Specialist palliative and end-of-life care for patients with cancer and SARS-CoV-2 infection: a European perspective

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Abstract:

Background: Specialist palliative care team (SPCT) involvement has been shown to improve symptom control and end-of-life care for patients with cancer, but little is known as to how these have been impacted by the COVID-19 pandemic. Here, we report SPCT involvement during the first wave of the pandemic and compare outcomes for patients with cancer who received and did not receive SPCT input from multiple European cancer centres.

Methods: From the OnCovid repository (*n*=1,318), we analysed cancer patients aged ≥18 diagnosed with COVID-19 between 26th February and 22nd June 2020 who had complete specialist palliative care team (SPCT) data (SPCT+ referred; SPCT- not referred).

Results: Of 555 eligible patients, 317 were male (57.1%), with a median age of 70 (IQR 20). At COVID-19 diagnosis, 44.7% were on anti-cancer therapy and 53.3% had >1 co-morbidity. 206 patients received SPCT input for symptom control (80.1%), psychological support (54.4%), and/or advance care planning (51%). SPCT+ patients had more DNACPR orders completed prior to (12.6% vs. 3.7%) and during admission (50% vs 22.1%, $P<0.001$), with more SPCT+ patients deemed suitable for treatment escalation (50% vs. 22.1%, $P<0.001$). SPCT involvement was associated with higher discharge rates from hospital for end-of-life care (9.7% vs. 0%, $P<0.001$). End-of-life anticipatory prescribing was higher in SPCT+ patients, with opioids (96.3% vs. 47.1%) and benzodiazepines (82.9% vs. 41.2%) being used frequently for symptom control.

Conclusions: SPCT referral facilitated symptom control, emergency care and discharge planning, as well as high rates of referral for psychological support than previously reported. Our study highlighted the critical need of SPCT for patients with cancer during the pandemic and should inform service planning for this population.

Background:

Since the start of the pandemic, coronavirus disease 2019 (COVID-19), the viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been linked to 740,809 deaths across Europe (as of 12th July 2021)[1], putting an unprecedented strain on international healthcare services[2].

Previous studies have shown that mortality from COVID-19 is higher for those of an older age and those with co-morbidities[3]. Since the beginning of the pandemic, the presence of cancer has been linked to an increased risk of developing severe COVID-19, with a 6.2-fold difference in mortality compared to individuals without cancer (5.6% versus 0.9%)[4]. The OnCovid study, the largest registry in Europe describing the natural history and outcomes from SARS-CoV-2 infection in patients with cancer, has shown that mortality from COVID-19 in unselected consecutive patients with cancer can be as high as 30%[5]. Although, provision of chemotherapy, targeted therapy, and immunotherapy did not worsen mortality[6]. Patients with COVID-19 often suffer from debilitating symptoms, such as fever, cough, and dyspnoea[4]. Specialist palliative care team (SPCT) support may be beneficial for patients with advanced malignancies and COVID-19 to control their symptoms as well as provide individualised end-of-life care[7]. The provision of specialist palliative and end-of-life care for patients can be challenging when services are under-resourced[7], independent of the challenges inherent during a pandemic.

Accumulating evidence shows that the early involvement of SPCT for patients with advanced cancer improves quality of life by providing specialist symptom control and support with advance care planning and end-of-life care[8]. The majority of patients with

cancer who acquire SARS-CoV-2 present with debilitating symptoms including fevers, dyspnoea and fatigue, and nearly two thirds of them rapidly evolve into life threathening disease[6], with a high proportion of respiratory failure and end organ damage sustained by the pro-inflammatory response elicited against the virus[9, 10]. Whilst a number of studies including OnCovid have extensively documented survival outcomes of patients with COVID-19 and cancer, the trajectory of decline and symptomatic burden that SARS-CoV-2-infected patients with cancer experience from the diagnosis of COVID-19 towards the end-of-life remain to be understood[4, 11] and must be fully characterised to enable effective symptom control.

In addition, whilst patients with cancer and concomitant COVID-19 may benefit from SPCT input to address their symptomatic needs[12], questions remain regarding the pandemic's impact on services and provision of palliative and end-of-life care in this patient subgroup. Whilst studies have been conducted to understand how palliative care services have rapidly responded to those who have been affected by COVID-19[13-16], such as providing education and protocols for symptom control and end-of-life care for non-specialist healthcare practitioners, leading psychological support and bereavement care services, and utilising community services, little is known with concern to their specific role in patients with cancer. The pandemic has reinforced the importance of individualised emergency care planning (i.e., treatment escalation planning and cardio-pulmonary resuscitation decisions) by forcing physicians to consider what is important to the patient weighed against the availability of resources[7, 17]. However, the translation of this practice for patients with concomitant COVID-19 and cancer is unknown. As COVID-19 continues to impose an ongoing threat to patients with cancer, it is important to develop direct knowledge of the needs of these

patients using an evidence-based approach. Here, we aim to describe the demographics of patients with cancer hospitalised with COVID-19, describe the patterns of referral to SPCTs, and compare emergency care planning and care in the last days of life among patients referred to and not referred to SPCTs. To address these aims, we evaluated the natural histories and outcomes of over 500 patients with cancer recruited to the OnCovid study.

Methods:

Study population, setting and data collection

This study focuses on a subset of patients accrued to the main OnCovid registry for whom data regarding SPCT referral was available for analysis. Methodology and clinical outcomes of the first 890 patients included in the main OnCovid study have been previously reported[6]. Briefly, main eligibility criteria for OnCovid included being ≥18 years of age, having a confirmed diagnosis of SARS-CoV-2 infection by reverse-transcriptase polymerase chain reaction (RT-PCR) of a nasopharyngeal swab, and history of solid or hematologic malignancy, either active (those receiving anti-cancer treatment) or in remission at the time of COVID-19 diagnosis. Patients with a history of non-invasive/premalignant lesions or with low malignant potential (i.e., basal cell carcinoma of the skin, non-invasive carcinoma in situ of the cervix, ductal carcinoma in situ) were excluded. For hematologic malignancies, only patients carrying an oncological diagnosis of defined malignant behavior (lymphoma, leukaemia, multiple myeloma) were included. For the purpose of the current analysis, participating investigators performed an *ad hoc* review of medical records of hospitalised patients for COVID-19 to assess whether or not referral to SPCT was made during hospitalisation. From 26th February to 22nd June 2020, 1,318 patients were

consecutively accrued to OnCovid across 24 European academic centres. Of these 1,318 patients, 555 patients (42%) who had been hospitalised for COVID-19 from 13 European academic centres had complete SPCT referral records and were included in this study **(Figure 1A, Supplementary Table 1)**. All patients were observed from the time of COVID-19 diagnosis, defined by SARS-CoV-2 PCR positivity until date of death or, in COVID-19 survivors, date of discharge from hospital or last outpatient follow-up post-discharge.

Within the UK, OnCovid was granted central ethical approval by the Health Research Authority (20/HRA/1608). Outside of the UK, this study was granted ethical approval by the corresponding ethics review boards at each participating site **(Supplementary Table 2)**. Competent authorities waived prospective informed consent due to the retrospective nature of data collection and the use of anonymised data. In order to maintain confidentiality standards, each patient enrolled into the study was assigned a unique pseudonymisation code through assignment of an identification number. Clinical data including patients' demographics, laboratory tests, and radiologic results were reviewed retrospectively by clinicians and collated into a case report form designed using the Research Electronic Data Capture (REDCap, Vanderbilt University) tool hosted by the Medical Statistics Unit in Novara, Italy[18, 19], which coordinated database access and curation.

Alongside data concerning features of COVID-19 including co-morbidities and requirement for and length of hospitalization[6], we collected timing, reason(s) for referral to the SPCT, patient outcome (discharge or place of death in the hospital setting), symptomatology, and use of anticipatory medications (classified as: opioids,

benzodiazepines, antipsychotics, antiemetics, antimuscarinics and antipyretics) in the final 72 hours of life. All medical records of cases recruited to this study were reviewed by physicians involved in delivering patients' care, with the final follow-up date for all patients being 22nd June 2020.

Study definitions

The diagnosis of COVID-19 and description of the clinical syndromes associated with the disease, including acute respiratory distress syndrome (ARDS), followed criteria published by the World Health Organisation[20]. All patients recruited to this study were confirmed positive for SARS-CoV-2 infection following RT-PCR testing of nasopharyngeal swab samples using validated methodology. Nosocomial SARS-CoV-2 contraction was defined in patients who developed symptoms and tested positive for COVID-19 whilst admitted to the hospital for other reasons. Recognising the significant heterogeneity in the referral pathways to palliative care across centres and countries, we elected to present patients who were referred to SPCT prior to COVID-19 and those who were referred at the point of COVID-19 diagnosis in a joint category (SPCT+).

Statistical analysis

Continuous data following nonparametric distribution are presented as median with interquartile range (IQR). Categorical data are described as percentages. To determine statistical significance of results, the Mann-Whitney U test was utilized for continuous data following nonparametric distribution and Fisher's exact test or the chi-squared test employed for analysis of categorical variables.

Role of the Funding Source

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Results:

Patient demographics

Of the 1,318 patients within the OnCovid database at data censoring (22nd June 2020), 555 patients had SPCT date collected and were eligible for inclusion in this study **(Figure 1A)**. Patient data was submitted by 13 centres from the United Kingdom *(n*=399, 71.8%), Spain *(n*=133, 23.9%), Belgium *(n*=19, 3.4%), and Germany *(n*=4, 0.7%, **Supplementary Table 1**). The median follow-up time was 28 days (IQR 47). Most patients were male *(n*=317, 57.1%) with a median age of 70 (IQR 20), carried a diagnosis of active malignancy *(n*=369, 66.5%), and had localised disease *(n*=229, 41.6%, **Table 1**). The commonest primary tumour sites were genitourinary *(n*=132, 23.8%), breast *(n*=83, 15%) and lung *(n*=67, 12.1%). The majority of patients had at least one co-morbidity *(n*=442, 79.6%), most commonly hypertension *(n*=273, 49.2%) and diabetes *(n*=131, 23.6%). At COVID-19 diagnosis, 248 (44.7%) patients were on systemic anti-cancer therapy, of whom 57 (10.3%) received therapy with palliative intent. 285 (51.4%) patients were not on active treatment.

In the 555 eligible patients **(Table 1)**, the most common presenting symptoms were fever *(n*=330, 59.5%) and cough *(n*=295, 53.2%). Of the 488 (87.9%) patients admitted to hospitals, ward-based care was deemed appropriate in 133 (24%) patients, whereas escalation to intensive or high-dependency care was deemed necessary in

62 (11.2%) patients. Hospitalisation lasted for a median duration of 10 days (IQR 10.5), whereas median stay in intensive or high-dependency care was 7 days (IQR 12.8). Supplemental oxygen therapy was required for 299 (53.8%) patients including high-flow delivery for 144 (25.9%) patients. Mechanical ventilation was initiated on 45 patients (8.1%), including non-invasive ventilation *(n*=33, 5.9%) and endotracheal intubation *(n*=18, 3.2%). In total, 314 (56.6%) patients received at least one form of treatment for COVID-19, most frequently broad-spectrum antibiotics *(n*=266, 47.9%), followed by hydroxychloroquine or chloroquine *(n*=115, 20.7%) and lopinavir/ritonavir *(n*=42, 7.6%). In total, 234 (42.2%) patients developed complicated COVID-19 disease, defined as the development of acute respiratory failure, acute respiratory distress syndrome (ARDS), acute kidney injury, secondary infection, sepsis, septic shock, acute cardiac injury, acute liver injury, or other conditions including disseminated intravascular coagulation.

Patterns of referral to specialist palliative care teams

Of all 555 eligible patients, 206 patients (37%) were referred to their respective SPCT during the observation time (SPCT+), whereas 349 patients (63%) were not (SPCT-, **Figure 1A**). As described in **Table 1**, the proportion of patients aged ≥65 years (SPCT+ *n*=141, 68.4%; SPCT- *n*=214, 61.3%; *P*=0.091) and those with higher co-morbid burden (i.e., ≥2 co-morbidities) were similar across groups (SPCT+ *n*=114, 55.4%; SPCT- *n*=182, 52.1%; *P*=0.46). Compared to the SPCT- cohort, SPCT+ patients were more likely to have metastatic disease at COVID-19 diagnosis (SPCT+ *n*=120, 58.3%; SPCT- *n*=79, 22.6%; *P*<0.001) and more likely to have developed a greater number of COVID-19 complications during observation (SPCT+ *n*=38, 18.4%; SPCT- *n*=42, 12%; *P*=0.037 between 0-1 vs ≥2 COVID-related complications). A

significantly larger proportion of SPCT+ patients were undergoing anticancer therapy (SPCT+ *n*=102, 49.5%; SPCT- *n*=146, 41.8%; *P*=0.008) and systemic anticancer therapy with palliative intent (SPCT+ *n*=77, 37.4%; SPCT- *n*=40, 11.5%; *P*<0.001) at COVID-19 diagnosis. Of the 206 SPCT+ patients, the majority had not previously received palliative care and were newly referred to the hospital SPCT *(n*=147, 71.4%). A smaller proportion of patients had previously received palliative care and were known to both hospital and community teams *(n*=39, 18.9%) or to community teams only *(n*=17, 8.3%). **Figure 1B** highlights most common reasons for SPCT referral, including symptom control *(n*=165, 80.1%), psychological support *(n*=112, 54.4%), and/or advance care planning (*n*=105, 51.0%).

Outcomes from COVID-19 and emergency care planning

Figure 1C depicts the outcomes of SPCT+ patients at data censoring. Of the 555 patients, 202 (36.4%) were deceased at data censoring. The median overall survival from COVID-19 diagnosis to last follow-up was 47 days (IQR 34.5). The unadjusted mortality rate of the SPCT+ group was more than double that of the SPCT- group (SPCT+ *n*=117, 56.8%; SPCT- *n*=85, 24.4%; *P*=0.008). In this study, there were 145 patients with nosocomial SARS-CoV-2 infection (SPCT+ *n*=69, 33.5%; SPCT- *n*=76, 21.8%) and 343 patients with community-acquired SARS-CoV-2 (SPCT+ *n*=134, 65%; SPCT- *n*=209, 59.9%). Patient outcome from COVID-19 infection (defined as recovery, in hospital mortality or discharge from hospital) was recorded in 518 patients (SPCT+ *n*=199, 96.6%; SPCT- *n*=319, 91.4%). In total, 355 patients were discharged home following recovery from COVID-19 (SPCT+ *n*=83, 40.3%; SPCT- *n*=272, 59%). 20 (9.7%) SPCT+ patients were discharged home for end-of-life care, whereas 115 patients died on oncology (SPCT+ *n*=23, 11.2%; SPCT- *n*=8, 2.3%) or general medical

297 wards (SPCT+ *n*=60, 29.1%; SPCT- *n*=24, 6.9%). 28 patients died in high-dependency
298 or intensive care units (SPCT+ *n*=13, 6.3%; SPCT- *n*=15, 4.3%). The median time
299 from COVID-19 diagnosis to discharge was 9 days (IQR 11), whereas the median time
300 from COVID-19 diagnosis to death amongst in-hospital decedents was 8 days (IQR
301 9). Emergency care plans, defined as written documentation of an escalation plan or
302 a do not attempt cardio-pulmonary resuscitation (DNACPR) order, were completed for
303 219 (39.5%) patients. SPCT+ patients had more DNACPR orders completed prior to
304 admission (SPCT+ *n*=26, 12.6%; SPCT- *n*=13, 3.7%) and during admission (SPCT+
305 *n*=103, 50%; SPCT- *n*=77, 22.1%; $P<0.001$; **Figure 1D**). At data censoring, of the 90
306 SPCT- patients with a DNACPR order, 51 (56.7%) had died. The median number of
307 days from completion of a DNACPR order to death was 3 days (IQR 7.5). Of the 129
308 SPCT+ patients with a DNACPR order, 99 (76.7%) had died. The median number of
309 days from completion of a DNACPR order to death was 11 days (IQR 19 days).
310
311 *Care in the final days of life*
312 For all 143 inpatients who were in-hospital decedents, complete data on end-of-life
313 care was available for 116 (SPCT+ *n*=82, 39.8%; SPCT- *n*=34, 9.7%). The distribution
314 of symptoms in the last 72 hours of life is illustrated in **Figure 2A**, with breathlessness
315 (*n*=100, 86.2%), agitation/restlessness (*n*=54, 46.6%), confusion/delirium (*n*=43,
316 37.1%), and respiratory secretions (*n*=43, 37.1%) comprising the most common
317 terminal symptoms. The median number of terminal symptoms was 3 (IQR 2), with 70
318 (60.3%) patients experiencing ≥3 symptoms in the last days of life **(Figure 2B)**.
319 Given the high burden of end-of-life symptoms, we evaluated patterns of prescription
320 of anticipatory medications. For in-hospital decedents, opioids were most commonly
321 prescribed for pain and breathlessness (SPCT+ *n*=79, 96.3%; SPCT- *n*=16, 47.1%),

followed by benzodiazepines or antipsychotics for agitation (SPCT+ *n*=68, 82.9%; SPCT- *n*=14, 41.2%). Ninety patients were simultaneously prescribed more than 1 class of symptomatic medication (SPCT+ *n*=77, 93.9%; SPCT- *n*=13, 38.2%; median number of classes: SPCT+ 3; SPCT- 0). The vast majority of patients prescribed anticipatory medications were in the SPCT+ cohort **(Figure 2C)**. Of in-hospital decedents with complete end-of-life care data (*n*=116), continuous subcutaneous infusions (CSCI) were prescribed for 25 patients (SPCT+ *n*=24, 29.3%; SPCT- *n*=1, 2.9%). Opioids comprised the most common class of symptomatic therapy delivered via CSCI (SPCT+ *n*=22, 26.8%; SPCT- *n*=1, 2.9%), followed by benzodiazepines or antipsychotics (SPCT+ *n*=17, 20.7%; SPCT- *n*=1, 2.9%). **Figure 2D** illustrates the distribution of CSCI therapies across SPCT groups.

Discussion:

Whilst increasing research efforts have been dedicated to understanding the impact of COVID-19 in the natural history of patients with cancer[6], this is the first observational study investigating specialist palliative care outcomes in this patient population, where guidance on clinical management rests on expert opinions rather than direct evidence[12]. This is particularly important when considering the potentially increased reliance on hospital-based services in providing psychosocial and supportive care given the closure and limited availability of third-sector face-to-face services through the pandemic[21]. In recent years, palliative medicine has progressively shifted from a specialty providing care to patients with advanced cancers who do not qualify for active anti-cancer therapy[22], or those who are dying[23], to a supportive-care service devoted to optimising quality of life alongside active anti-cancer treatment[24]. However, the relative contribution of palliative care in the context of a highly lethal and often rapidly

fatal diagnosis such as COVID-19 has remained relatively unaddressed in patients with cancer[25].

In this purposely designed sub-study, including 42% of the patients recruited to the OnCovid repository, provision of palliative care by specialised teams was sought in 37% of the accrued patients. Throughout the observation period, patients with active malignancy, metastatic disease, higher tumour burden, and higher proportion of COVID-19-related complications were more likely to have received SPCT input, which, in over 70% of the cases, was provided for the first time during inpatient admission. Interestingly, half of the SPCT+ patients were on active anti-cancer therapy at COVID-19 diagnosis. This suggests that a high proportion of patients possessed a good performance status prior to SARS-CoV-2 infection and highlights the impact of COVID-19 as a dominant driver of the acute clinical and symptomatic deterioration leading to instigate palliative care support. Based on our data, symptom control (i.e., breathlessness) was in fact the predominant reason for SPCT referral in over 80% of our patients, most of whom suffered from a multitude of symptoms as a likely consequence of higher tumour burden and higher complication rates from COVID-19.

The second leading cause instigating SPCT review was psychological support. This is a particularly interesting finding given that previous studies demonstrate SPCT referral for emotional and psychological support to be much less frequently cited reasons for referral: previous literature from Japan[26] and Australia[27] identified much lower referral rates for emotional issues (22% and $<$40% respectively) than those found in our analysis (54.4%). It is possible that the increase observed during the pandemic is related to the fact that many of these patients with cancer are being cared

for outside of oncology and palliative wards and thus healthcare staff in these different settings may feel less prepared to deal directly with the emotional and psychological issues at end-of-life compared to the specialist oncology workforce. Furthermore, anxiety has been shown to be prevalent amongst hospitalised patients due to isolation from families and fear of deterioration[28].

It is important also to be cognisant that a paramount component of the ethos of SPCT is to provide psychological support not only to the patient but also to their families and loved ones[22]. In the case of cancer, patients' families may be expecting this support towards end-of-life. Where COVID-19 infection has prompted an unexpectedly rapid health decline, that usual level of psychosocial and emotional support for family members may be difficult—if not impossible—to access. SPCTs will be more aware of this and, perhaps, more able to provide a heightened level of support for these patients' families.

An important aim of our research was to describe emergency care planning in patients with cancer in the context of a COVID-19 diagnosis, a theme of high clinical interest given the unprecedented strain on healthcare systems imposed by rapidly diffusing infection with heightened strain on intensive care capacity at the peak of the SARS-CoV-2 pandemic, posing difficult ethical issues of health care rationing[17]. Clear documentation of a designated treatment escalation plan is of utmost importance in patients with cancer as it prevents distressing or unnecessary investigations that are inappropriate in patients with limited life expectancy, whilst on the other hand recognises circumstances where aggressive medical treatment and end-organ support is warranted where chances of recovery are reasonable[29, 30]. SPCTs have

been shown to help facilitate and lead this decision-making process especially when patients are being primarily cared for by generalist staff[31].

Careful review of patients' records revealed that >90% of SPCT+ patients had documented evidence of an escalation plan compared to approximately 40% of SPCT- patients. Whilst it may be argued that the higher frailty of the SPCT+ subgroup might have favoured clinicians' increased engagement in DNACPR discussions with SPCTs, our data surprisingly demonstrate that almost a third of SPCT+ patients were deemed appropriate for CPR during admission. Whilst it should be remembered that our study is a retrospective account of routine clinical practice during the COVID-19 pandemic, we believe this to be a clinically important finding as it suggests that SPCT input in the context of the multi-disciplinary team is not only essential to prevent futile interventions in clinical care but also to support clinical decision making and address the needs of patients whose clinical deterioration is deemed reversible.

In cases where SPCT support was sought, we noted a significantly longer interval between DNACPR order completion and death compared to patients with no documented SPCT input, highlighting that SPCT involvement may facilitate earlier end-of-life care discussions and planning, avoiding treatment escalation decisions in the final days of life, a time in which involvement of patients and relatives becomes increasingly difficult and potentially distressing[32].

A further aim of our study was to describe patterns of deterioration and symptomatic burden in patients who succumbed to COVID-19. Interestingly, our study shows that the vast majority of in-hospital deaths occurred in clinical areas not specifically

dedicated to the care of oncology patients (i.e., emergency areas, medical wards, intensive care, COVID-19 isolation wards). This is an important finding giving that preferred place of death for patients with cancer is usually either a specialist palliative care (hospice) setting[33] or at home[34], and that those patients with cancer who die in hospital or intensive care units typically experience greater emotional distress and poorer quality of end-of-life[35]. Death in a hospital setting is likely appropriate where symptom burden is higher, and the increase of deaths in the hospital setting during the first wave[36] is known to have negatively impacted caregiver bereavement outcomes when compared to death at home[37]. This is especially relevant in the case of COVID-19 related deaths where access to SPCT for families may be reduced more than usual.

In addition, symptom burden in the last days of life was prevalent, with breathlessness and agitation being the most prevalent symptoms in the final hours of life, reflecting the symptoms experienced by a non-selected population of patients dying with COVID-19[38]. The majority of in-hospital decedents displayed multiple symptoms, highlighting the complex symptomatic needs of this patient population. Consequently, most patients required more than one therapeutic class of symptomatic agent including opioids to reduce breathlessness and pain and benzodiazepines or neuroleptics to address terminal restlessness. Generalist medical staff may lack confidence in the prescription of anticipatory end-of-life medications, and the support of SPCTs can ensure adequate higher dose prescriptions to meet patients' symptomatic needs[39]. Taken together, these findings further reinforce that the involvement of SPCT is crucial in patients with cancer who have a high symptomatic burden, as this allows (i) adequate recognition of deteriorating patients, (ii) judicious

447 and effective anticipatory prescribing, and (iii) better management of psychosocial
448 concerns leading to improved quality of life and affective state[24, 40, 41]. Our study is
449 consistent with previous knowledge in this field as it highlights more prevalent use of
450 pharmacologic symptomatic care in patients with access to SPCT input[42]. This is
451 particularly true when we consider prescription of CSCI, a safe and effective drug
452 administration route that can optimise symptom control in patients who cannot tolerate
453 oral medications. Perhaps unsurprisingly, prescription of CSCI was significantly higher
454 in the SPCT+ cohort in our study.
455
456 OnCovid and other studies have shown that the mortality from SARS-CoV-2 can be
457 as high as 30% in patients with cancer[5, 43]. Meeting preferred place of end-of-life care
458 can be challenging in a pandemic due to risk of transmission and an unpredictable
459 course of patient deterioration. Here, we show that planning of domiciliary end-of-life
460 care was possible in 10% of patients, all of whom had received input from SPCT.
461 Whilst challenging, planning end-of-life care outside of hospital is deliverable, clinically
462 appropriate in a subset of patients with concomitant SARS-CoV-2 infection and
463 cancer, and supports patient and family preferences for care delivery.
464
465 It is important to acknowledge a number of limitations to our study. OnCovid is a
466 retrospective study and appraisal of the sources of patient data shows a clear
467 imbalance of SPCT data, where four centres (one in Spain and 3 in UK) contributed
468 to >75% of the patients. SPCT referral data in this study were in fact mainly collected
469 from tertiary cancer centres in London, United Kingdom, and Barcelona, Spain. Not all
470 the centres involved in the OnCovid study group had the capacity to input SPCT data.
471 This could limit the generalisation of our findings and reflect improved access to SPCT

services in these cities. The majority of patients enrolled in this sub-study were from the UK, which is known for its high standards in end-of-life care, with comprehensive national policies and a strong hospice movement[44]. Therefore, the practices described in this investigation may disproportionately reflect practice within the UK than other European countries. In addition, the provision of symptomatic care and SPCT capacity may be different across these countries. Furthermore, the data presented focus on patients managed within large tertiary hospitals, and there may be valuable lessons to be learnt from the challenges faced in SPCT provision in smaller centres and in the community setting[45].

The aim of this study was not to prospectively assess patient characteristics leading to referral to SPCT and subsequently compared outcomes. This retrospective analysis is a description of referral patterns to SPCT. The key part of our analysis was to attempt and describe reasons for referral and symptomatic needs of patients so that clinical services can subsequently capitalise on this data in the context of an unresolved pandemic. Sufficiently powered prospective studies may help understand any statistical significance differences between the outcomes for patients referred to SPCT and those who were not. Furthermore, prospective studies may facilitate better understanding of the decision-making processes clinicians make when referring patients to SPCTs.

In conclusion, this study describes the challenges of implementing SPCT in patients with COVID-19 and cancer and highlights the value of SPCT involvement in the management of patients with cancer and COVID-19. We found that patients accessing SPCT support often have a higher number of co-morbidities, higher tumour burden,

497 and complex clinical needs. We have shown that the multifaceted role of SPCTs
498 extends beyond symptom control as it frequently embraces broader roles including
499 assistance with complex clinical decision making, discharge planning, end-of-life care,
500 and psychological support. We found SPCT referral for psychological concerns to be
501 at a higher rate than elsewhere reported, raising important questions about the
502 availability of adequate psychosocial support for patients and their families. End-of-life
503 was characterised by high symptomatic burden, suggesting the need for specialist
504 oversight of pharmacological and non-pharmacological interventions to best support
505 deteriorating patients. Therefore, integration of SPCTs in the management of patients
506 with cancer and COVID-19 is necessary to provide equitable, specialist care for this
507 vulnerable population.
508

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Figure Legends:

Figure 1: Patient disposition, referral, outcomes, and emergency care planning. (A.) Study design and patient assortment. **(B.)** Causes for specialist palliative care team (SPCT) involvement (*n*=206). **(C.)** Outcomes for all eligible patients (*n*=555). **(D.)** Emergency care planning for patients in the SPCT+ (*n*=206) and SPCT- (*n*=349) cohorts.
SPCT: Specialist palliative care team; EOLC: End-of-life care; HDU: High-dependency unit; ICU: Intensive care unit; DNACPR: Do not attempt cardio-pulmonary resuscitation; CPR: Cardio-pulmonary resuscitation

Figure 2: Patient end-of-life symptoms and prescriptions. (A.) Symptoms in last 72 hours of life for all eligible patients (*n*=116). **(B.)** End-of-life (EOL) symptom burdens (*n*=116). **(C.)** EOL prescriptions for SPCT+ (*n*=82) and SPCT- (*n*=34) cohorts. **(D.)** CSCI prescriptions for SPCT+ (*n*=82) and SPCT- (*n*=34) cohorts.
EOL: End-of-life; CSCI: Continuous subcutaneous infusion; SPCT: Specialist palliative care team

749 **Table:**

750

751 **Table 1: Demographic data of patients with SARS-CoV-2 infection and SPCT**

752 **referral data.**

	SPCT+ n=206	SPCT- n=349	Total n=555
Age (years), median (IQR)	71 (18.75)	68 (20)	70 (20)
Age			
<65 years, no. (%)	65 (31.6)	135 (38.7)	355 (64.0)
≥65 years, no. (%)	141 (68.4)	214 (61.3)	200 (36.0)
Sex, no. (%)			
Male	99 (48.1)	218 (62.5)	317 (57.1)
Female	106 (51.5)	129 (37)	235 (42.3)
Information unavailable	1 (0.5)	2 (0.6)	3 (0.5)
Smoking history, no. (%)			
Never smoker	93 (45.1)	157 (45)	250 (45)
Current/ former smoker	89 (43.2)	138 (39.5)	259 (46.7)
Unknown	22 (10.7)	49 (14)	46 (8.3)
Cancer type, no. (%)			
Head & neck	6 (2.9)	11 (3.2)	17 (3.1)
Lung & thoracic	11 (3.2)	31 (8.9)	42 (7.6)
Gastroesophageal	13 (6.3)	10 (2.9)	23 (4.1)
Hepatobiliary	8 (3.9)	10 (2.9)	18 (3)
Duodenal & lower GI tract	25 (12.1)	38 (10.9)	63 (11.4)
Breast	34 (16.5)	49 (14.1)	83 (15.0)
Gynecological	16 (4.6)	23 (11.2)	39 (7.0)
Genitourinary	38 (18.4)	94 (26.9)	132 (23.8)
Skin	8 (3.9)	18 (5.2)	26 (4.7)

Lymphoma	3 (1.5)	24 (6.9)	27 (4.9)
Other	9 (4.4)	55 (15.8)	64 (11.5)
Tumor stage, no. (%)			
Localized	52 (25.2)	177 (50.7)	229 (41.6)
Locoregional	29 (14.1)	59 (16.9)	88 (15.8)
Metastatic	120 (58.3)	79 (22.6)	199 (35.9)
Number of metastatic sites			
0	72 (35)	236 (67.6)	308 (55.5)
1	3 (1.5)	4 (1.1)	7 (1.26)
2	57 (27.7)	41 (11.7)	98 (17.66)
≥3	65 (31.6)	38 (10.9)	103 (18.56)
Unknown	9 (4.4)	30 (8.6)	39 (7.03)
Tumor status at COVID-19 diagnosis, no. (%)			
Active malignancy	161 (78.2)	208 (59.6)	369 (66.49)
Remission	42 (20.4)	124 (35.5)	166 (29.91)
Unknown	3 (1.5)	17 (4.9)	20 (3.6)
Ongoing anticancer therapy at COVID-19 diagnosis, no. (%)			
Yes	102 (49.5)	146 (41.8)	248 (44.68)
No	101 (49)	184 (52.7)	285 (51.35)
Unknown	3 (1.5)	19 (5.4)	22 (3.96)
Prior radical therapies, no. (%)			
Surgery	102 (49.5)	150 (42.9)	252 (45.41)
Adjuvant/ neoadjuvant chemotherapy	82 (39.8)	89 (25.5)	171 (30.81)
Prior curative systemic therapy, no. (%)	7 (3.4)	38 (10.9)	45 (8.11)
Prior radiotherapy, no. (%)	68 (33)	89 (25.5)	157 (28.29)
Prior palliative systemic therapy, no. (%)			

Chemotherapy	17 (8.3)	9 (2.6)	26 (4.68)
Immunotherapy	16 (7.8)	4 (1.1)	20 (3.6)
Endocrine therapy	15 (7.3)	7 (2)	22 (3.96)
Targeted therapy	7 (3.4)	7 (2)	14 (2.52)
Ongoing palliative systemic anticancer therapy, no. (%)			
Yes	77 (37.4)	40 (11.5)	117 (21.08)
No	113 (54.9)	262 (75.1)	375 (67.57)
Unknown	16 (7.8)	47 (13.5)	63 (11.35)
Comorbidities, no. (%)			
Hypertension	106 (51.5)	167 (47.9)	273 (49.19)
Diabetes	43 (20.9)	88 (25.2)	131 (23.6)
Cardiovascular disease	48 (23.3)	49 (14)	97 (17.48)
Chronic pulmonary disease	34 (16.5)	56 (16)	90 (16.22)
Chronic kidney disease	28 (13.6)	52 (14.9)	80 (14.41)
Cerebrovascular disease	15 (7.3)	34 (9.7)	49 (8.83)
Dementia	16 (7.8)	25 (7.2)	41 (7.39)
Peripheral vascular disease	6 (2.9)	8 (2.3)	14 (2.52)
Liver impairment	2 (1)	12 (3.4)	14 (2.52)
Immunosuppression	9 (4.4)	27 (7.7)	36 (6.49)
Steroid therapy in progress	8 (3.9)	15 (4.3)	23 (4.14)
Other	42 (20.4)	85 (24.4)	127 (22.88)
Number of comorbidities, no. (%)			
0	37 (20)	76 (21.8)	113 (20.36)
1	55 (26.7)	91 (26.1)	146 (26.31)
2	56 (27.2)	65 (18.6)	121 (21.8)
≥3	58 (28.2)	117 (33.5)	175 (31.53)

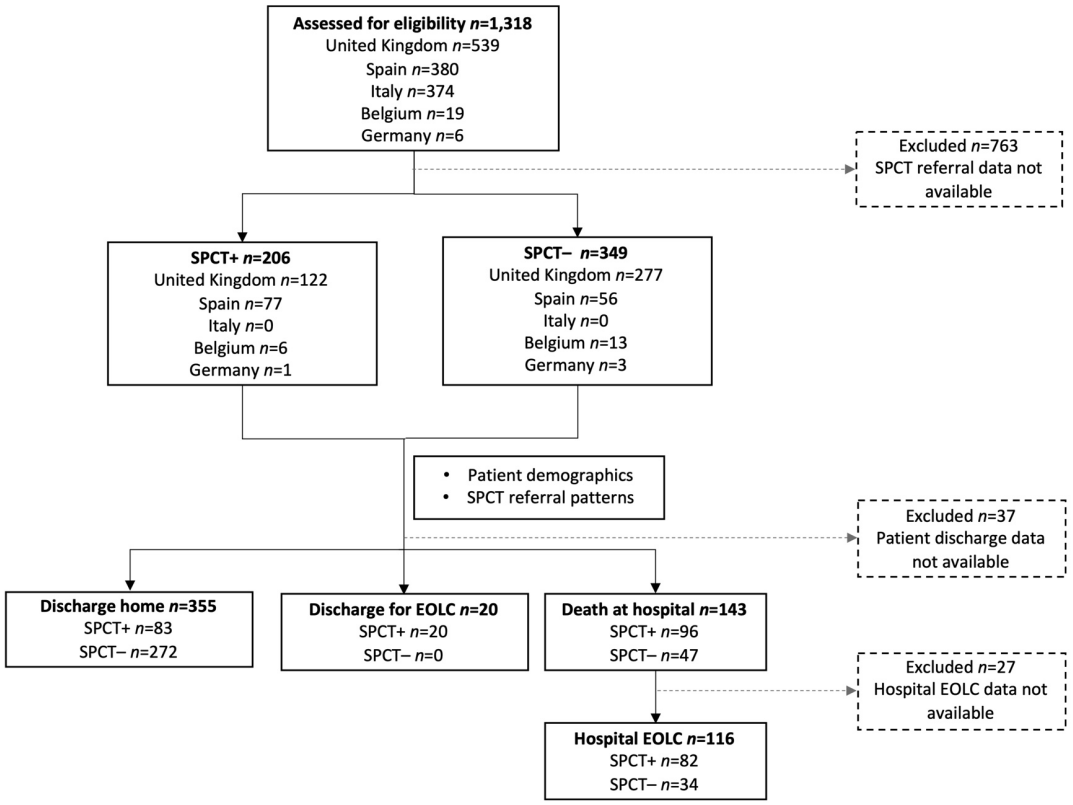
COVID-19 symptoms at diagnosis, no. (%)			
Fever	125 (60.7)	205 (58.7)	330 (59.46)
Cough	109 (52.9)	186 (53.3)	295 (53.15)
Dyspnea	30 (14.6)	41 (11.7)	71 (12.79)
Fatigue	43 (20.9)	80 (22.9)	123 (22.16)
Myalgia	19 (9.2)	45 (12.9)	64 (11.53)
Diarrhea	30 (14.6)	41 (11.7)	71 (12.79)
Coryzal symptoms	21 (10.2)	28 (8.0)	49 (8.83)
Nausea or vomiting	23 (11.2)	27 (7.7)	50 (9.01)
Sore throat	7 (3.4)	3 (1)	10 (1.8)
Headache	7 (3.4)	15 (4.3)	22 (3.96)
Dysgeusia	5 (2.4)	8 (2.3)	13 (2.34)
Anosmia	6 (2.9)	8 (2.3)	14 (2.52)
Other (i.e. confusion, delirium, etc.)	33 (16)	100 (28.7)	133 (23.96)
Number of symptoms at diagnosis, no. (%)			
0	10 (4.9)	31 (8.9)	41 (7.39)
1	46 (22.3)	70 (20.1)	116 (20.9)
2	60 (29.1)	90 (25.8)	150 (27.03)
≥3	90 (43.7)	158 (45.3)	248 (44.68)
Hospitalization rate, no. (%)			
Community-acquired (self-isolation	2 (1)	58 (16.6)	60 (10.81)
recommended)	134 (65)	209 (59.9)	343 (61.8)
Community-acquired (admission required)	69 (33.5)	76 (21.8)	145 (26.13)
Hospital-acquired			
Admission to intensive or sub-intensive care unit, no. (%)	16 (7.8)	45 (12.9)	61 (10.99)
COVID-19-specific drug treatments, no. (%)			

Antibiotics	93 (45.1)	173 (49.6)	266 (47.93)
Hydroxychloroquine or chloroquine	58 (28.2)	57 (16.3)	115 (20.72)
Systemic corticosteroids	14 (6.8)	20 (5.7)	34 (6.13)
Lopinavir/ ritonavir	25 (12.1)	17 (4.9)	42 (7.57)
Remdesivir	5 (2.4)	0 (0)	5 (0.9)
Tocilizumab	8 (3.9)	13 (3.7)	21 (3.78)
Others	9 (4.4)	14 (4.0)	23 (4.14)
COVID-19-specific oxygen interventions, no. (%)			
Oxygen therapy	132 (64.1)	167 (47.9)	299 (53.87)
Mechanical ventilation	12 (5.8)	33 (9.5)	45 (8.11)
High-flow oxygen therapy	62 (30.1)	82 (23.5)	144 (25.95)
COVID-19 complications, no. (%)			
Acute cardiac injury	6 (2.9)	13 (3.7)	19 (3.42)
Acute kidney injury	21 (10.2)	28 (8.0)	49 (8.83)
Acute liver injury	2 (1)	5 (1.4)	7 (1.26)
Acute respiratory failure	83 (40.3)	74 (21.2)	157 (28.29)
ARDS	27 (13.1)	35 (10.0)	62 (11.17)
Disseminated intravascular coagulation (DIC)	2 (1)	2 (1)	4 (0.72)
Secondary infection	21 (10.2)	35 (10.0)	56 (10.09)
Others	6 (2.9)	7 (2)	13 (2.34)
Number of complications, no. (%)			
0	90 (43.7)	234 (67)	324 (58.38)
1	78 (37.9)	73 (20.9)	151 (27.21)
2	31 (15)	20 (5.7)	51 (9.19)
≥3	7 (3.4)	22 (6.3)	29 (5.23)

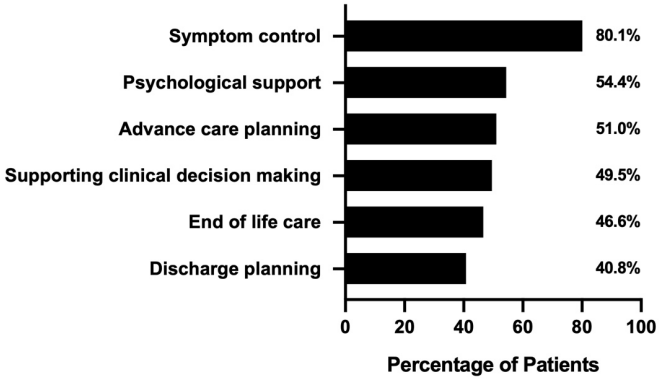
753

754 SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SPCT: Specialist
755 palliative care team; IQR: Interquartile range; GI: Gastrointestinal; COVID-19:
756 Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome; DIC:
757 Disseminated intravascular coagulation

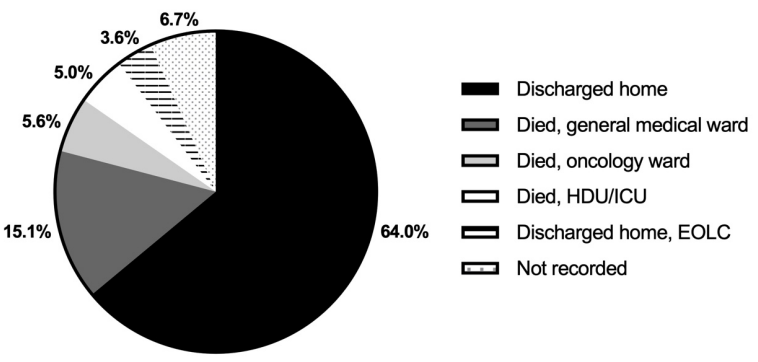
A.


Assessed for eligibility n=1,318
United Kingdom n=539
Spain n=380
Italy n=374
Belgium n=19
Germany n=6
Excluded n=763
SPCT referral data not available
SPCT+ n=206
United Kingdom n=122
Spain n=77
Italy n=0
Belgium n=6
Germany n=1
SPCT– n=349
United Kingdom n=277
Spain n=56
Italy n=0
Belgium n=13
Germany n=3
Patient demographics
SPCT referral patterns
Excluded n=37
Patient discharge data not available
Discharge home n=355
SPCT+ n=83
SPCT– n=272
Discharge for EOLC n=20
SPCT+ n=20
SPCT– n=0
Death at hospital n=143
SPCT+ n=96
SPCT– n=47
Excluded n=27
Hospital EOLC data not available
Hospital EOLC n=116
SPCT+ n=82
SPCT– n=34

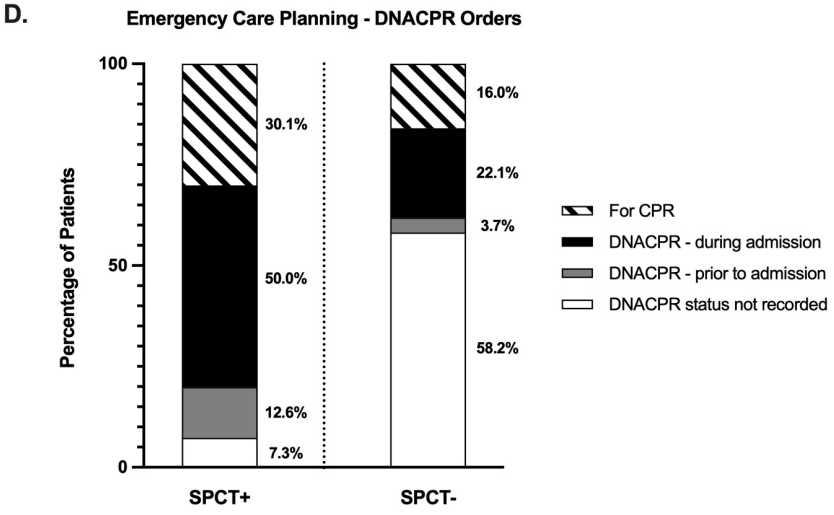
B.


Reasons for SPCT Referral/Input
Symptom control
80.1%
Psychological support
54.4%
Advance care planning
51.0%
Supporting clinical decision making
49.5%
End of life care
46.6%
Discharge planning
40.8%
0
20
40
60
80
100
Percentage of Patients

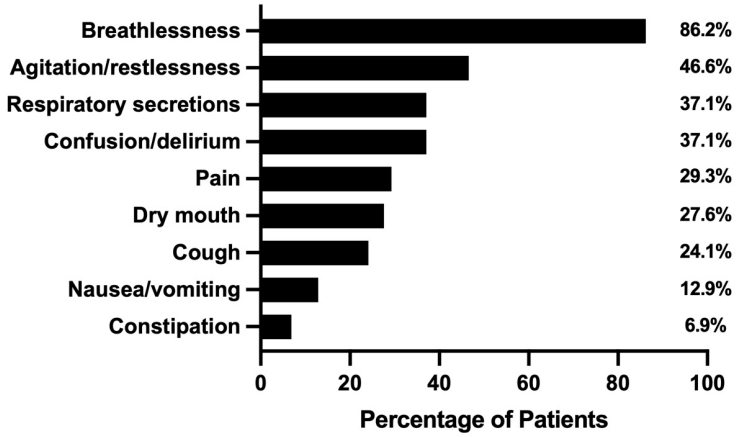
C.


Patient Outcomes at Data Censoring
6.7%
3.6%
5.0%
5.6%
15.1%
64.0%
Discharged home
Died, general medical ward
Died, oncology ward
Died, HDU/ICU
Discharged home, EOLC
Not recorded

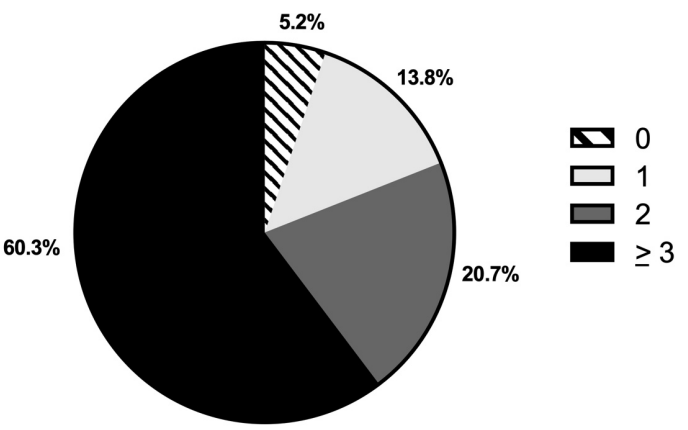
D.


Emergency Care Planning - DNACPR Orders
Percentage of Patients
100
50
0
30.1%
50.0%
12.6%
7.3%
16.0%
22.1%
3.7%
58.2%
SPCT+
SPCT-
For CPR
DNACPR - during admission
DNACPR - prior to admission
DNACPR status not recorded

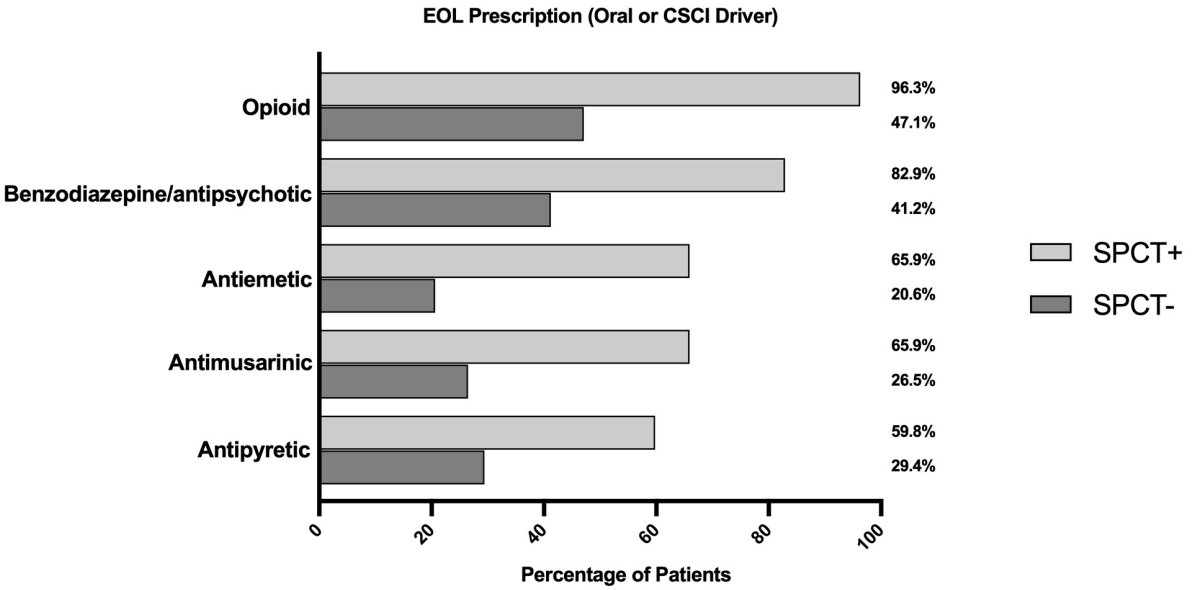
A.


Symptoms in Last 72 Hours of Life
Breathlessness
Agitation/restlessness
Respiratory secretions
Confusion/delirium
Pain
Dry mouth
Cough
Nausea/vomiting
Constipation
86.2%
46.6%
37.1%
37.1%
29.3%
27.6%
24.1%
12.9%
6.9%
0
20
40
60
80
100
Percentage of Patients

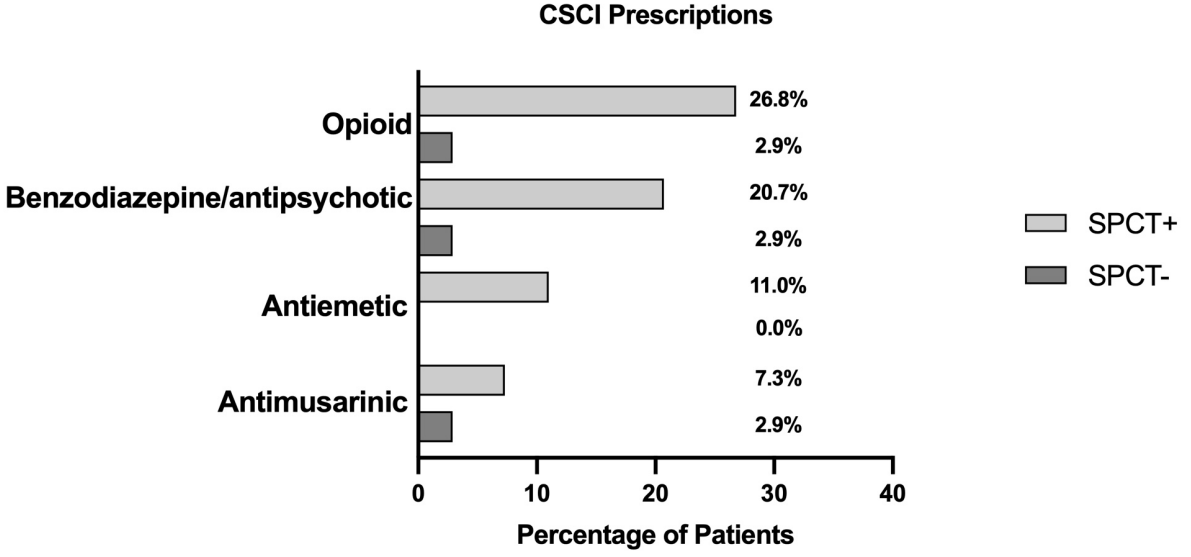
B.


Inpatient EOL Symptom Burden
5.2%
13.8%
60.3%
20.7%
0
1
2
≥ 3

C.


EOL Prescription (Oral or CSCI Driver)
Opioid
Benzodiazepine/antipsychotic
Antiemetic
Antimusarinic
Antipyretic
96.3%
47.1%
82.9%
41.2%
65.9%
20.6%
65.9%
26.5%
59.8%
29.4%
0
20
40
60
80
100
Percentage of Patients
SPCT+
SPCT-

D.


CSCI Prescriptions
Opioid
Benzodiazepine/antipsychotic
Antiemetic
Antimusarinic
26.8%
2.9%
20.7%
2.9%
11.0%
0.0%
7.3%
2.9%
0
10
20
30
40
Percentage of Patients
SPCT+
SPCT-

Supplementary Table 1: Distribution of SPCT+ and SPCT- groups.

Study site	SPCT+ *n*=206	SPCT- *n*=349
United Kingdom	**122**	**277**
Barts Health NHS Trust (London)	29	95
Chelsea and Westminster Hospital NHS Foundation Trust (London)	3	15
Guy's and St Thomas' NHS Foundation Trust (London)	40	89
Imperial College Healthcare NHS Trust (London)	9	10
University College London Hospitals NHS Foundation Trust (London)	39	55
Velindre Cancer Center (Cardiff)	2	13
Spain	**77**	**56**
Catalan Institue of Oncology (Girona)	4	7
Hospital Clínic de Barcelona (Barcelona)	1	0
ICO L'Hospitalet de Llobregat (Barcelona)	60	26
Institut Català d'Oncologia Badalona (Barcelona)	11	15
Vall d'Hebron University Hospital (Barcelona)	1	8
Belgium	**6**	**13**
Institut Jules Bordet (Brussels)	6	13
Germany	**1**	**3**
Medical Center of the University of Munich (Munich)	1	3

SPCT: Specialist palliative care team; NHS: National Health Service; ICO: Catalan Institute of Oncology

Supplementary Table 2: Ethics board approval by site.

Study site	Ethics review board
United Kingdom Barts Health NHS Trust (London) Chelsea and Westminster Hospital NHS Foundation Trust (London) Guy's and St Thomas' NHS Foundation Trust (London) Imperial College Healthcare NHS Trust (London) University College London Hospitals NHS Foundation Trust (London) Velindre Cancer Center (Cardiff)	Central ethical approval by the Health Research Authority (20/HRA/1608)
Catalan Institute of Oncology (Girona)	Catalan Institute of Oncology Institutional Review Board
Hospital Clínic de Barcelona (Barcelona)	Clinical Research Ethics Committee of the Hospital Clínic de Barcelona
ICO L'Hospitalet de Llobregat (Barcelona)	Catalan Institute of Oncology Institutional Review Board
Institut Català d'Oncologia Badalona (Barcelona)	Catalan Institute of Oncology Institutional Review Board
Vall d'Hebron University Hospital (Barcelona)	The Hospital Universitario Vall d'Hebron Clinical Research Ethics Committee
Institut Jules Bordet (Belgium)	Jules Bordet Institute Ethics Committee
Medical Center of the University of Munich (Munich)	The Ethics Committee of the University Hospital of Munich

NHS: National Health Service; HRA: Health Research Authority; ICO: Catalan Institute of Oncology