# REPORT WP 8.5

## Literature review on pain prevalence in cancer patients and Recommendations

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## Contents

# Abbreviations

| | |
|---|---|
| EAPC | European Association for Palliative Care |
| ECPC | European Cancer Patient Coalition |
| EU | European Union |
| IASP | International Association for the Study of Pain |
| INT | National Cancer Institute of Milan |
| ICO | Instutut Catalan Oncologia |
| iPAAC | Innovative Partnership for Action Against Cancer |
| NCCN | National Comprehensive Cancer Network |
| OECI | Organisation of European Cancer Institutes |
| PC | Palliative Care |
| PI | Pain Intensity |
| PROMs | Patient reported outcomes |
| WP | Work Package |

# Executive summary

The aim of the Innovative Partnership for Action Against Cancer (iPAAC) is to define strategies to improve the quality of cancer care by optimising the use of healthcare resources and promoting realistic and evidence-based responses to existing needs. While cancer care has evolved, showing better organisation and specificity with regards to treating different cancer diseases, cross-cutting and disease-based challenges remain.

One of the cross-cutting cancer care challenge is pain management (WP 8 task 5). Pain should be regarded as a priority in cancer care and a factor of continuity across cancer treatment, survivorship care and palliative care. The implementation of pain measurement in practice should be seen as the basis  to include pain and other symptom assessment in cancer clinical records, databases and registries. In this report, specific attention is given to long term survivors developing chronic pain. .

In order to identify the need of pain control, a literature review of data on pain prevalence has been performed, pointing out prevalence of chronic pain, its causes and its relationship with underlying cancer with specific focus on the prevalence of pain in cancer survivors

WP8 tasks 5 and 6 on pain management and palliative care have been the focus of a special group meeting promoted by iPAAC at the XI European Association for Palliative Care (EAPC) Congress on October, 2020. The meeting remit was to share, discuss and disseminate iPAAC contributions on pain controll barriers in cancer patients and in cancer survivors, PROMs implementation in clinical practice and in research and palliative care integration with oncology. The meeting built on the communication between EAPC, International Association for the Study of Pain (IASP), Organization of European Cancer Institutes (OECI) and European Cancer Patient Coalition (ECPC) representatives

# 1  Introduction

The aim of the work package 8 (WP8) is to define strategies to improve the quality of cancer care by optimising the use of healthcare resources and promoting realistic and evidence-based responses to existing needs. While cancer care has evolved, showing better organisation and specificity with regards to treating different cancer diseases, cross-cutting and disease-based challenges remain.

**<u>The problem of cancer related pain</u>**

One of the cross-cutting cancer care challenge is pain management (task 5). Pain should be regarded as a priority in cancer care and a factor of continuity between cancer treatment , survivorship care and palliative care. The implementation of pain assessment and measurement in clinical practice is a condition for including pain as well as other PROMs cancer registries. This report will focus in particular on the specific requirements posed by adressing survivorship care as far as survivors developing chronic pain is concerned.

Cancer pain recognizes different causes of onset (table 1).

Table 1. Causes of pain in cancer patients

| |
|---|
| Direct tumor involvement of bone, nerves, viscera, or soft tissue by primary, recurrent or metastatic cancer |
| Anticancer therapy (surgery, chemo-hormono-therapy, radiation therapy, immunotherapy, biological response modifiers) |
| Causes unrelated to cancer or its therapy |

Cancer pain remains a widespread symptom with high-impact both on patients' quality of life. Nevertheless, studies on prevalence of cancer pain are extremely uneven in terms of clarifying disease stage, number of patients, study methodology pain causes and diagnosis.

Infact, one major unanswered question is what is the clinical impact of chronic pain in the cancer survivors population distinguishing its causes, as described in table 1, the population affected as result of cancer treatments, prognosis and related comorbities.

The present emphasis on survivorship care does not always allow to understand and address the different clinical needs of patients who are cancer free and potentially cured , patients with active metastatic cancer undergoing or not antineoplastic treatment with

different prognosis and patients are going to die in a relatively short time (Marzorati et al 2017)

For these reasons, the systematic review by van den Beuken-van Everdingen and colleagues published in 2016 is a very helpful starting point in identifying the prevalence characteristics of cancer pain, in general and in the subpopulations of patients in different stages of the disease and treatment. In this work 122 articles were included. The results of the metanalysis are shown in table 2. One hundred seventeen studies described pain prevalence which resulted in 39.3% (95% CI 33.3 – 45.3) after curative treatment; 55% during anticancer treatment (95% CI 45.9 – 64.2); 66.4% (95% CI 58.1-74.7) in advanced, metastatic, or terminal disease.

Table 2. Prevalence of pain in cancer patients according to disease stage in systematic literature review and metanalysis 2005–2014 (Van den Beuken-van Everdingen M. et al 2016)

| Patient group | N | Pooled pain prevalence | 95% Confidence Interval |
|---|---|---|---|
| After curative treatment | 18,832 | 39 % | 33 – 45 |
| During anticancer treatment | 6904 | 55% | 46 – 64 |
| With advanced metastatic or terminal  disease | 9653 | 66 % | 58 – 75 |

From 52 studies it is also possible to estimate pain severity. Overall 38% of the patients reported moderate to severe pain (numerical rating scale score greater than or equal to five). Pain was rated as moderate to severe by 27.6% of the patients after curative treatment; by 32.4% of the patients on anticancer treatment and by 51.9% of the patients with advanced, metastatic, or terminal disease. Some factors resulted associated with pain prevalence and severity such as cancer diagnosis, study geographical provenence, performance status and time referral of pain assessment.

As importantly, this review highlights limitations due to the high heterogeneity of methods used, in particualar as far as pain cause, diagnosis and population characteristics. It is infact impossible to understand in most epidemiological studies the cause of pain (table 1) and the

impact of chronic pain in groups of patients with good prognostic conditions, while still on antineoplastic treatment, from those who are receiving antineoplatic treatment with only palliative intent. These kind of patients overlap in group 2 (table 2) but also in group 3 as we know that some antineoplastic treatments are nowadays available and appropriate while patients have advanced disease making the distinction with a „terminal" phase less clearcut.

The three group partition makes it therefore difficult to identify cancer survivors as a patient population and as well as to evidentiate their needs.

## Cancer Survivors

The question about the definition of who is a „cancer survivor" has not a simple answer (Bell et al 2013). A good review of this topic can be found in Marzorati et al (2017). The term was originally introduced in health care documents by the Center for Disease Control and prevention of the United States of America National Cancer Institute for advocacy reasons and to commit research to a new area of social and health care needs posed by „surviving" the diagnosis of cancer. It is originally meant to address the needs of patients who, with a cancer diagnosis since years, experience physical, psycological or social consequences that are not due to the cancer itself but from treatment side effects, and also to cultural and psychosocial adaptation processes.

It is clear that the terminology was used for a range of epidemiological, health policy and clinical perspectives and therefore it lacked of an uniform and universally accepted definition. Cancer survivors clinics can be found especially in the US (see for example Bevilacqua et al 2018), and medical journals are also dedicated to cancer survivorship. Though it is still necessary to operationally identify to what definition of survivorship is someone referring in a specifc context case by case. Infact in some cases cancer patients and survivors are kept as two separate entities while in others expressions like „An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life" (Marzorati et al 2017) prevail making it impossible to make any classification. Most operational definitions refer to three different variables to identify survivors:

1. Time since diagnosis
2. Evidence of disease
3. Continuing or not active antineoplastic treatment

Different combination of these three characteristics are then used for different case series description, epidemiological, organizional or health politics purposes. Usually a defined time since daignosis is required (2–3–5 years), in some cases to be cancer free and not undergoing antineoplastic treatment.

This semantic and classification ambiguity results nowadys more useful as rhetoric than in identifying the diverse patients needs, if we want to distinguish between chronic conditions and patients with active disease who are going to die with 6–12 months, who can or cannot be included in one of the former survivors group according to the definition. We will make an

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example of the special problems posed by this lack of homegenous definition in addressing our topic that is the identification, classification and care of pain in cancer survivors.

In order to update these data, and to clarify the special problems posed by considering cancer survivors, a new literature review on pain prevalence has been performed, pointing out prevalence and causes of pain with a specific focus on the prevalence of pain in cancer survivors. These data were also discussed in an international symposium.

# 2  Methods

The literature search was conducted on MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases, over a time frame ranging from 1 January 2014 to 31 October 2020.

The search strategy for the MEDLINE database, which used both text words and MeSH/EMTREE terms, is reported in Table 3, and appropriately revised strategies were developed for each database; a hand search of the reference lists of identified papers was also performed.

The search was conducted in the title, abstract, and keyword fields of the databases Inclusion criteria for relevant study selection were: to have been conducted in human, adult patients with cancer pain; to reported data on pain prevalence and/or pain intensity; to be written in the English language.

Table 3. Search strategy

| |
|---|
| #13 #5 AND #12 AND [2014-2020]/py AND [humans]/lim AND [english]/lim |
| #14 #4 AND #5 AND #13 AND #12 |
| #13 prevalence |
| #12 #6 OR #7 OR #8 OR #9 OR #10 OR #11 |
| #11 palliative therapy |
| #10 hospice |
| #9 advanced cancer |
| #8 endstage |
| #7 terminal care |
| #6 survivor* |
| #5 malignant neoplasm |
| #4 #1 OR #2 OR #3 |
| #3 quality of life |
| #2 symptom |
| #1 'pain'/exp OR 'pain' |

# 3 Results

Figure 1 shows that 5941 papers were identified using the search strategy described above on the three databases. Abstract screening lead to the full text examination of 80 papers, 38 of which were excluded because or referred to a field which was not relevant to our search or not reported pain prevalence and/or pain intensity data or full-texts were not accessible.
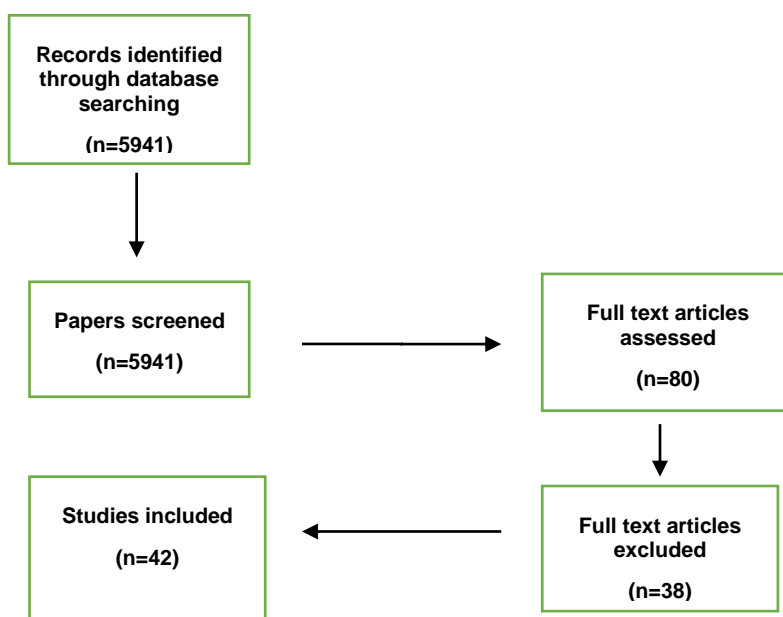
```
┌─────────────────────┐
│ Records identified  │
│ through database    │
│    searching        │
│     (n=5941)        │
└─────────────────────┘
          │
          ▼
┌─────────────────────┐         ┌─────────────────────┐
│  Papers screened    │────────▶│  Full text articles │
│     (n=5941)        │         │      assessed       │
│                     │         │       (n=80)        │
└─────────────────────┘         └─────────────────────┘
                                           │
                                           ▼
┌─────────────────────┐         ┌─────────────────────┐
│  Studies included   │◀────────│  Full text articles │
│       (n=42)        │         │      excluded       │
│                     │         │       (n=38)        │
└─────────────────────┘         └─────────────────────┘
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Figure 1. Search strategy

**Pain during cancer treatment and Pain in advanced cancer**

Eleven studies (Raj SX 2014, Rohrl K 2016, Al Qadire M 2016, Alawneh A 2017, Teo I 2017, Kiely F 2017, Madsen M 2017, Hamieh NM 2018, Brunello A 2019, Shaulov A 2019, Smith TG 2019) included patients receiving curative or palliative oncological treatment and pain prevalence was 25-85.5% and moderate to severe pain intensity was present in 22.2-42%.

Eleven studies reported data about patients with advanced or end of life disease (Al Zaharani O 2014, Gough N 2017, Goto H 2017, Soares LGL 2018, Hallet J 2019, Mejin M 2019, Tung S 2019, Hammad A 2019, Bubis LD 2020, Bubis LD 2020, Hagarty 2020). Table 4 summarizes study characteristics

Pain prevalence ranged from 31% to 85.5% and moderate-severe pain intensity from 14% to 82.1% (table 5).

In pancreatic cancer the data from Ontario linking cancer registries with administrative database and the Cancer Care Ontario Symptom Management Reporting Database, shows that , in unresected pancreatic carcinoma, pain from moderate to severe can be experienced by 61.8% of patients, opioids are administered in 75% of patients with pain, radiation therapy is used by 13% and nerve blocks in 1–2 % for pain control. The complementary study by Haddad et al (2019) shows, with the same methods, that in the last 6 months of life, patients with pancreatic cancer have moderate pain (>/= 4 over 10) in 34.5% and severe pain (>/= 7 over 10) in 34.5% of cases.

The study by Hagarty (2020) is also based on several health care administrative and clinical databases used in the delivery of terminal home care in Ontario in the general population, and it documents that pain is experienced in the last 30 days of life by 70% of all those dying with home care, it is moderate in 36% and severe in 14%. Pain medication are not controlling pain adequately in 26%. The diagnosis of cancer is associated with more severe pain.

In general , the pain cause is never objectively identified in these studies, pain prevalence and severity is more often associated with advanced and metastatic disease and just in one case it is referred to the presence of bone metastases (Goto et al 2017).

Table 4. Characteristics of studies on pain in different disease stages

| AUTHOR/YEAR | STUDY DESIGN | TUMOUR TYPE | STAGE | N° PATIENTS |
|---|---|---|---|---|
| **Different disease stages during antineoplastic treatment** | | | | |
| Raj SX 2014 | Cross-sectional Study | Solid and hematologic tumours | I-II-III-IV stage, during palliative or curative treatment | 305 |
| Rohrl K 2016 | Longitudinal study | Colorectal tumours | Curative cht vs palliative cht | 120 68 curative 52 palliative |
| Al Qadire M 2016 | Cross-sectional Study | Solid and hematologic tumours | I-II-III-IV stage, during palliative or curative treatment | 498 |
| Alawneh A 2017 | Cross-sectional Survey | Solid tumours | I-II-III-IV stage, during palliative or curative treatment | 175 |
| Teo I 2017 | Cross-sectional Survey | Gynecological Tumours | I-II-III-IV stage | 104 |
| Kiely F 2017 | Cross-sectional Survey | Multiple myeloma | Pts during treatment | 41 |
| Madsen M 2017 | Cross-sectional Survey | Neuroendocrine tumours | All stages radical surgery and non curative | 207 |

| AUTHOR/YEAR | STUDY DESIGN | TUMOUR TYPE | STAGE | N° PATIENTS |
|---|---|---|---|---|
| **Different disease stages during antineoplastic treatment** | | | | |
| Hamieh NM 2018 | Cross-sectional study<br><br>Convenience sample | Solid and hematologic tumours | I-II-III-IV stage | 400 |
| Brunello A 2019 | Observational prospective Study | Solid tumours | I-II-III-IV stage | 745<br>(≥70 years old) |
| Shaulov A 2019 | Obervational prospective study | Acute leukemia | Newly diagnosed or relapsed AL | 318 |
| Smith TG 2019 | Cross-sectional survey | Breast and colon tumours | I-II-III stage | 2257 |
| **Advanced and terminal illness** | | | | |
| Al Zaharani O 2014 | Cross-sectional Survey | Solid and hematologic tumours | Advanced cancer (palliative care outpatients) | 124 |
| Gough N 2017 | Cross-sectional Study | Soft tissue sarcoma | Advanced stage non surgical | 113 |
| Goto H 2017 | Retrospective study | Skin tumours | From 3 months to 3 days before death | 224 |
| Soares LGL 2018 | Retrospective Cohort | Solid tumours | Advanced cancer<br>Last 3 days of life<br>Palliative care Unit | 54 |
| Hallet J 2019 | Retrospective cohort study<br>ESAS Ontario^ | Neuroendocrine tumours | End of life | 677 |
| Mejin M 2019 | Observational prospective cohort study consecutive sample | Solid tumours (no brain) | Advanced cancer (palliative care unit) | 151 |
| Tung S 2019 | Prospective cohort study | Pancreatic tumours | Advanced non-resected cancer | 2623 |
| Hammad A 2019 | Retrospective cohort study<br>ESAS Ontario ^ | Pancreatic tumours | Last 6 months of life | 2538 |

| AUTHOR/YEAR | STUDY DESIGN | TUMOUR TYPE | STAGE | N° PATIENTS |
|---|---|---|---|---|
| **Advanced and terminal illness** | | | | |
| Bubis LD 2020 | Retrospective study ESAS Ontario^ | Solid tumours | Last 6 months of life | 22650 |
| Bubis LD 2020 | Retrospective study ESAS Ontario^ | Metastatic gastric tumours | Last 6 months of life | 788 |
| Hagarty AM 2020 | Observational study Population based linked datasets RAI-HC database | Not specified | End of life | 1164 |

^ Cancer Care Ontario Symptom Management Reporting Database

## Table 5. Pain prevalence in patients with different stages disease

| AUTHOR/YEAR | N° PATIENTS | % PATIENTS WITH PAIN | % MODERATE-SEVERE PAIN | FACTORS/RISKS ASSOCIATED WITH CHRONIC PAIN |
|---|---|---|---|---|
| **Different disease stages during antineoplastic treatment** | | | | |
| Raj SX 2014 | 305 | // | 22% **95% CI 19-24%** | presence of breakthrough pain, age >70y, treatment with palliative intent, comorbidity |
| Rohrl K 2016 | 120 68 curative 52 palliative | 44.1% curative 59.6% palliative | // | previous curative treatment |
| Al Qadire M 2016 | 498 | 85.5% | // | diagnosis > 1 year |
| Alawneh A 2017 | 175 | 71% | median severity score=50% | not reported |

| AUTHOR/YEAR | N° PATIENTS | % PATIENTS WITH PAIN | % MODERATE-SEVERE PAIN | FACTORS/RISKS ASSOCIATED WITH CHRONIC PAIN |
|---|---|---|---|---|
| **Different disease stages during antineoplastic treatment** | | | | |
| Teo I 2017 | 104 | 25% | // | younger age |
| Kiely F 2017 | 41 | 66% | // | presence of incident pain, cognitive impairment |
| Madsen M 2017 | 207 | 41% | Median PI=5 | advanced stage |
| Hamieh NM 2018 | 400 | 29.75% | moderate=37.8% severe=4.2% | female, living in rural areas; pts with colon cancer were at lower risk of developing pain compared to those with breast cancer |
| Brunello A 2019 | 745 (≥ 70 years old) | 35.7% | 22.2% | female, advanced stage, poorer performance status, comorbidity |
| Shaulov A 2019 | 318 | 49.2% | 35.3% | younger age, worse performance status, longer time from chemotherapy initiation to study assessment, ALL |
| Smith TG 2019 | 2257 | 61% | // | female, breast cancer, surgery or chemotherapy within 6 months |
| **Advanced and terminal illness** | | | | |
| Al Zaharani O 2014 | 124 | 85.5% | 51% | no factors detected |
| Gough N 2017 | 113 | 77% **95% CI 68-84%** | severe=24% **95% CI 16-33%** | distress levels |

| AUTHOR/YEAR | N° PATIENTS | % PATIENTS WITH PAIN | % MODERATE-SEVERE PAIN | FACTORS/RISKS ASSOCIATED WITH CHRONIC PAIN |
|---|---|---|---|---|
| **Advanced and terminal illness** | | | | |
| Goto H 2017 | 224 | 43% | // | presence of bone or lung metastases, last few days before death |
| Soares LGL 2018 | 54 | 57% | 46% | cancer was the only indipendent factor associated with pain |
| Hallet J 2019 | 677 | 65.4% | 55% | female, last 2 month of life |
| Mejin M 2019 | 151 | 81.5% 95% CI 75-88% | 42.2% | not reported |
| Tung S 2019 | 2623 | // | 61.8% | younger age, comorbidity |
| Hammad A 2019 | 2538 | 67.3% | 34.5% | female, older age, comorbidity, urban residence |
| Bubis LD 2020 | 22650 | 31% | 25% | female, elderly, comorbidity |
| Bubis LD 2020 | 788 | // | 56% | female, cancer-direct therapy, urban residence |
| Hagarty AM 2020 | 1164 | 70% | moderate=36% severe=14% | female, younger age, functionally impaired |

## Pain in cancer survivors

Pain prevalence in survivors was considered in 20 (Table 6 and 7) studies (Gjeilo KH 2020, Bjerkeset E 2020, Gallaway MS 2020, Farrukh N 2020, Mandelblatt JS 2020, Cox-Martin E 2020, Manfuku M 2019, Tan SY 2019, Tung S 2019, Sanford NN 2019, Davis LE 2018, Bao T 2018, Cramer JD 2018, Hamood R 2018, Huang IC 2017, Terkawi AS 2017, Drury A 2017, Edmond SN 2017, Schou Bredal I 2014, Moye J 2014). In 14 of them survivors were specifically identified already in the title as the object of the study. Most (16) gave an

operational definition on survivors using in different ways three different classification dimensions :

1- Time since diagnosis

2- Absence of active disease (no evidence of disease)

3- Not undergoing anti-neoplastic treatment

Table 6 :Characteristics of studies on pain in survivors

| AUTHOR/YEAR | DEFINITION OF SURVIVORS | STUDY DESIGN/ EVALUATION METHOD | TUMOUR TYPE | N° PATIENTS |
|---|---|---|---|---|
| Schou Bredal I 2014 | Adult women who were treated for breast cancer two to six years before the onset of the study | Cross-sectional/ Postal survey | Breast tumour | 832 |
| Moye J 2014 | Participants of all cancer stages as long as the individual was not in end of life care | Cross-sectional study/ Face to face interviews 6, 12, and 18 months following their cancer diagnosis. | Head&neck, esophageal, gastric, colorectal tumours | 170 |
| Huang IC 2017 | Patients after cancer diagnosis | Cross-sectional survey/ National Health interview survey data | Solid and hematologic tumours | 604 |
| Terkawi AS 2017 | Patients who had completed their therapy for tumour after at least 3 months | Cross-sectional survey/ Face to face interviews | Head&Neck tumours | 102 |
| Davis LE 2018 | Adult women diagnosed with stage I-III breast cancer who received surgery as their primary treatment | Retrospective cohort study/ CCO Symptom Management Database | Breast tumour | 23840 |
| Sanford NN 2019 | Participants reporting a diagnosis of cancer more than 2 years | Cross-sectional survey/ National Health Interview Survey data | Solid and hematologic tumours | 7565 |
| Tung S 2019 | Adults who were undergoing pancreatico-duodenectomy within 6 months of diagnosis | Prospective cohort study/Administrative health care data | Pancreatic tumour | 615 |
| Gallaway MS 2020 | People who received a diagnosis of cancer | Cross-sectional survey/Behavioral Risk Factor Surveillance System telephone survey | Solid and hematologic tumours | 12019 |

| AUTHOR/YEAR | DEFINITION OF SURVIVORS | STUDY DESIGN/ EVALUATION METHOD | TUMOUR TYPE | N° PATIENTS |
|---|---|---|---|---|
| Bjerkeset E 2020 | Patients who have lived beyond 2–5 or 10 years from diagnosis, without recurrence | Cross sectional study/ Postal survey | Breast tumour | 834 |
| Gjeilo KH 2020 | Patients after surgery(1-12 months) for a non metastatic cancer | Prospective study/ Postal survey | Lung tumour | 264 |
| Farrukh N 2020 | Patients undergoing blood or marrow transplantation at an age $\geq$ 60 years, surviving at least 2 years after transplantation | Retrospective cohort study/ Interview survey data | Hematologic tumours | 736 |
| Mandelblatt JS 2020 | Patients aged $\geq$60 years, with newly diagnosed non-metastatic cancer | Longitudinal study; report on 36-month data/ Face to face interviews | Breast tumour | 362 |
| Cox-Martin E 2020 | Participants with a history of cancer who indicated that they completed treatment | Cross-sectional study/ Behavioral Risk Factor Surveillance System telephone data | Solid and hematologic tumours | 1702 |
| Manfuku M 2019 | Participants underwent surgery at least 6 months before and completed cancer treatments at least 3 months before | Cross-sectional study/Face to face interview | Breast tumour | 93 |
| Tan SY 2019 | Adult cancers who have completed potentially curative primary treatment that includes chemotherapy, with no evidence of disease recurrence | Longitudinal study/ Postal survey | Solid and hematologic tumours | 385 |
| Bao T 2018 | Patients with a history of stage I to III hormone receptor-positive breast cancer who had taken or were currently taking an AI. | Cross-sectional survey/ Face to face interview | Breast tumour | 1280 |
| Cramer JD 2018 | Patients living 1 year after diagnosis | Retrospective cohort study/ Face to face interview | Head&Neck tumours | 175 |

| AUTHOR/YEAR | DEFINITION OF SURVIVORS | STUDY DESIGN/ EVALUATION METHOD | TUMOUR TYPE | N° PATIENTS |
|---|---|---|---|---|
| Hamood R 2018 | Female at least one-year after diagnosis who were treated for early-stage or regionally advanced invasive cancer | Cross-sectional survey/ Telephone interviews | Breast tumour | 410 |
| Drury A 2017 | Adult who were between six months and five years post-diagnosis | Cross-sectional quantitative study/ Face to face interview | Colorectal tumour | 252 |
| Edmond SN 2017 | Women at their first post-surgical surveillance mammogram (6-15 months post-surgery) | Cross-sectional study/ Face to face interview | Breast tumour | 200 |

Table 7. Pain prevalence in studies on survivors

| AUTHOR/YEAR | N° PATIENTS | % PATIENTS WITH PAIN | % MODERATE-SEVERE PAIN | FACTORS/RISKS ASSOCIATED WITH CHRONIC PAIN |
|---|---|---|---|---|
| Schou Bredal I 2014 | 832 | 41% | moderate=51% severe=8% | younger age, axillary lymph node dissection, other illness, depression, anxiety |
| Moye J 2014 | 170 | 50% | 32.4% | younger age |
| Huang IC 2017 | 604 | 73.47% (71.87% recent survivors) (74.56% long term survivors) | // | decrease in physical health-related quality of life, cognitive disturbance, fatigue, depressive symptoms |
| Terkawi AS 2017 | 102 | 30% | // | female, surgery, older age, advanced stage, radiotherapy |

| AUTHOR/YEAR | N° PATIENTS | % PATIENTS WITH PAIN | % MODERATE-SEVERE PAIN | FACTORS/RISKS ASSOCIATED WITH CHRONIC PAIN |
|---|---|---|---|---|
| Davis LE 2018 | 23840 | // | moderate=35.5% severe=13.2% | higher comorbidity score, advanced stage, younger age, urban residence, treatment course |
| Sanford NN 2019 | 7565 | 30.8% | // | female, current or former smoker, no moderate physical activity |
| Tung S 2019 | 615 | // | 44.9% | female, younger age, comorbidity, lower income |
| Gallaway MS 2020 | 12019 | 9.5% | 20.1% | fair or poor general health |
| Bjerkeset E 2020 | 834 | 41% | // | genetic, immunological and/or hormonal factors |
| Gjeilo KH 2020 | 264 | 40% before 69% (1mo) 55% (12 mo) | 20% 40% 35% | perioperative use of pain and psychotropic medicine |
| Farrukh N 2020 | 736 | 39.4% | // | less education,lower incomes, active chronic graft-versus-host disease |
| Mandelblatt JS 2020 | 362 | 65% | // | chemotherapy |
| Cox-Martin E 2020 | 1702 | 17% **95% CI 13.94-19.58%** | // | female, white non hispanic, non-employed, breast cancer |
| Manfuku M 2019 | 93 | 45% | // | axillary lymph node dissection, chemotherapy |
| Tan SY 2019 | 385 | // | 34% | overweight, no aerobic exercise |

| AUTHOR/YEAR | N° PATIENTS | % PATIENTS WITH PAIN | % MODERATE-SEVERE PAIN | FACTORS/RISKS ASSOCIATED WITH CHRONIC PAIN |
|---|---|---|---|---|
| Bao T 2018 | 1280 | 34% | // | younger age, body mass index>25, chronic pain before diagnosis, < 5 years since diagnosis, less than 3 years of duration on an aromatase inhibitor |
| Cramer JD 2018 | 175 | 45.1% | severe=11.2% | surgery, adjuvant chemoradiation |
| Hamood R 2018 | 410 | 74.4% | moderate=62% | younger age, mastectomy, radiotherapy, regionally advanced disease, recency of breast cancer |
| Drury A 2017 | 252 | 36% **95% CI 30-42%** | // | female, younger age, current chemotherapy treatment, previous radiotherapy treatment. |
| Edmond SN 2017 | 200 | 46.5% | 28.5% | // |

Table 8 shows how different combinations of the three classification were used. Time since diagnosis was used alone in 5 studies and in combination with another criterion in 8 of the studies. All three criteria were present in only one study on patients post bone marrow transplantation (Farrukh et al 2020) but no evidence of disease together with another criterion was uses in 7 studies.

In three studies (Moye et al 2014, Huang et al 2017, Gallaway 2020) no specification was used to limit the population of survivors and the broader definition consistent with the one offered by the National Cancer institute of the USA was used: „an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life". In one study (Drury et al 2017) althought they also used this definition a limitation was introduced to exclude patients on primary anticancer treatment, more specific limitations were used in several studies as described below.

## Table 8. Use of different criteria for survivorship definition

| AUTHOR/YEAR | A<br>Time since diagnosis (months mths , years ys) | B<br>No evidence of disease | C<br>Not undergoing concurrent antineoplastic therapy | PAIN PREVALENCE |
|---|---|---|---|---|
| Schou Bredal I 2014 | A (3 ys) | - | - | 41% |
| Moye J 2014 | - | - | - | 50% |
| Drury A 2017 | A (6 mths – 5 ys) | - | - | 36% |
| Edmond SN 2017 | A (6 – 15 mths) | B | - | 46.5% |
| Bao T 2018 | - | B | C | 34% |
| Cramer JD 2018 | A (1 ys) | - | - | 45.1% |
| Hamood R 2018 | A (1 ys or more) | - | - | 74.4% |
| Huang IC 2017 | - | - | - | 73.47% |
| Terkawi AS 2017 | A (3 mths) | - | C | 30% |
| Davis LE 2018 | - | - | - | 48.7% |
| Sanford NN 2019 | A (2 ys or more) | - | - | 30.8% |
| Tung S 2019 | A (6 mths) | - | - | 44.9%(severe) |
| Manfuku M 2019 | A (6 mths after surgery and 3 mths after completing treatment) | B* | C | 45% |
| Tan SY 2019 | - | B | C | 34%(severe) |
| Gallaway MS 2020 | - | - | - | 9.5% |
| Bjerkeset E 2020 | A( 2- 5 up to 10 ys) | B | - | 41% |
| Gjeilo KH 2020 | A (1 – 12 mths) | B | - | 55% |
| Farrukh N 2020 | A ( 2 ys or more) | B | C | 39.4% |
| Mandelblatt JS 2020 | A (3 ys) | B | | 65% |
| Cox-Martin E 2020 | - | - | C | 17% |

Time from diagnoses were very different ranging from 3 months to several years; in one case time frame was set by the time of surgery (no less than 6 months before the study) and the time of last non surgical therapy (no less than 3 months before the study) (Manfuku et la 2019). Many more articles address an individual tumor anatomical site at least (12) with a prevalence of breast cancer studies (8), other included all diagnoses.Pain prevalence ranged from 9.5% (Gallaway et al 2020) to more than 70% (Huang et al 2017) in two population based studies.

**General epidemiological studies and broad definitions**

The studies using the broader definition of Cancer survivors are also not all using the same inclusion criteria to select the population of interest.

- In a convenience sample of 252 cancer survivors with  colon cancer , "regardless of their disease status" , those receiving "primary cancer treatment" were excluded and pain was reported by 36% (Drury et al 2017). Pain cause is unknown.

- A population based telephone interview survey ,on unselected cancer survivors ,with a response rate of 51.4% (total participants 1702), estimated, based on the patients' response to a single question, that cancer related pain (pain due to cancer or cancer treatment ) was present in 17% of cases (Cox- Martin 2020).

- A cancer registry based study (Moye 2014) included patients with head and neck, gastric and colon cancer and excluded only patients end-of-life or hospice care. This study used the PROMIS in a convenience cohort of 167 patients who were followed up for 18 months, in about 50% of cases pain interfered with daily activities. Pain cause is unknown

- An epidemiological study (Huang et al 2017) based on the National Health Interview study by the US Center for disease control and prevention on quality of life, showed that cancer survivors have an odds ratio of more than 2 (95% CI = 1.71 – 2.64) of experiencing pain than the non cancer population with a prevalence of 73% versus 56%

- Another subsequent article (Sandford et al 209) based also on the National Health Interview study, but which included patients only 2 years passed a cancer diagnosis confirmed that cancer survivors had an increased risk of chronic pain with a prevalence of 30.8% versus 15.7% with the diagnosis of sarcoma associated with the higher odds of chronic pain

- In a population representative telephone interview study (Behavioral Risck factors Surveillance System) (Gallaway et al 2020), the prevalence of current pain due to cancer or cancer treatment was estimated, based on a single telephone question, equal to 9.5% over 12019 interviews.

-  A consecutive sample of patients (410) attending a survivorship clinic in Sydney (Australia) reported pain in 34% of cases (Tan et al 2019).

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- Symptoms longitudinal monitoring from the Cancer Care Ontario Symptom Management Reporting and the Ontario Cancer Registry Databases, were used to describe the course of symptoms over 12 months after pacreaticoduodenoctomy for pancreatic adenocarcinoma (Tung et al 2019). Over the 704 eligible patients one symptom assessment over 12 months was available in 87% . Pain of at least moderate severity was reported in more than 40% of patients, at least once, and around 20% of patients reported pain >/= 4/10 in all monthly assessments, across 12 month study period.

## **Clinical studies**

Clinically oriented studies investigated specific patients populations

Breast cancer

- Eight studies focused on chronic pain in patients after surgery for breast cancer ; in the study by Schou Bredal et al 2014) chronic pain was found in 41 % , with moderate to severe intensity in almost 60% and associated with neuropathic symptoms in 60% of them. Pain was more frequent when axillary dissection was performed.

- In the study by Bao et al (2018) 34% of women who had taken or were taking aromatase inhibitors had pain, 25% had new chronic pain (13% had chronic pain also before surgery). In this group 60% could have AI arthralgias, 30% had pain at the site of surgery 40% had symptoms consistent with peripheral neuropathy and 20% with lymphedema. Of the patients with pain 13% had taken opioid medication in the week before the survey.

- In another study (Edmond 2017) breast pain was found in 46% of patients but with a low mean intensity (1.63 over 10 numerical scale) while 28.5% of patients had significant breast pain. An higher prevalence of pain is reported in the study by Hamood (2018) (74% ) with 60% of these cases reporting allodynia at telephone interviews. This unusually high pain prevalence is due to the method for defining chronic pain, if chronic pain definition would be limited to pain in the surgery area and ipsilateral arm present at least 4 days a week with intensity of 3 over 10 prevalence would drop to 13%.

- In the remaining breast studies the impact of pain and its potential causes is not clarified more than generically (Davis et al 2018, Mandelblatt 2020, Bjerkeset 2020). In one small study Manfuku (2019) looked at a very specific subjective features, such central sensitization , predisposing to chronic pain without details on type of pain found.

- In patients with head and neck cancers Cramer et al (2018)administered pain and quality of life questionnaires to 175 patients based on the National Cancer Institute definition of survivors, but living at least 1 year after diagnosis attending a survivorship clinic appointment, 45% reported pain. Severe pain was found in 11.5% of cases, more than 20% were taking pain medications and 2% had pain not controlled by medication. The cause of pain is not reported. Terkawi and colleagues (2017) published a convenience sample (102) of patients who had completed since at least 3 months surgery, radiotherapy and chemotherapy, for all diagnoses of head and neck cancers. Thirty per cent had pain which was more frequent after surgery and in the patients who already had pain at cancer presentation.

- A prospective cohort study (Gjeilo et al 2020) of patients operated for lung cancer used a postal questionnaire on pain i at 1, 5, 9 and 12 months after surgery. Over 307 patients included 194 returned the completed questionnaire. Forty percent of patients had pain before surgery and 69% had pain after 1 months. This percentage decreased to 55% across follow up until 12 months later. Pain location and vulnerability factors are discussed but pain cause remains unknown.

- A retrospective hospital cohort of 735 patients with more than 60 years of age , surviving at least 2 years after blood marrow transplantation was studied by an ad hoc questionnaire and 63% completed it. Siblings were used as a control group . Patients reported pain in about 40% of cases versus 21% of siblings. Pain risk was associated with suffering GVH disease and with increased use of opioids (6%) in comparison with siblings (Farrukh 2020).


**European Association for Palliative Care Open workshop**


At the XI World research conference of the European Association for Palliative Care iPAAC workpackage 8 sponsored the open workshop on "Pain Control and Palliative Care Integration from iPAAC workpaackge on Challeges in Cancer Care„ The workshop presented the evidences and recommendations from the workpackage members on use of PROMs and their implementation in cancer care, pain prevalence and priorities in advanced cancer and survivorship care. The European Cancer Patient Coalition presented a patients' point of view of priorities about end-of-life care. The presentation were discussed by a panel composed of the president of European Association for Palliative Care (EAPC), the chair of the International Association for the Study of Pain, Special Interest Group on Cancer Pain (IASP) and the chair of the Organization of European Cancer Institutes (OECI) Working group on supportive and palliative care. The discussion was moderated by the chair of iPAAC workpackage 8 and by the responsible of iPAAC WP8 task 5 and 6 on pain and palliative care. The participants in this meeting shared the priorities summarized in this report as well as those included in the report on palliative care integration.

# 4 Discussion

The aim of this review was to estimate the prevalence of pain in cancer patients, starting from and updating the review by van den Beuken-van Everdingen published in 2016, focus on pain in cancer survivors and recommend practical steps to improve pain assessment , and management across the continuum of cancer care, in patients during anticancer treatment, in palliative care of uncurable diseases and in cancer survivors after completing treatment.

Pain due to cancer during cancer treatment and during palliative and end-of-life care

Our review confirmed that  the  estimate prevalence of pain in advanced cancer ranges from 60 to 70% and suggest that in some cases pain is severe at the end of life and not well controlled. Prevalence data are also high (46–65%) across disease and treatment stages although more strongly associated with advanced cancer. Pain and symptom assessment still suffers of diversity in methods of collection and registration in clinical records therefore not always clinical and epidemiological data can provide a robust base of evidence for targeted interventions. Registry based and database linked studies can offer some broad real world data using patients interviews or posted questionnaires (Gallaway et al 2020, Huang et al 2017, Hagarty 2020).

The only example of a prospective implementation of symptom screening using PROMs is the Symptom Assessment Database of the province of Ontario in Canada (Seow H et al 2011) as a tool for monitoring the general cancer population attending a cancer center network . This experience proves that pain can be monitored as an indicator of quality of care and to highlight clinical needs during the cancer experience until death  (Hammad et al 2019).

The history of pain in pancreatic carcinoma as illustrated by Canadian researchers from Ontario is one example (Tung et al 2019, Tung et al 2019, Hammad et al 2019) showing that pain is highly prevalent in this population , it is associated with advanced disease and survival, opioids are the first line of treatment and specialized palliative care is very often involved in pain management.  Looking at clinical outcomes the Authors conclude that the role of palliative radiation therapy and nerve blocks in this population for pain control lacks of homogenous clinical guidelines.

The available evidence suggest that, on one side, clinical routine implementation of pain measures and outcomes is a priority and that, on the other side, accurate clinical assessment of specific pain conditions associated with cancer and its treatment is necessary both at the clinical and research level to identify effective, innovative intervention or to guarantee equitable access to services to patients in need of them.

The generic administration of quality of life questionnaire, though giving useful information, (Eichler et al 2020) cannot be used to understand the patient's pain problem.

## Guidelines for the management of pain due to advanced cancer

Guidelines on the management of pain due to advanced cancer dates back to the World Health Organization (WHO) pain three-step analgesic ladder (WHO 1986)This simple, straightforward treatment algorithm was presented is still relevant. The use of the WHO pain ladder has been shown to result in adequate pain relief in the majority of patients.

A systematic review on pain relief based on the WHO ladder, twenty years after its introduction, demonstrated adequate pain relief in 45% -100% of patients (Azevedo São Leão Ferreira K 2006). However, the evidence provided by the included studies was considered insufficient to grant the effectiveness of the WHO guidelines. Nevertheless, one-third of the patients still did not receive pain medication proportional to their pain intensity levels. Current curative treatment, non advanced disease, the presence of comorbidities, a better performance status, and belonging to a minority group were associated with undertreatment.The publication and dissemination of WHO guidelines have stimulated many scientific societies and associations (for example EAPC, ESMO, ASCO, NCCN) to produce their own guidelines on the management of cancer pain. Not all guidelines are evidence-based and in some the sequential WHO analgesic ladder or the usefulness of step II opioids have been questioned.

A recent scoping review by Chapman et al. examined the evidence supporting the use of guideline-recommended interventions in pain management practice. The authors concluded that interventions commonly recommended by guidelines are not always supported by a robust evidence base and that efficacy still needs to be carefully evaluated in cancer pain diagnoses and therapeutic indications of non-steroidal anti-inflammatory drugs, anti-convulsants, anti-depressants, corticosteroids, some invasive anaesthetic techniques, complementary therapies and transcutaneous electrical nerve stimulation.

There is urgent need for independent research studies, which should be designed and funded to upgrade the level of evidence and the grades of recommendations.

The implementation and sharing of evidence-based knowledge on the use of opioids in cancer pain management may be a pragmatic and effective way to prevent the opioid misuse and abuse among patients.

## Barriers to advanced cancer pain management

A review by Oldenmenger and colleagues (Oldenmenger 2009) aimed at identifying the major barriers hindering adequate pain management and reviewed interventions aiming at overcoming them. The most frequently mentioned barriers for both patients and professionals were knowledge deficits, inadequate pain assessment and misconceptions regarding pain.

Different types of barriers are recognized:

-Patient-related barriers. The most significant patient-related barriers are patient reluctance to report pain and adhere to treatment recommendations.

Findings of all these studies have shown that there were three types of patients' cognitive barriers to cancer pain management: concerns about analgesic use (fear of addiction, tolerance, and side effects), concerns about pain communication (willingness to tolerate pain, to be "a good patient", and prioritizing that physicians cure cancer instead of relieving pain), and maladaptive beliefs about possibility to control pain in general (belief that pain related to cancer is inevitable).

-Physician-related barriers. Health professionals are cautious when prescribing opioids because of fear of adverse effects, tolerance, and addiction. Moreover, they may consider pain in specific patients as a result of emotional distress for which pain killers are not a solution

According to the WHO standards, the first choice for moderate-to-severe cancer pain should be strong opioids, administered orally on an around-the-clock basis and by long-acting formulations. Rescue medications for breakthrough pain as well as medications to counteract the most common opioid side effects (e.g., constipation, nausea, sedation) should be prescribed concomitantly. The opioid dose should be continuously adjusted based on the patient's individual reactions in terms of pain relief and severity of side effects.

In the majority of surveys (Jacobsen R 2009) on the adequacy of opioid prescription to cancer pain, physicians' general knowledge about the principles of cancer pain management varied a lot: from 25-30% to almost 100% of physicians reporting knowledge of WHO recommendations, but no more than 50% of them prescribed opioid analgesics for moderate-to-severe cancer pain and the percentage of respondents reporting adequate prescription of rescue medications was much lower. Results regarding management of side effects of opioids were even worse: only 30% or less of physicians reported routinely prescribing laxatives and antiemetics.

Inadequate pain assessment was reported as one of the main barriers to cancer pain management by 20-80% of respondents (Jacobsen R 2009). The majority of physicians did not evaluate the types of pain and did not use instruments to measure pain intensity.

-Institutional barriers. In many countries, institutional barriers cover health care system-related barriers, such as complicated bureaucratic regulations governing the supply, regulations of prescription and administration of opioids. Lack of mandatory pain assessment in clinical records

Pain in cancer survivors

In the introduction we described how the cancer survivor population can identify different patients groups according to the definition adopted. Our review confirms that this can be a problem also in evaluating the evidences from the scientific literature.

As a summary comment it seems unlikely that the broadest definitions of survivorship can be useful from a clinical and clinical research point of view (Gallaway et al 2020). On the opposite it would be very useful to recognize and address the needs of patients who are free of cancer disease , for defined periods of time , undergoing or not cancer treatments. It il likely that specific cancer diagnoses should receive specific attention to offer useful information given the totally different cancer survivoship experiences associated with different disease characteristics and therapeutic approaches (Tung 2019, Eichler 2020, Gjelo 2020, Schou Bredal 2014).

As in the case of pain due to cancer the lack of clinically defined pain syndrome diagnoses (Caraceni and Portenoy 1999, Shkodra et al 2020) in many studies contributes to the poor understanding of the epidemiology of pain and pain related clinical needs The trend of pain prevalence and intensity in women operated for breast cancer (Davis et al 2018) gives important general information but does not allow to understand how many of them have pain due to arthritis, aromatase inhibitors induced arthralgias of postsurical neuropathic pain. Clinical data about these diagnoses (Schou Bredal etal 2014) is still insufficient for many cancer survivors.

Also from an health policy point of view the use of the broad survivorship definition can missdefined patients needs and the focus on precise therapeutic and health service interventions. In fact by including all cancer patients diagnosed with cancer at any stage in the surivorship definition as in the sentence: „An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life" it is possible to classify in the same group a patient who had a breast malignant nodule and is her 12th year since diagnoses, together with a patient with unresectable pancreatic carcinoma in his or her last 6 months of life.

It is also debatable how this health care political decision relates to the patients' understanding and accceptance of this term. A qualitative article by Khan and collegues (2012) found that more patients did not endorse this terminology and concluded that researchers and policy makers should consider avoiding the term 'cancer survivor' in favour of descriptive terms when discussing this population.

Ethical and psycological consideration about stigmatizing language should also be carefully regarded, in fact a beneficial positive meaning for one group may be damaging in a more global sense. In light of the connotations of survival as an accomplishment and/or psychological progress, some have rejected the implication that the term survivor is a title earned for surviving the battle with cancer (Bell K et al 2013). As Ehrenreich notes, "once the

treatments are over, one achieves the status of 'survivor'. Did we who live 'fight' harder than those who've died? Can we claim to be "braver,' better, people than the dead?"

At the same time a growing number of people are living with incurable but controlled disease and will die in longer or shorter periods of time. They will not beat cancer, but are living for increasingly longer periods with the malignancy. These issues suggest that the current focus on the survivorship phase,may serve to clarify certain feature of the cancer experience at the expense of others (Bell K et al 2013).

Using the term cancer survivor in a constructive way requires that generalization is avoided and specific features of survivoships considered (table 8). Pain is certainly to be better studied in this population as we show that it can complicate the course of surivorship from (30% to more than 70%). Interestingly the broader the definition the more extreme ranges in estimate are found (Hamood et al, Gallaway et al) confirming the probable role of heterogeneity in determing the range of estimates. Less variable prevalence estimates can be found ad in some cases it is possible to describe the relationship of pain with previous interventions. This wide range of prevalence rates can depend on cancer subtype, treatments received, pain metric, and time since completion of oncological therapy. The prevalence and severity of pain are expected to decrease over time, but despite tissue integrity, complete recovery is sometimes never achieved

Important research question still need to be answered to identify the impact of therapy related toxicities on chronic pain development such as neurotoxicity of chemotherapy immmune and target therapies, surgical sequelae (Gjelo et al) and complications such as neuropathic pain or lymphedema (Schou Bredal et al).

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# 5 Conclusion

Despite the progress in therapies and management pain remains one of the most frequent symptoms complained by patients.

The prevalence of pain has not substantially changed in recent decades although the attention of clinicians and patients has definitely improved. At the same time quality of research , guidelines for clinical pathways integration clinical and public health outcomes assessment require more efforts to clarify the impact of pain , its to different causes and the assosicated clinical conditions in patients with different stages of cancer

The following priorities emerged as discussed also with other stakeholders (EAPC, OECI, IASP and ECPC) , and they are shared across  other iPAAC workpackags as well as when addressing Comprehensive cancer networks (WP 10) and particular needs as in the case of pancreatic cancer clinical challenges (WP8).

- Cancer pain assessment and diagnoses of cancer pain syndromes

- Implement PROMs inlcuding pain assessment in routine cancer care

- Improve guidelines for cancer pain management based on patient centerd decision making

- Guarantee Equitable access to pain therapy and palliative care and integration between oncology and palliative care services in comprehesive cancer care networks

- Identify cancer survivors special needs without blurring individual patients needs across supportive care, survivorship care and palliative care strategies

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