Compared to Manual, Semi-automated and Fully automated extraction methods for RNA from archival FFPE tissue

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Background: For the analysis of RNA-based biomarkers, formalin-fixed, paraffin-embedded (FFPE) tissue represents a valuable resource. For this purpose, good laboratories and clinical routine testing, a robust and automated RNA extraction method applicable for high sample throughput is required. The goal of this study was to compare the extraction performance of four silica-based RNA extraction protocols on FFPE tissue.

Methods: The following four methods were applied for RNA extraction: a) a fully automated, bead-based RNA isolation procedure currently in development at Siemens Healthcare Diagnostics on the Versant kPCR Molecular System; b) its manual counterpart; c) a semiautomated, bead-based extraction system (Qiagen EZ1 robot); and d) a manual, column-based extraction kit (RNeasy FFPE kit, Qiagen). In total, RNA from 360 sections (90 sections/method) of 30 FFPE tumor blocks up to 20 years of age was purified and analyzed using RT-kinetic PCR for ERα, PGR, HER2 total, RNA from 360 sections (90 sections/method) of 30 FFPE tumor blocks up to 20 years of age was purified and analyzed using RT-kinetic PCR for ERα, PGR, HER2 total, RNA from 360 sections (90 sections/method) of 30 FFPE tumor blocks up to 20 years of age was purified and analyzed using RT-kinetic PCR for ERα, PGR, HER2.

Results: The best yield was achieved using the semiautomated protocol employing overnight lysis. The three bead-based methods showed good correlations to each other in both yield and relative mRNA expression (r = 0.86–0.95 and 0.98, respectively). In contrast, correlation coefficients between each of the bead-based methods to the manual column-based method were lower (r = 0.77–0.89 and 0.96, respectively). Regarding section-to-section variability, the fully automated method showed the best performance (RMSE: 0.32–0.35 Ct) and required by far the least hands-on time.

Conclusion: The fully automated RNA purification method showed the best reproducibility for expression analyses of breast cancer biomarkers in neighboring sections of tissue blocks between 3 and 20 years of age. It outperformed the other three tested methods with regard to overall and hands-on time. Therefore, it is well suited for high-throughput RNA analyses in clinical routine testing as well as for translational research studies in archived FFPE material.

Introduction: Growing clinical evidence shows cognitive impairment in cancer patients treated with chemotherapy, especially women treated for breast cancer. This is commonly referred to as chemotherapy- or chemo-related cognitive decline. Clinical studies have difficulties in defining which drugs are responsible for the cognitive changes and published papers evaluating single agents in experimental models are scanty. Doxorubicin (DOX) is one of the most commonly used drugs in the adjunct treatment of breast cancer.

Aim: To investigate the effect of DOX, in doses similar to those used in humans on memory for inhibitory avoidance conditioning (IA), a type of emotionally motivated memory dependent of the hippocampus and amygdala, in an experimental animal model.

Methods: Adult male Wistar rats housed with food and water ad libitum in 12 h light/ dark cycles were divided into groups treated with escalating doses of DOX (0.5 mg/kg, 2 mg/kg and 8 mg/kg) or placebo. All experiments were done according to the NIH Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care. When given before training, higher doses of DOX (2 mg/kg and 8 mg/kg) impaired IA memory retention measured 24 h and 7 days, but not 3 h after training (p=0.022, p=0.004 and p=0.14, respectively). When retrained 7 days after the drug administration, animals were able to learn and there was no difference between groups in memory retention. DOX did not affect IA retention when given after training in any of the different dosage groups. Multi-trial repeated acquisition done with the 8 mg/kg dosage and placebo showed no differences between lattences (p=0.76), number of trainings (p=0.29) or retention testing after 24 h (p=0.45). DOX (8 mg/kg) produced a decrease in exploratory behavior assessed by the number of rearings performed during exploration of an open field (p=0.004).

Conclusion: These results indicate that a single injection of DOX before training in doses similar to those used in women with breast cancer caused a reversible impairment in long-term aversive learning, a type of emotionally motivated memory dependent of the hippocampus and amygdala, in adult male rats.

Results:

- Median age was 47.3. ER positive rate was decreased from young group to postmenopausal group, and then was elevated in old group. The pattern of the positive rate of PR was similar to ER. The rate of HER2 overexpression was increased from premenopausal group to postmenopausal group (26.2% to 35.2%, p=0.015), and was decreased in old group (13.3%, p=0.042). Axillary lymph node positive rate was high in young group (37.3%, p=0.048), and the positive rate of P53 was also high (63.6%, p=0.062). In survival analyses, only LN status was a significant independent factor affecting survival (DFS and OS) in young group (p=0.003). LN status and PR, tumor size were strong independent factor affecting DFS and LN status and PR, HER2 were strong independent factor affecting OS in porenopausal group. LN status and PR were significant independent factor affecting DFS and LN status and tumor size were significant independent factor affecting OS in postmenopausal group. HER2 overexpression was a significant factor affecting DFS in old group (p=0.070).

Conclusion: Clinicopathologic characteristics were different in each age group of breast cancer patients. The prognostic factors affecting survival were also different. The age-specific characteristics of Korean breast cancer patients are different from that of Western countries.

In Vivo Radiation Responses of Normal Human Breast Epithelium Xenografts

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Radiotherapy is a key treatment for breast cancer patients yet the molecular responses of normal human breast tissue to irradiation in vivo are unclear. We have developed a murine xenograft model in which non-neoplastic human breast tissue implanted subcutaneously can be subsequently irradiated for dose-response and time-course studies. We demonstrated that radiation induces p53 stabilization and activation by N- and C-terminal phosphorylation events in normal human breast epithelium. Activation of p53 pathway responses varied between epithelial cell types, with basal cells showing greater induction of p21 than luminal cells, which may signal differences in the response of basal-type breast carcinomas compared to luminal tumour types. The magnitude of p53 stabilization, phosphorylation and transcriptional activation...
showed inter-individual variation, compatible with a genetic component of the response to ionizing radiation. By investigating the number of residual DNA double strand breaks we also found differences in repair kinetics in different patients. The use of xenografted normal human breast tissues has allowed us to investigate the molecular response to ionizing radiation in vivo for the first time and has revealed differences between different cell populations within an individual and substantial inter-individual variation between patients.

200P  BREAST CANCER IN LATIN AMERICA: EXPERT PERCEPTIONS COMPARED WITH MEDICAL CARE STANDARDS (MCS)

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Breast cancer is the number one tumor in incidence in women. However, all knowledge available about this disease is only applicable to the population. Latin America represent approximately 10% of the world’s breast new cancer cases each year and the lack of official data and statistics is common in the region. In order to have a vision of the reality about the breast cancer situation we made a questionnaire about diagnosis, treatment and health care aspects of the disease that was sent to 100 breast cancer experts to know their perception of the situation about breast cancer care in 12 countries. All questions were answered in reference to where they work and the whole country. (ref. Garap et al, Cancer. 2008 Oct 15; 113(8 Suppl):2359-65. In this study we analyzed the norms or guidelines (MCS) that the countries of the region acknowledge to have according to the governmental bodies and health care systems to compare them with the experts of the first study. Finally, we proposed recommendations or plans to improve the situation of global control of breast cancer in Latin America. The following were considered MCS: Specific programs on breast cancer; protocols; clinical guidelines; regulations and/or specific norms and public education programs. The selected questions were related with education, prevention, diagnosis, accessibility and follow-up.

Results: All countries surveyed have MCS’s either published by National Health Authorities or by recognized bodies and important differences were found in the experts perceptions between breast care in medical centers compared with the whole country.

Conclusions: The differences could be due to: unknowingness on behalf of the physicians of the MCS; lack of education and/or information by the population and accessibility to the health care system. We conclude that it is not necessary to generate new MCS since they exist and are similar among them and in relation with the international ones. Therefore, the Governments are who should implement active policies and control mechanisms for the implementation and compliance of the MCS guaranteeing their applicability. Supported by a grant from The Breast Cancer Research Foundation (BCRF)
A STUDY OF EIGHTY-SIX CASES OF TRIPLE NEGATIVE BREAST CANCER FROM REGIONAL CANCER CENTER IN WESTERN INDIA

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Background: Triple negative breast cancer is a different subset of breast cancer with aggressive course. With aim to study the pattern in our region, the retrospective analysis was conducted. Material and methods: From December 1999 to January 2006, a total of 86 (13%) cases were found to have triple negative tests assessed by IHC analysis. Results: The median age at presentation was 45 years. Stage distribution and survival is shown in table-1. All 59 patients were undergone to the modified radical mastectomy and received adjuvant anthracycline chemotherapy. Twenty patients received additionally taxane. Among analyzed patients with stage IV disease, common site of metastatic involvement was bone, lung, brain, and pleural effusion/pulmonary metastases - 8 cases. The response to anthracycline was 46%, to taxane 57%, to cisplatin combination 59%, and to gemcitabine 22%. Two patients were offered bevacizumab with 50% RR. Conclusion: Triple negative breast cancer is aggressive disease with vast majority of patients presenting with advanced stage of the disease (69.3%); bone is the common site of metastatic involvement; good response to cisplatin-based combination chemotherapy, lack of effective and available targeted molecules. It poses a special therapeutic problem for the patients with bone as only site of metastatic disease. As microarray analysis is not available in the developing world, immunohistochemistry markers to subtype the disease and refine the art of treatment are required. Stage distribution and survival of breast cancer patients Stage Percentage 5-year survival

Results: The median age was 49 years (29-69). Tumor size ranged from 2.5 to 15 cm (median 7 cm), most pts had T4 disease (82%) and ER/PR positive tumors (68%). All pts underwent MRM after neoadjuvant chemotherapy. Clinical response was partial in 25 pts (86%), complete in 2 pts (7%) and stable disease in 2 pts (7%). Complete path response (including axillary nodes): 2 pts (7%). As a median follow-up of 50 months (95% CI 15-88), 17 pts (59%) progressed and 14 (48%) died. Five pts (17%) had loco-regional relapse and 6 (21%) developed brain metastases. The estimated median progression-free survival (PFS) and overall survival (OS) were 26 months (95% CI 19-35) and 42 months (95% CI 25-59), respectively. The Estimated 4-year PFS and OS rates were 24% and 44%, respectively.

Conclusions: The prospective evaluation of combined modality treatment in patients with path confirmed isolated supraclavicular nodal metastases, at presentation, is in agreement with the previous retrospective series (Olivotto, J Clin Oncol 2003; Brito, J Clin Oncol 2001). These data reinforce the role of local therapy in the management of women with stage IIIC breast cancer.

CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY AS A PREDICTOR OF NEUROPATHIC PAIN IN BREAST CANCER PATIENTS PREVIOUSLY TREATED WITH PACITAXEL

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Neuropathic pain (NP) remains difficult to control for a significant proportion of patients with cancer. Chemotherapy induced peripheral neuropathy (CIPN) is postulated as an initial stage to the development of NP. We conducted a survey of breast cancer patients who previously participated in clinical trials for pacitaxel and assessed the extent to which those who experienced CIPN (NCI toxicity criteria ≥ grade 2 sensory neuropathy) during the chemotherapy trial were at risk of developing chronic NP, controlling for disease- and treatment-related variables (e.g., stage of disease, location of tumor chemotherapy and other cancer therapies, dose of chemotherapy and duration of treatment), clinical health status (e.g., comorbid conditions), and sociodemographic characteristics (e.g., age, race). Results showed that, of the 430 potential respondents, 240 responded to the survey. Mean follow-up was 9.5 years (SD=2.1). Sixty three percent of the respondents had grade 2 or greater sensory neuropathy during their previous treatment with pacitaxel. Follow-up survey data showed that 18% (43/240) were subsequently diagnosed by their physician to have NP. Logistic regression analysis showed that those with CIPN during the trial were 3 times more likely to report a diagnosis of NP (OR=3; 95%CI=1.2; 7.2; p<0.001), which persisted in the multivariable logistic model. We also found that those with NP reported twice as many visits to their health care provider (p=0.028); had taken more prescription (50% versus19%; p=0.0001) and over-the-counter medications (62% versus 43%; p=0.098) for pain relative to those without NP. We provide empirical evidence on the importance CIPN as a risk factor for NP in breast cancer patients. Prospective studies with larger cohorts are needed to validate our findings.
response rate was 83.3% (35/42), CR 38.1% (16/42), and PR 45.2% (19/42). The average time from therapy beginning to pain relieves was 1.8±0.8 days. The skin lesion of HFS including dermatitis, pruritus, ulceration have been improved after treatment. The mean score of the Qol before and after treatment were 77.24±25.69 and 109.17±20.53 (P<0.01). No side effect such as allergy related to LC07 was found.

Conclusions: Compound external Chinese herbal medicine LC07 can treat capecitabine-induced HFS, which is fast effective for relieving pain, easy for use and has not caused allergy. Thus improve the Qol in pts with MRC and HFS.

PSYCHOPHYSIOLOGICAL PTSD DYNAMICS IN FEMALE BREAST CANCER PATIENTS: A NOVEL DYNAMIC APPROACH FOR AN OLD DYNAMIC SYSTEM

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Introduction: Post-traumatic stress disorders (PTSD), frequently observed in breast cancer patients, affect the balance between the parasympathetic (PNS) and the sympathetic branch (SNS) of the autonomic nervous system (ANS). The PNS-SNS balance is computed using power spectral density (PSD) indirectly derived from ECG recordings (1). It was the aim of this study to compare computational approaches used to assess PNS-SNS balance helpful to improve PTSD diagnosis in breast cancer patients.

Methods and Results: ECG and respiration were recorded in a blocked design in controls and postoperative female breast cancer patients under variable sensory loads. LF/HF-ratios computed as described in (1) and with a new gliding window technique (2) were compared. Averaged results from dynamic computations showed no statistical differences (paired T-test) with standard computations. LF/HF-ratios computed with a gliding window, however, exhibited dynamics suppressed by conventional routines.

Discussion: Dynamic LF/HF-assessment yielded consistent results with standard computations. Using this novel approach, there is evidence that the LF/HF-ratio is frequently governed by dynamics which are eliminated by commonly employed statistical analyses.

Literature

EFFICACY OF LOW ENERGY LASER THERAPY FOR BREAST CANCER PATIENTS

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Backgrounds: Many kinds of systemic chemotherapies and endocrine therapies are performed for breast cancer patients. However it is a fact that these drugs induce peripheral neuropathy, hot flush and joint pain in many patients. We generally try to control these symptoms, peripheral neuropathy, due to Taxans (especially Paclitaxel), and hot flush due to LH-RH, and joint pain, especially due to aromatase inhibitor (AI) by medication. However many patients are still anxious about these symptoms.

Aim: To study the influence of the changing hormonal environment (the change of hormonal environment during the oestrus cycles) on tumour growth and character of change of the receptors level in mammary tumors in C3H/Sn mice.

Methods: Female C3H/Sn mice were used in the study. The dextran-coated charcoal radioactive ligand-binding ER assay was used followed by Scatchard analysis. Total protein was measured by Lowry method. The data obtained were statistically processed, and the statistical significance of differences was evaluated according to the Student’s test.

Results: In the course of progressive growth of ER-positive mammary tumours, the wave-like changes of tumor volume are evident coinciding with fluctuations of hormone levels during 4-days mouse oestrus cycle. When tumor volume is maximal, ER are present only on half of tumor cells. Thus the cell population becomes heterogeneous in the content of estrogen receptors. Therefore, half of the cells will respond to hormonal therapy. High sensitivity tumour cells to short-term changes of the hormonal environment at a level of physiological concentration cause formation of heterogeneous tumours. Then the application of hormones or agonists (about 2 weeks) leads to heterogeneity reduction. Alternating treatment with estrogen and tamoxifen arrest further growth of tumour but does not lead to the remission.

Conclusion: Tumour cells are highly sensitive to hormone background alterations. Simultaneous or a small interval application of various hormones can increase heterogeneity of a tumour. In order to control this robustness, an effective therapy is required to reduce or at least avoid increasing such diversity.
CHEMOTHERAPY, THE WORST EXPERIENCE IN THE BREAST CANCER PATIENTS
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Background: Chemotherapy is a common treatment for breast cancer. Side effects of chemotherapy, especially hair loss, are the most important concerns in women receiving breast cancer treatments. Some women even describe chemotherapy as more traumatic than the loss of a breast. The aim of this study was to explore and understand more about the patients’ experiences of chemotherapy.

Methods: In-depth interviews were conducted with 46 breast cancer patients at the Iranian Breast Cancer Center. The interviews were taken verbatim and thematic analysis was performed.

Results: All of patients had surgery and chemotherapy treatments. The mean age was 48.3 (SD = 16.5) years, 76% were married and 54% had secondary or higher educations. 3 major subjects from analysis emerged: 1) trust in God as the greatest power to overcome their cancer problems, 2) family support (especially husband or a close relative) as the most important coping strategy and 3) chemotherapy side effects as the worst experience of the treatment.

Conclusion: It seems that prior to commence of chemotherapy, clinicians should have enough information about patients about treatment and management of its side effects. Also it is needed to listen to the patient concerns and advise information to their family, especially their husbands or close relatives to provide a better supports to the patients.

PSYCHOPHYSIOLOGICAL RESPONSES TO TRAUMATIC STRESS MEMORIES IN FEMALE BREAST CANCER PATIENTS
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Introduction: Post traumatic stress disorders (PTSD) can be triggered by events exceeding the individuals coping capacities. Therefore, PTSD in female breast cancer patients (FBCP) may result from past biographical events as well as from cancer and surgical treatment. Since the autonomic nervous system (ANS) mediates PTSD associated physiological responses, such responses are commonly studied as a response to script-driven imagery. We screened FBCP for past traumatic experiences and studied their physiological responses.

Methods and Results: Following SKID PTSD diagnostic interviews (DSM IV based), heart rate variability (HRV) and the LF/HF-ratio as an expression of ANS balance were determined during self-read or neutral voice read traumatic accounts in FBCP (n=10). While there was a prevalence of 30% of full blown PTSD, 50% reported of grave stressful life events. For the overall study sample, this showed significant increases (p<0.017, student t-test) for both experimental conditions.

Discussion: In our study we observed significant increases in ANS responses following voice controlled traumatic script exposition. These responses need further differentiation since stressful life events and PTSD differ as for their clinical symptoms profoundly.

PREVENTING THE DEVELOPMENT OF LYMHOEDEMA IN BREAST CARCINOMA PATIENTS
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Background: Lymphoedema following surgical treatment for the cancer patients is a chronic debilitating condition. Once it sets there is no different treatment. In recent literature the role of venous hypertension in the affected arm is been proposed as an important etiological factor.

Aim: To evaluate the influence of class II compression stockings in reducing the incidence of lymphoedema which is measured in directly by calculating the arm volume in the pre & post op period.

Materials and methods: Randomized prospective double arm blinded study involving 2 groups (group 1 study, group 2 control). Pre and 10 th post operative day, the mid arm circumference and arm volume were measured. According to the computer generated randomization number, Siguvaris class II compression stockings [with mitten was applied in the study group] throughout the day except in the night. The trained nursing staff was blinded for the intervention.

Results: 12 patients in each arm, all of them had simple mastectomy and axillary node clearance. The mean age was 35 yrs, BSA was 16. Stage II was seen in majority with 60 %. The average number of nodes to present in group I was 16(2 to 19) and positive nodes were 3.8(range 0 to 4 ). The average total and positive nodes in group II was 16 and 2. The Mean size in Group I=1.77 SD in Group II=1.08; Mean size in Group I=1.86 SD in group II=0.56, P value =0.73. The average preoperative arm volumes in group I and II were 2622 and 2059 ml and in the 10 th postoperative period the average arm volume was 2545 and 2318 ml. There is statically significant increase in the arm volume in control group [Median difference between pre and post in Group I=100 Median difference between pre and post in Group II=300; P value = 0.01]. In arm circumference, there was also statistically significant increase in the control [Median difference between pre and post in Group I=1. Median difference between pre and post in Group II=1 P value =0.01]. There was no difference in arm volume in relation to the stage, nodal stage and BSA. There was no skin excoriation secondary to the usage of arm stockings.

Conclusion: There is significant increase in the arm value in the control group which will definitely have an impact on the long term development of lymphoedema. However it has to be done in a larger number of patients with at least one year follow-up.

RELIABILITY OF PSYCHOPHYSIOLOGICAL RECORDINGS IN FEMALE BREAST CANCER PATIENTS
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Introduction: Post-traumatic stress disorders (PTSD) are frequently observed in female breast cancer patients (FBCP). This may be due to biographical events, but also to the impact of diagnosis and surgical treatment of breast cancer. Since PTSD associated physiological responses are mediated by the autonomic nervous system (ANS), they are regularly studied in laboratory settings. These settings might also to the impact of diagnosis and surgical treatment of breast cancer. Since the autonomic nervous system (ANS) mediates PTSD associated physiological responses, such responses are commonly studied as a response to script-driven imagery. We screened FBCP for past traumatic experiences and studied their physiological responses.

Methods and Results: Following SKID PTSD diagnostic interviews (DSM IV based), heart rate variability (HRV) and the LF/HF-ratio as an expression of ANS balance were determined during self-read or neutral voice read traumatic accounts in FBCP (n=10). While there was a prevalence of 30% of full blown PTSD, 50% reported of grave stressful life events. For the overall study sample, this showed significant increases (p<0.017, student t-test) for both experimental conditions.

Discussion: In our study we observed significant increases in ANS responses following voice controlled traumatic script exposition. These responses need further differentiation since stressful life events and PTSD differ as for their clinical symptoms profoundly.

LITERATURE
Background: Bone metastatic lung cancer or breast cancer pts often have neuropathic pain which has poor reaction to opioids. This clinical trial aims to investigate efficacy of electroacupuncture (EA) in cancer pts with neuropathic pain.

Methods: Inclusion criteria were bone metastatic lung cancer or breast cancer pts; at least one of the symptoms as burning pain, shooting pain, dysesthesias or allodynia; numerical rating scale (NRS) of pain intensity >=4.0; stable dose of opioids for at least 72 hours. Exclusion criteria were chemotherapy or radiotherapy 15 days before or during the study. Hormone or adjuvant therapy could be started before the study, but the dose could not be changed afterwards. Opioids could be increased step by step according to the pain intensity. The EA was manipulated with low frequency (2 Hz) and high frequency (100 Hz) dense-disperse waves alternatively, 30min per day, 5-days therapy with 2-days interval, 3 weeks continuously. Acupoints were selected as ST36, SI3, SI5, LI3, L14 bilateral. Controlled group accepted non-acupoint treatment close the right acupoint.

Results: Ninety pts with neuropathic pain participated in this randomized, control designed trial from 2006 to 2008. Overall, 45 pts accepted EA treatment and 34 completed the study. In the control group 45 pts accepted to participate and 32 completed the study protocol. There was no difference in initial NRS which was 6.3 ± 2.1 in EA group and 7.2 ± 1.8 in control, P=0.0669. The decrease in NRS was significantly higher in the EA group compared to the control (3.2 ± 1.7 vs. baseline, P<0.0001; 5.4 ± 2.2 vs. baseline, P=0.0007). Analysis showed a significant difference in NRS between EA group and control at the end of survey, P<0.0001. Mean analgesics consumption variety in EA group was: transdermal fentanyl increased by 51.2% (16 pts) and 77.3% (21 pts) in EA and control, P=0.0005; oxycodone increased by 85.5% (18 pts) and 115.6% (11 pts) in EA and control, P<0.0183. Functional Assessment of Cancer Therapy-General (FACT-G) scale did not show difference at the beginning while it was 102±18 and 85±12 in EA group and control at the end of survey, P=0.0001.

Conclusion: EA can alleviate neuropathic pain in bone metastatic cancer pts, decrease analgesics consumption, and increase quality of life.