Current Oncology Reports (2019) 21:100
https://doi.org/10.1007/s11912-019-0854-7

PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Managing Pain in the Older Cancer Patient

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Abstract

Purpose of Review This paper aims to give the specialist and non-specialist alike an overview of the considerations involved in the management of cancer-related pain in the older population.

Recent Findings Comprehensive guidelines on cancer pain management have been published recently by expert bodies. Cancer pain differs in many respects to other pain conditions and we are likely to encounter it more frequently in older patients in the future. The elderly are more sensitive to the effects of many analgesic medications.

Summary The elderly patient with cancer pain presents a unique challenge to the treating physician. The biological effects of ageing impact on the efficacy of many pain management strategies as well as its diagnosis and assessment. Treatment options can be broadly divided into pharmacological, non-pharmacological and interventional. A multidisciplinary approach and frequent re-assessment are essential in achieving favourable outcomes in this patient group.

Keywords Cancer pain · Analgesia · Older patient · Elderly · Geriatric · Oncology · Pain management · Gerontology · Bone pain

Introduction

The proportion of the world's older population (> 60 years) is expected to increase significantly over the next few decades. In 2013, individuals > 60 years made up 12% of the world's population, which will increase to 21% (> 2 billion) by 2050 [1]. Not surprisingly, the number of older patients with a cancer diagnosis can also be expected to rise in the future [2] because the incidence of cancer increases with increasing age and also the increasing life expectancy of cancer patients. More than 60% of cancer survivors in the USA are > 65 years and this group will increase in the future [3].

Currently cancer incidence is 11-fold higher in the > 65 age group compared with younger age groupings [4] and 70% of all cancer deaths occur in this age group [5]. Cancer, and its associated pain management in the older patient, presents a unique set of challenges for the treating physician and the sub speciality of Geriatric Oncology has evolved to meet this previously unmet need. The normal physiological changes associated with ageing have important implications for the pathophysiology of cancer and the clinical effects of many therapies.

Pain in the setting of cancer is a common problem for patients of all ages. A recent systematic review and meta-analysis of 122 articles reported pain prevalence rates of 39% after curative treatment, 55% during chronic cancer treatment and 66% in metastatic or terminal disease [6]. Of the studies that reported on pain severity, the prevalence of moderate to severe pain was 38%. Pain appears to be a more prominent feature in certain cancers such as pancreatic and head and neck cancer [7].

It is worth noting that non-cancer pain is a significant issue within the older population, with 40–70% of the ambulatory elderly population experiencing pain for greater than 6 months [8]. As co-morbid conditions such as arthritis and osteoporosis are more common in the elderly, they may also contribute to the pain burden of elderly patients who are subsequently diagnosed with cancer [9]. A prospective observational study of

This article is part of the Topical Collection on *Palliative Medicine*

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Published online: 14 November 2019

cancer patients > 70 highlighted that nearly half these patients suffer from non-cancer-related pain [10•].

Historically, the plight of the older cancer patient has not been dealt with effectively by the medical community. A 1998 study by Bernabei et al. showed that 38% of cancer patients who were nursing home residents exhibited signs of pain daily, with 26% of these patients receiving no analgesia. Patients > 85 years were more likely to receive no analgesia and only half of elderly patients with cancer-related pain were receiving opiates [11]. Substantial improvements have been made in the pain management of elderly cancer patients over the past decade [12].

Assessment of Cancer Pain in Older Patients

Many elderly patients under-report cancer pain due to incorrect beliefs that their pain will not benefit from treatment [13] or that it may signal worsening of the underlying malignancy [14]. Concomitant conditions such as dementia make it more challenging to elicit an accurate pain history from an older cancer patient. A number of tools such as "Pain Assessment Checklist for Seniors with Limited Ability to Communicate" and the "Doloplus–2 Scale" have been validated to provide an accurate assessment of pain even in patients with severe cognitive impairment [15]. Self-reporting of pain where possible provides the most accurate assessment of a patients' pain as numerous studies have shown that both clinicians and family members frequently underestimate pain severity as reported by patients [16–18]. The Faces Pain Scale, Numeric Rating Scale and Verbal Descriptor Scale have all been validated for use in assessing pain in the elderly patient [19]. The Verbal Descriptor Scale asks patients to classify their pain in to mild, moderate or severe and is more accurate and user friendly for patients with mild to moderate cognitive impairment in comparison with the other scales above [15].

It is also important to adopt a holistic approach to the assessment of pain in the older cancer patient and consider the potential psychological impact that pain may have. Depression can alter the perception of pain and reduce coping mechanisms, while on the other hand, pain and its resultant loss of function can be the trigger for a depressive episode [20]. Pain and depression frequently co-exist in the elderly cancer patient with both conditions exacerbating the other.

Mechanisms of Cancer-Related Pain

Cancer pain in the elderly is often multifactorial in nature. As mentioned previously, pre-existing non-cancer pain conditions are often present which may be exacerbated in the setting of cancer treatment. Pain can also result from diagnostic or therapeutic interventions such as radiotherapy-associated mucositis, or a chemotherapy-induced peripheral neuropathy. Tumour masses commonly exert a pressure effect as they increase in size on surrounding tissues causing stimulation of pain fibres. Subsequent pain relief may arise when the tumour decreases in size as a result of embolisation, radiotherapy, surgical resection etc. An animal model of cancer pain involved the injection of sarcoma cells into the mouse femur [21•]. This and other models give insights into the mechanisms by which tumour cells cause pain apart from the mechanical effect of compression and traction in surrounding tissues (Table 1).

Malignant cells themselves release chemical mediators which stimulate nociceptors. Substances such as endothelins, VEG-F and prostaglandin E2 (PGE2) [22] are secreted by tumour masses and their respective receptors are present on the cell membrane of pain receptors. Activation of these receptors reduces the threshold for excitability and hence propagation of the painful stimulus to the spinal cord and brain.

Tumours are made up of many cell types apart from cancer cells including cells of the immune system such as macrophages, neutrophils and T cells. These also secrete mediators which sensitise or excite pain receptors and include tumour necrosis factor-α (TNF-α) [23], Interleukin 1 and 6 [24],

Table 1 Mechanisms of cancer pain

Cell type	Chemical messenger/ mechanism	Effect on pain transmission
Tumour cells	Tumour mass exerts pressure effect on surrounding tissue	Stimulation of pain receptors
	Endothelins, VEG-F, PGE2	↓ threshold of excitability
Immune system cells (macrophages, neutrophils, T cells)	Interleukin 1 & 6, TNF-α, EGF, PDGF, TGF	Sensitise and stimulate pain receptors
Osteoclasts, inflammatory cells, tumour cells	↓ pH of surrounding environment	↑ pain transmission via stimulation of pH-sensitive receptors VR1 & ASIC3
Nerve cells	↑ Substance P, ↑ c-Fos	↑ glutamate, ↓ threshold for transmission of pain signals
	Anti-neuronal antibodies directed against nerve cells, chemo agents (e.g. vincristine, cisplatin)	Development of neuropathic pain

ASIC3 acid-sensing ion channel 3, *EGF* endothelial growth factor, *PDGF* platelet-derived growth factor, *PGE2* prostaglandin E2, *TGF* transforming growth factor, *TNF-α* tumour necrosis factor-α, *VEG-F*, vascular endothelial growth factor

epidermal growth factor (EGF) [25], transforming growth factor (TGF) [26] and platelet-derived growth factor (PDGF) [27].

Tumour cells tend to have a lower intracellular and extracellular pH than their surrounding environment [28]. Sensory neurons can be stimulated by an acidic environment and two main classes of pH receptors have been identified on pain receptors: VR1 [29] and acid-sensing ion channel 3 (ASIC 3) [30]. As inflammatory cells attempt to destroy the invading tumour mass, they release protons which lower the pH of their microenvironment, which in turn activates the acid-sensing cells expressed by nociceptors [22]. Tumour masses also undergo a high rate of cell turnover, where large numbers of cells undergo apoptosis, and their intracellular ions leak into the extracellular tissues, adding to the acidity.

The observation that tumour-associated acid production stimulates pain pathways is relevant to bone cancer pain. Many bone tumours are characterised by high levels of osteoclast activity, whose function is to resorb bone [31]. Osteoclasts create a microenvironment with a low pH. Many nociceptors that innervate bone contain the pH sensing channels VR1 and ASIC 3, hence sensory neurons are activated [27].

Sensitisation of sensory pain cells is important in the understanding of the mechanisms of cancer pain. Sensitisation is a complex process whereby the threshold for the neuron to transmit a pain impulse is reduced. Sensory impulses which were previously not painless are now perceived as painful (allodynia) and similarly mildly painful sensations now register by the brain as being extremely painful (hyperalgesia). The sensitisation of peripheral nerves has been demonstrated in the mouse model of bone cancer and is thought to be facilitated by the release of the neurotransmitter substance P and expression of the transcription factor c-Fos [32]. This recalibration of the peripheral nervous system is also seen at the level of central nervous system in animal models of cancer-related pain [33]. The downstream effects of this are an increase in glutamate (an excitatory neurotransmitter) and increased spinal cord expression of the pronociceptive members of the opioid family resulting in a lower transmission threshold for spinal cord neurons [22].

Once a pain impulse reaches the spinal cord, it is transmitted to the brain. Traditionally, the spinothalamic tract was viewed as the predominant route through which this journey occurred. Evidence now exists that cancer pain transmitted from visceral organs can be transmitted in a number of parallel ascending pathways apart from the spinothalamic tract [34, 35]. The presence of these accessory pathways of pain transmission partly explain why the treatment of cancer-related pain is notoriously difficult to manage to a satisfactory level. Once the impulse arrives in the cerebral cortex, the final individualised pain sensation is experienced by the patient. Noradrenergic and serotonergic pathways are likely to play a role in modulating pain transmission. The presence of these pathways not only provide a plausible mechanism of action for the role of antidepressants in cancer pain [36] but also provide insight into the complex interaction between mood and anxiety levels and subsequent perception of pain [37].

Neuropathic pain often coexists with the pain subtypes described above. It occurs when there is direct injury to nerve tissue peripheral or central and may occur directly as a result of tumour invasion in to nerve trunks. Neuropathic pain in cancer can also arise as a result anti neuronal antibodies type 1 (anti hu) from paraneoplastic syndromes or as a result of a peripheral neuropathy secondary to certain chemotherapeutic drugs notably cisplatin and vincristine. These drugs inhibit the function of tubulin which is necessary for axonal transport in nerve cells. This disruption in normal neuronal function causes degeneration and subsequent release of pro inflammatory cytokines which sensitise nearby nociceptors [38]. Neuropathic pain is associated with motor, sensory or autonomic dysfunction and patients often characterise the pain as having a burning or electric shock–like quality to it [39]. Cancer pain often has a significant neuropathic element, a systematic review of > 13,600 cancer patients found the overall prevalence of neuropathic pain 19–39% [40].

Consequences of Poorly Managed Cancer Pain in the Elderly

Pain is one of the most feared symptoms of cancer among patients. Poorly managed cancer pain affects mood and anxiety levels [41], the prevalence of clinically relevant depression among elderly cancer patients being as high as 25% in some studies [42]. Ongoing pain may result in reduced motivation for patients to engage with cancer therapies [43]. Overall, it has a negative impact not only on patients' quality of life but also on the family caregivers of cancer patients [44]. For some elderly patients, the primary goal of chemotherapy may not be to cure but rather to achieve an increase in functional status [45]. Pain, fatigue, insomnia and mood disturbance occur with a high prevalence among elderly cancer patients and has a significant impact on quality of life [39]. Therefore, optimal treatment of cancer pain in the elderly requires a holistic approach with input from a multidisciplinary team involving oncologists, psychologists, psychiatrists, pain physicians and gerontologists.

There is also an economic cost to society from poorly managed cancer pain in older patients. In a US survey of 1000 cancer patients, those experiencing breakthrough pain incurred higher medical costs as compared with those that had more adequately controlled pain management. This extra financial burden arises from an increased occurrence of pain-related hospital admissions, emergency department visits and outpatient appointments among patients with suboptimal pain

control [46]. A Swedish group reported that as the severity of pain in elderly patients increased so does their use of medical resources as well as the overall cost of their medical care [47]. Adherence by physicians to evidence-based cancer pain management guidelines not only results in improved analgesia for patients [48] but leads to only a moderate increase in resource use [49].

Poorly controlled pain in the peri-operative cancer surgery setting has been shown to be a driving force for cancer recurrence in an animal model [50]. Pain itself is thought to have an immunosuppressive effect via stimulation of the sympathetic system and the hypothalamic pituitary adrenal axis hence reducing the body's defence systems against invading malignant cells. Painful stimuli increase circulating levels of beta–endorphin which reduces the cytotoxic effects of NK cells [51], one of the body's main weapons against invading malignant cells. Similarly, catecholamines released by the sympathetic system bind to adrenoreceptors that are found on the surface of many tumour cells. When activated, they secrete substances such as Interleukin 6 (IL-6), vascular endothelial growth factor (VEG-F) and matrix metalloproteinase (MMP) enzymes, which all increase the propensity for tumour cells to invade and multiply [52]. Numerous cancer model experiments have shown that effective analgesia can reduce the incidence and number of metastasis. [53]

Therapy for the Older Cancer Patient with Pain

Pain management in the older patient with cancer can be challenging for several reasons. Altered pharmacokinetics, polypharmacy, comorbidities and the potential for cognitive impairment should all be taken into consideration. These factors, along with the patient's oncological diagnosis and expected treatment trajectory, are important in tailoring an individualised analgesic regimen. Ideally, there should be a multidisciplinary approach with specialist input to optimise pain control while minimising the adverse effects.

In the absence of large studies, it is important to cautiously implement clinically guided decisions with frequent reassessment of the patient's individual pain requirements.

Pharmacological

The pharmacological management of pain in the older cancer patient requires careful assessment. The nature, site and intensity of the pain should be elicited. The ability of the patient to communicate is imperative in both the assessment of the pain and assessing an adequate response to each treatment. An understanding of potential side effects of each medication particularly in the context of present comorbidities is crucial. Prior to commencing any new agents, the altered pharmacokinetics and pharmacodynamics of the older patient should be considered. Changes in body composition, decreased hepatic and renal blood flow, lower levels of albumin and cerebral volume and blood flow can alter pharmacokinetics and pharmacodynamics of many drugs [54, 55]. The World Health Organisation originally developed the analgesic ladder in 1986 as part of cancer analgesia guidelines. Although the original ladder has been modified, with the option to add adjuvants, the basic 3 steps remain core to managing cancer pain. In 2018, The European Society of Medical Oncology published a comprehensive guideline on the management of pain in the cancer patient [56••]. Although the guideline does not focus specifically on the older patient it emphasises the importance of careful assessment of pain in the older patient particularly those with cognitive impairment.

Simple analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS) should be considered for all patients with mild to moderate pain but are unlikely to be adequate alone if the pain is severe or progressive. Paracetamol is an attractive agent in the older patient because it has no cognitive side effects and in recommended doses is extremely safe and well tolerated. A recent Cochrane review, however, found no evidence that paracetamol in cancer pain, either alone or with a morphine based drug, had any impact on levels of pain [57]. NSAIDs are often avoided in the older population due to the numerous side effects including gastric ulceration, renal dysfunction and coronary artery thrombosis [58]. They should not be overlooked completely as in the appropriate older patient with cancer pain they can offer substantial benefit, particularly for moderate to severe pain [59].

In the context of cancer, opioids and the older patient are poorly studied. In the older cancer patient, the use of opioids can be complicated by increased sensitivity to the medication in addition to increased side effects. There is larger individual variability in response to opioids and hence a commencement of a low dose with careful titration is required [60•]. Regarding which opioid to choose there is no evidence that one agent is superior to another (Table 2).

In the older cancer patient, careful titration of low-dose oral morphine to effect is recommended [63]. More potent opioid preparations including oxycodone, hydromorphone and fentanyl are also available. While the oral route is preferred, if unavailable, then buccal or transdermal routes of administration should be considered.

In severe pain where more rapid control is required, subcutaneous or intravenous routes can be used, either by continuous infusion or bolus doses for breakthrough cancer pain. Careful titration, assessment of response and vigilance for opioid-related side effects is imperative when using parenteral opioids in the older cancer [64].

A less commonly used opioid for severe cancer pain is methadone. Methadone has potent opioid action but also

Table 2 Characteristics of specific opioids [61, 62]

Specific agent	Characteristics
Morphine	Available in multiple preparations,
	Extensive experience with its use,
	Inexpensive,
	Widely available
Oxycodone	More potent than morphine
	Similar side effect profile
Hydromorphone	Much more potent that morphine
	Similar side effect profile
	Longer half-life
Codeine	Variable potency and tolerability
	Weak opioid
Tramadol	Dual activity-weak opioid agonist and serotonin-norepinephrine reuptake inhibition
	Variable potency
	Risk of serotonin syndrome
Buprenorphine (transdermal)	Partial opioid antagonist
	Ceiling effect of respiratory depression
	Poorly titratable
	Suitable in renal impairment
Fentanyl (transdermal)	Potent ++ when compared with oral morphine
	Not suitable for opioid-naïve patients
	Poorly titratable

antagonises the NMDA receptor which is implicated is abating opioid induced hyperalgesia and in the management of neuropathic pain. Therefore, methadone is a potentially useful agent in patients with refractory pain already on high-dose opioids but also for patients for severe neuropathic pain [63]. The value of methadone may be limited by its highly variable bioavailability, volume of distribution and half-life resulting in an unpredictable effect and necessitating very careful titration [65].

There are several adjuvants that can be added to opioid therapy to either reduce the requirement for opioid and hence the opioid-related side effects or as an additional agent for severe refractory pain. Gabapentinoids including pregabalin and gabapentin are frequently used in cancer pain. These agents are recommended for the treatment of neuropathic pain regardless of the aetiology. Cancer pain often has a neuropathic component [66].The side effects of these medications include confusion, somnolence, peripheral oedema and weight gain. The effects on the CNS can be exaggerated in the elderly and so commencement of a low dose with careful titration is recommended [67]. Antidepressants namely duloxetine, venlafaxine and amitriptyline have proven efficacy in treating neuropathic pain [68]. In older cancer patients with comorbidities, these medications are more likely to be contraindicated due to cardiac arrythmia, ischaemic heart disease and glaucoma. They also have numerous common side effects that lead to high rates of discontinuation. Topical agents such as lidocaine or capsaicin for the treatment of cancer-related neuropathic pain are attractive due to the low incidence of systemic side effects but are only likely to have benefit for isolated peripheral neuropathic pain [68].

Ketamine is gaining traction in the treatment of refractory cancer pain. To date, the evidence does not support its routine use but there may be specific patient groups that could benefit from ketamine as an adjuvant to other pain therapies [69, 70].

Dexamethasone is also indicated for metastatic spinal cord compression [56••].

Delirium in older patients with cancer is a frequent problem associated with increased mortality [71]. The relationship between pain, opioid analgesics and delirium is complex. Both undertreatment of pain and the use of opioids for pain can both precipitate delirium [72]. Where opioids are found to be exacerbating or causing delirium despite dose reduction and opioid rotation then alternatives for managing pain should be explored.

Non-pharmacological

The role of education and psychosocial support in managing pain in the older cancer patient should not be overlooked. Educating both the patient and their caregivers can reduce pain intensity and

improve quality of life [73, 74]. Complementary therapies also have a role and while not studied specifically in the older population, it is intuitive to add a therapy which is recognised as safe. Transcutaneous electrical nerve stimulation has been widely studied and may provide benefit [75]. Acupuncture is another commonly used complementary therapy which also has a long-established safety profile, which may reduce pain and other cancer-related side effects [76, 77]. It is well established that psychological distress amplifies pain. Cognitive behavioural therapy has a clear role in helping patients mitigate distress and improve coping strategies. In the cancer pain population, psychological and behavioural interventions can have a meaningful impact on the pain and suffering [78].

Interventional Pain Procedures

A significant number of patients with advanced malignant disease will have pain refractory to systemic pharmacological management [79]. Interventional techniques such as peripheral nerve blocks (Table 3), sympathetic blockade and intrathecal drug delivery should be considered in the older cancer patient. Specific interventional procedures should be considered on a case by case basis depending on the patient's symptoms and pathoanatomical findings.

The limitations or indeed the practicalities of these procedures is vigilance to prevent catheter relation infection, safe delivery of local anaesthetic infusion and preventing unwanted catheter dislodgement [83]. Other peripheral nerve, plexus or interfascial plane blocks can be used as deemed appropriate. These techniques are attractive for the older cancer patient, because in terms of cognitive effects or systemic side effects, these techniques are safe and have the potential to significantly reduce the requirement for opioids.

For refractory visceral cancer pain, sympathetic blocks should be considered (Table 4).

Sympathetic blocks are usually performed initially with local anaesthetic for diagnostic purposes. If there is substantial but transient benefit from the diagnostic block, then it can be repeated using a neurolytic agent such as alcohol or phenol, which should deliver a more permanent inhibition of pain. The neurolysis should give a longer duration of relief but is also associated with a higher number of complications [87].

Intrathecal drug delivery is a means of delivering an analgesic drug, usually opioids, directly into the cerebrospinal fluid via a catheter, to reduce the required dose or limit the systemic side effects. Intrathecal drug delivery systems (IDDS) may be a useful option for refractory cancer pain. IDDS can reduce pain scores with fewer adverse effects than traditional systemic opioid treatment [88•, 89]. Older cancer patients should be considered for IDDS when conventional medical management fails to adequately control their pain. Besides opioids, other drugs available for intrathecal delivery include bupivacaine, clonidine and ziconotide. Practically, if a patient has life expectancy of 3 months or less, a tunnelled intrathecal catheter can be used with an internalised port that can be connected to the appropriate drug infusion externally. With a longer life expectancy, an entirely internalised implantable drug delivery pump can be used. Typically, these pumps need to be refilled at intervals of weeks to months. Infection necessitating explantation is the most significant risk associated with IDDS, which occurs in 3% of patients [90].

Neuromodulation, namely spinal cord stimulation, using electrical current has been extensively studied as a drug-free therapy in the non-cancer pain population. The evidence to guide its use in the older cancer patient is sparse [91]. In theory, there could be a role for this therapy in severe neuropathic cancer pain that is refractory to other therapies but there needs to be randomised controlled trials looking specifically of its use and efficacy in the cancer population.

Surgery

Surgery has a role in the management of cancer-related pain beyond curative intent. Spinal cord compression secondary to vertebral malignancy or instability with impending cord compression may be treated surgically with decompression and stabilisation [56••]. Advanced age in the cancer patient should not preclude them from surgical intervention. The likely benefit of the surgery, performance status of the individual and the patients' wishes should all be considered when deciding if surgical intervention is appropriate. Other painful conditions related to malignancy including pathological fracture of other sites or bowel obstruction should also be considered for surgery on a risk benefit basis.

Table 3 Peripheral nerve blocks for cancer pain

Peripheral nerve block	Indication
Intercostal nerve blocks (local anaesthetic + neurolytic)	Invasive lung malignancy/Chest wall malignancy
Brachial plexus block (single shot/continuous infusion via catheter)	Brachial plexopathy/upper limb pain secondary to malignancy [80, 81]
Femoral nerve block (single shot/continuous infusion via catheter)	Lower limb pain secondary to malignancy e.g. femoral sarcoma [82]

Table 4 Sympathetic blocks for cancer pain

Sympathetic block	Indication
Celiac plexus block	Upper GI malignancy-pancreatic/stomach/hepatobilary [84]
Superior hypogastric block	Pelvic malignancy [85]
Ganglion of impar block	Low pelvic/perineal malignancy [86]

Radiotherapy and Other Therapies

Radiotherapy is indicated for the treatment of metastatic spinal cord compression which can cause an acute neurological deficit and is often associated with severe pain [56••, 92]. Other treatments for painful bone metastasis include bisphosphates and the newer agent denosumab, a RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitor which reduced bone degradation, but these should be used a part of a multimodal analgesic regimen for the management of cancer-related pain in the older patient [93].

Conclusion

Pain management in the older cancer patient is complex for a number of reasons. There should be an individualised management plan involving input from multidisciplinary specialists experienced in managing cancer pain in older adults. Therapeutic options may be summarised as pharmacological, non-pharmacological, interventional, surgical and radiotherapy.

The requirement for and effect of each therapy may change over the course of their care and so careful reassessment at regular intervals is important for pain management and outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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