**(6): 1353-60.
23. Australian Bureau of Statistics. Socio-Economic Indexes for Areas. 2013. http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa (accessed October 3 2013).
24. Statistics ABo. Remoteness Structure 2013. http://www.adelaide.edu.au/apmrc/research/projects/category/about_aria.html.
25. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; **47**(11): 1245-51.

26. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**(6): 649-55.
27. Sobin L, Gospodarowicz M, Wittekind C. The TNM Classification of Malignant Tumours. Seventh ed; 2009.
28. Verslype C, Van Cutsem E, Dicato M, Arber N, Berlin J. The management of metastatic pancreatic cancer:expert discussion and recommendations from the 14th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2012. *Annals of Oncology* 2013; **24**(suppl 4): iv5 - iv10.
29. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**(6): 2403-13.
30. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; **25**(18): 2607-15.
31. Gong Z, Holly EA, Bracci PM. Survival in population-based pancreatic cancer patients: San Francisco Bay area, 1995-1999. *Am J Epidemiol* 2011; **174**(12): 1373-81.
32. Oberstein PE, Hershman DL, Khanna LG, Chabot JA, Insel BJ, Neugut AI. Uptake and patterns of use of gemcitabine for metastatic pancreatic cancer: a population-based study. *Cancer Invest* 2013; **31**(5): 316-22.
33. Bernards N, Haj Mohammad N, Creemers GJ, de Hingh IH, van Laarhoven HW, Lemmens VE. Ten weeks to live: a population-based study on treatment and survival of patients with metastatic pancreatic cancer in the south of the Netherlands. *Acta Oncol* 2015; **54**(3): 403-10.
34. Kuroda T, Kumagi T, Yokota T, et al. Improvement of long-term outcomes in pancreatic cancer and its associated factors within the gemcitabine era: a collaborative retrospective multicenter clinical review of 1,082 patients. *BMC Gastroenterol* 2013; **13**: 134.
35. Haj Mohammad N, Bernards N, Besselink MG, et al. Volume matters in the systemic treatment of metastatic pancreatic cancer: a population-based study in the Netherlands. *J Cancer Res Clin Oncol* 2016.
36. Enewold L, Harlan LC, Tucker T, McKenzie S. Pancreatic cancer in the USA: persistence of undertreatment and poor outcome. *J Gastrointest Cancer* 2015; **46**(1): 9-20.
37. Haj Mohammad N Bernards N CG, de Hingh IH, van Laarhoven HW, Lemmens VE. Ten Weeks to Live: A Population-Based Study on Treatment and Survival of Patients with Metastatic Pancreatic Cancer in the South of the Netherlands. *Acta Oncologica* 2015; **54**: 403-10.
38. Sehgal R AM, Larck C, Edwards P, Gress T. Pancreatic cancer survival in elderly patients treated with chemotherapy. *Pancreas* 2014; **43**: 306-10.
39. Khanal N US, Dahal S, Bhatt VR, Silberstein PT Systemic therapy in stage IV pancreatic cancer: a population-based analysis using the National Cancer Data Base. *Therapeutic Advances in Medical Oncology* 2015; **7**: 198-205.
40. Weeks JC Krzyzanowska MK EC. Treatment of Locally Advanced Pancreatic Cancer in the Real World: Population-Based Practices and Effectiveness. *Journal of Clinical Oncology,* 2003; **21**: 3409-14.
41. Carsin AE Sharp L C-FD, O'Driscoll D, Comber H. Is There under-Treatment of Pancreatic Cancer? Evidence from a Population-Based Study in Ireland. *European Journal of Cancer* 2009; **45**: 1450-59.
42. Oberstein PE HD, Khanna LG, Chabot JA, Insel BJ, Neugut AI. Uptake and patterns of use of gemcitabine for metastatic pancreatic cancer: a population-based study. *Cancer Investigation* 2013; **31**: 316-22.
43. Aldoss IT TT, Gonsalves W. Role of chemotherapy in the very elderly patients with metastatic pancreatic cancer - a Veterans Affairs Cancer Registry analysis. *Journal of Geriatric Oncology* 2011; **2**: 209-14.
44. Berger AK AU, Komander C, Harig S, Jäger D, Springfeld C. . Chemotherapy for advanced pancreatic adenocarcinoma in elderly patients (≥70 years of age): A retrospective cohort study at the National Center for Tumor Diseases Heidelberg. *Pancreatology*; **14**: 211-5.
45. Abraham A A-RW, Parsons HM, Dudeja V, Vickers SM, Habermann EB. Disparities in pancreas cancer care. *Annals of surgical oncology* 2013; **20**: 2078-87.
46. Sehgal R AM, Larck C, Edwards P, Gress T. Pancreatic cancer survival in elderly patients treated with chemotherapy. *Pancreas* 2014; **43**: 306-10.
47. Berger AK, Abel U, Komander C, Harig S, Jager D, Springfeld C. Chemotherapy for advanced pancreatic adenocarcinoma in elderly patients (>/=70 years of age): a retrospective cohort study at the National Center for Tumor Diseases Heidelberg. *Pancreatology* 2014; **14**(3): 211-5.
48. Vickers MM, Powell ED, Asmis TR, et al. Comorbidity, age and overall survival in patients with advanced pancreatic cancer - results from NCIC CTG PA.3: a phase III trial of gemcitabine plus erlotinib or placebo. *Eur J Cancer* 2012; **48**(10): 1434-42.
49. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a Barrier to Cancer Diagnosis and Treatment: Review of the Literature. *Oncologist* 2015.

50. Kagedan DJ, Abraham L, Goyert N, et al. Beyond the dollar: Influence of sociodemographic marginalization on surgical resection, adjuvant therapy, and survival in patients with pancreatic cancer. *Cancer* 2016.
51. Prades J, Remue E, van Hoof E, Borras JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. *Health Policy* 2014; **119**(4): 464-74.
52. Schiffman S, Abberbock S, Windters S, et al. A pancreatic cancer multidisciplinary clinic:insights and outcomes. *Journal of Surgical Research* 2016; **In press**.
53. Cancer Australia. Multidisciplinary care. 20 September 2012 2014. http://canceraustralia.gov.au/clinical-best-practice/service-delivery/key-elements-cannet/multidisciplinary-care (accessed 11 November 2014).
54. European Partnership Action Against Cancer consensus group, Borras JM, Albreht T, et al. Policy statement on multidisciplinary cancer care. *Eur J Cancer* 2014; **50**(3): 475-80.
55. Wilcoxon H, Luxford K, Saunders C, et al. Multidisciplinary cancer care in Australia: a national audit highlights gaps in care and medico-legal risk for clinicians. *Asia Pac J Clin Oncol* 2011; **7**(1): 34-40.
56. Burmeister EA, Jordan SJ, O'Connell DL, et al. Using a Delphi process to determine optimal care for patients with pancreatic cancer. *Asia Pac J Clin Oncol* 2016; **12**(2): 105-14.
57. Bjerregaard JK, Mortensen MB, Schonnemann KR, Pfeiffer P. Characteristics, therapy and outcome in an unselected and prospectively registered cohort of pancreatic cancer patients. *Eur J Cancer* 2013; **49**(1): 98-105.
58. Eloubeidi MA, Desmond RA, Wilcox CM, et al. Prognostic factors for survival in pancreatic cancer: a population-based study. *Am J Surg* 2006; **192**(3): 322-9.