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Significance of Prognostic Score for Cancer Patient

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ABSTRACT

The main object of this study was to obtain a reliable determination of symptoms prevalence in patients with cancer due to performing the systematic review of studies assessing related topic multiple biomedical imaging techniques are used in various phases of cancer management. Imaging forms an important part of cancer clinical protocols and it is probable to furnish morphological, structural, metabolic and functional information. Integration with other diagnostic tools such as *in vitro* tissue and fluids analysis assists in clinical decision-making. Care and treatment of advanced care are focused on the management and relief of symptoms, as well as increase the patient's satisfaction and quality of life. Information of symptom prevalence is important for clinical practice. For ensure the safety and optimize efficacy and careful patient selection for involving in the phase I trials is warranted. Therefore a validation study on existing phase I prognostic scores and subsequently aimed to make it an even more simple prognostic score. The results of this study should be used to guide doctors and nurses in symptoms management. Proper attention to symptoms burden and suffering should be the basis for individually tailored treatment aimed at improving or maintaining quality of life of patient.

Keywords: prognostic, cancer, phase-1, chemotherapy, imaging

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INTRODUCTION

Cancer

Advanced cancer will be occurred when the disease has migrated from its original site and other areas of the body. In some cases, it will be locally advanced in a vital organ, but is not reached distant sites it may have metastasized or spread on the whole body by the lymph system or bloodstream. Care and treatment of advanced care are focused on the treatment and relief of symptoms, with improving the patient comfort and quality of its life [1].

Symptoms

The symptoms of advanced cancer will different from one patient to another. According to the National Cancer Institute some of the commonly treated symptoms of advanced cancer include lethargy, upset stomach, shortness of breath, blocked bowels, weakness, nausea, sputum/cough, weight loss, vertigo, confusion, depression, forgetfulness, anxiety, swollen legs and ankles, skin rashes, tastelessness, bladder or bowel issues, loss of appetite, sleep disturbances and pain [2].

Treatment Approaches

Individuals diagnosed with advanced cancer may benefit from a variety of treatment approaches depending on the location and type of cancer. It is entirely within the patient's discretion which choice of treatment is best for him. Typically advanced cancer is not addressed through surgery except in cases where it can eliminate pain, stop bleeding or enhance the quality of life. Also referred to as palliative radiation, radiation therapy enables patients to decrease pain and other symptoms by shrinking tumors. Systemic therapy such as hormonal therapy or chemotherapy, which is administered intravenously or orally, the treatment recommended for cancer cells that have spread [2].

Biomarker is derived from the genome and proteome will be targeted using chemistry that selectively binds to the biomarkers and amplifies their imaging signal. Imaging biomarkers have been development in order to identify the presence of cancer the tumor stage and aggressiveness as well as the response to therapy. Different pharmaceutical formulation is under development for cancer that are classed as cytotoxic, antihormonal, molecular targeted and immunotherapeutic. The molecular targeted formulation tend to imaging for control of their effectiveness and include signal transduction inhibitors, angiogenesis inhibitors, apoptosis inducers, cell cycle inhibitors, multi-targeted tyrosine kinase inhibitors and epigenetic modulator.

Palliation denotes a shift from cure and control of the disease to improvement or maintenance of quality of life. This shift in focus is an important event for cancer patients and their likes ones, and also for doctors and nurses [3-5].

Physical symptoms functional deficits with the feelings of loss of control become the focus of care. The World Health Organization (WHO) has defined palliative care as ‘‘an approach to care which improves quality of life of patients and their families suffering from life threatening illness through the prevention and relief of suffering by means of identification and impeccable assessment of pain and other problems, physical, psychosocial and spiritual.’’ The palliative phase has different dynamics in every patient. However, the suffering of these patients is determined to a large degree by the presence and intensity of the symptoms of their disease. To study of symptom prevalence is essential for clinical practice as it is not able doctors and nurses to target on the more prevalent symptoms and it help to anticipate problems and plan care for patients to educate clinical staff, to direct assessments of health care need and to plan services. Various studies have addressed this issue in patients with incurable diseases, most often in with cancer. Whatever, these information are heterogeneous with regard to patients and assessment method and the many patients involved are often relatively low. The main objective of this study was to obtain easy to estimation of symptom prevalence in patients with incurable cancer by performing a systematic review of studies assessing this topic.

Secondary aims were

1) To study differences in symptom prevalence during the last one to two weeks of life,
2) To assess the influence of assessment method, gender and age on symptom prevalence.

DETAILING OF CANCER

1) Image contrast

Imaging systems produce images that have differences in contrast. The differences in contrast can be due to changes in physical properties caused by the endogenous nature of the tissue or by the use of exogenous agents [6-10].

Endogenous mechanisms include [12]

a) Radiation absorption, reflection and transmission
b) Magnetic relaxivity
c) Magnetic susceptibility
d) Water molecule diffusion
e) Magnetic spin tagging
f) Oxygenation
g) Spectral distribution
h) Temperature
i) Electrical impedance
j) Acoustic frequency shifts
k) Mechanical elasticity

Exogenous mechanisms include

a) Radiation absorption, reflection and emission
b) Spin hyper-polarization
c) Magnetic relaxivity
d) Magnetic susceptibility
e) Magnetization transfer
f) Saturation transfer
g) Isotope spectra
h) Fluorescence
i) Bioluminescence
j) Perfusion
k) Extracellular pH
l) Hypoxia

Diagnostic imaging agents introduced intravenously, intra arterially or via natural orifice play an increasing role in cancer imaging.

2) X-Ray-based systems

Digital imaging technology is expanding the role of X-ray based systems in the imaging of cancer as the use of picture Dual energy systems can use two stacked detectors separated by a copper plate and using one X-ray exposure or one detector with dual X-ray exposure. In both cases images flow and high energy X-rays are produced. As a result soft tissue images or bone and calcium images can be obtained. Dual-energy subtraction eliminates rib shadows and allows accurate, computerized measurement of lung nodule volume. Energy subtraction images have important advantages over standard radiographic images. Intra-pulmonary lesions and bone may appear superimposed when projected in two dimensions. The soft-tissue image, with bone removed, can improve the ability to detect these lesions. The more clear margins of these lesions in the soft-tissue image can assist in lesion characterization. Calcified nodules may be distinguished from non-calcified nodules [13-16].

3) Magnetic resonance systems

Magnetic resonance is used in cancer detection, staging, therapy response monitoring, biopsy guidance and minimally invasive therapy guidance. Imaging techniques that have been Automated Analysis

• Segmentation
• Vessel & wall extraction
• 3D lesion sizing (± 4%)
• Doubling time estimate, developed to image cancer are based on relaxivity-based imaging with and without contrast agents, perfusion imaging using contrast agents, diffusion weighted imaging, endogenous spectroscopic imaging, exogenous spectroscopic imaging with

hyperpolarized contrast agents, magnetic resonance elastography and Blood Oxygen Level Determination (BOLD) imaging. Nuclear Magnetic Resonance (NMR) spectroscopy had existed for over 30 years before the possibility to distinguish tumor tissue from T1 and T2 relaxation time measurements in vitro was the catalyst that started the development of Magnetic Resonance Imaging (MRI) systems. MRI of the human body became possible only after the application of local gradient fields [17-18].

4) MRI of breast cancer

Breast cancer was one of the first to be examined using MRI. After more than 10 years of clinical use breast MR is now starting to be accepted as a complementary technique on a par with mammography and ultrasound. This has happened through the development of surface coils, advanced gradient coils, parallel imaging, contrast agents and new fast imaging sequences that have greatly improved MRI of the breast. Dedicated breast imaging tables provide complete medial and lateral access to the breast, enabling unimpeded imaging and intervention including biopsies. New surface coils allow the simultaneous imaging of both breasts to indicate involvement of the contra-lateral breast. The move to higher field strengths with T3 MRI systems has been aided by parallel imaging that can reduce the effect of T1 lengthening, reduce susceptibility artifacts and avoid too high Specific Absorption Rate (SAR) values. Breast MRI has a higher sensitivity for the detection of breast cancer than mammography or ultrasound. Due to cost reasons, access and high false positives MRI is not yet considered a screening exam for breast cancer except for special cases. As a result of not utilizing ionizing radiation, breast MRI has been recommended in the repeated screening of high-risk patients who have increased risk of radiation induced DNA mutations. These include individuals with the BRCA1 or BRCA2 gene mutation. It is used to screen women with a family history of breast cancer, women with very dense breast tissue, or women with silicone implants that could obscure pathology in mammography. It is also useful to look for recurrence in patients with scar tissue. The American Cancer Society has given a strong endorsement for MRI, to detect lymph node involvement and contra-lateral disease extension in breast cancer. Staging is probably the most important use of breast MRI because it can show chest wall involvement, multi-focal tumors, lymph node metastases and retraction of the skin. It has a better performance in imaging invasive lobular carcinoma than other methods [19].

5) Diffusion weighted imaging

Diffusion weighted imaging (DWI) has been around for over 23 years with a first application in detecting cytoxic odema in stroke. DWI MRI measures the diffusion of water molecules (Brownian movement) and is a promising technique for the identification of tumors and metastases and could have an application in characterizing breast lesions as benign or malignant. DWI MRI provides endogenous image contrast from differences in the motion of water molecules between tissues without the need for exogenous contrast agents. It is possible to obtain both qualitative and quantitative information related to changes at a cellular level demonstrating the influence of tumor cellularity and cell membrane integrity [20].

6) Antibody imaging

Genetically engineered antibody fragments have been developed for positron emission tomography (PET) with suitable targeting specificity and systemic elimination properties for the imaging of cancer based on expression of tumor associated antigens. Targeted imaging using antibodies requires longer half-life PET isotopes such as 124I, 64Cu, 86Y and 74As to match the biological half-lives of the antibodies. Pre-clinical imaging has been performed using antibody fragments such as anti-HER-2 labelled with and anti-CEA labelled with 124I and 64Cu A 74As labeled chimerical monoclonal antibody that binds to phosphatidylserine expressed on tumor endothelial cells, has been used for the pre-clinical PET imaging of solid tumors [22-25].
Future clinical imaging with longer-lived isotopes will require correct patient management to avoid radiation risk to persons coming into contact. Radio-immunotherapy with 90Y monoclonal antibodies (mAbs) has been approved. As 90Y is mainly a b-emitter, 86Y-labelled mAbs are used as surrogates to determine the bio-distribution and the dosimetry of 90Y labelled mAbs in patients [22-25].

7) Pharmacokinetics and micro-dosing

It makes possible to determine drug distribution and concentration *in vivo* in man with drugs labelled with a positron emitting radionuclide that does not change the biochemical properties. Imaging is used to measure the efficiency of chemotherapy by evaluating delivery and targeting approaches to maximize drug concentration in tumors relative to normal tissues. PET radiotracers are used to evaluate bio-distribution between normal and tumors tissues, metabolism, toxicity, response prediction and dosimeters for radio immunotherapy [26-28].

8) Apoptosis imaging

Direct imaging of apoptosis has also been attempted using agents that bind to a cell surface protease that attracts phagocytes to dying cells. Annexin V has been used in optical and nuclear medicine imaging. The C_2 domain of synaptotagmin, a protein, also binds to phosphatidyl serine. MRI detection of apoptotic cells, *in vitro* and *in vivo*, has been demonstrated using the C_2 domain of synaptotagmin, tagged with super paramagnetic iron oxide (SPIO) particles [41-44].

9) Non-ionizing electromagnetic imaging

Thermo-acoustic imaging Near-infrared spectroscopy, electrical impedance spectroscopy and tomography, microwave imaging spectroscopy and photoacoustic and thermoacoustic imaging are often referred to as electromagnetic imaging. They use non-ionizing electromagnetic radiation between the optical and RF wavelengths. MRI uses RF as well but is not normally classified as part of electromagnetic imaging. Thermo- and photo-acoustic imaging systems use hybrid imaging techniques that are able to combine the high contrast in microwave, RF and light absorption between healthy and tumors tissues with the high resolution of ultrasound. These systems use non-ionizing radiation and are hybrid because they

use both the transmission of electromagnetic energy and reception of ultrasound waves generated by tissues. The electromagnetic energy is deposited as a very short time impulse as uniformly as possible throughout the imaging object that causes a small amount of thermal expansion. Typical pulse widths for optical excitation are of the order of 5–10 ns. The photoacoustic technique depends precisely on the absorbed photons for a signal and avoids the issues due to light scattering in optical imaging [29-32].

10] Angiogenesis imaging

Cell adhesion molecules, such as integrins, have a major role in angiogenesis and metastasis. There is a developing interest in using scientigraphy to follow drug delivery using nanoparticles as drug delivery systems Pre-clinical studies can use radio-labelling to evaluate the biodistribution of carbon functionalized nanotubes (CNT). Future drug delivery systems may use carbon CNT to transport and translocate therapeutic molecules. It is possible to functionalize CNT with bioactive nucleic acids, peptides, proteins and drugs for delivery to tumors cells. Functionalized CNT have increased solubility and biocompatibility, display low toxicity and are not immunogenic [11].

11] Multi-drug resistance imaging

Radiopharmaceutical agents with lipophilic or cationic properties signal the presence or absence of P-glycoprotein. 99mTc-MIBI, 99mTc-tetrofosmin, 99mTc-Q58 and several 11C agents share these characteristics but 99mTc MIBI has shown the most promise. In the absence of P-glycoprotein the lipophilicity of 99mTc-MIBI enables it to translocate across the cell membrane and its cationic charge allows it to concentrate inside the cell and be sequestered in the mitochondria. The agent uptake is consequently high.

12] Hypoxia imaging

Activates various agents including Hypoxia-inducible factor- 1 (HIF-1a and HIF-1b), activation protein-1 (AP-1) and heat shock proteins (HSP). These agents affect the behavior of genes that control angiogenesis cell cycle regulation and apoptosis. In combination, they encourage cancer cells to divide and metastasize more rapidly through anaerobic glycolysis that is a transcription factor for HIF-1. Hypoxia reduces the Oxygen is an important mediator of radiation-induced DNA damage. As a result low PO_2 levels in the tumor significantly impede the ability of radiation to kill tumor cells by as much as 300%. Hypoxia can vary regionally and over time. As a result radiotherapy plans based on a static image of hypoxia may be misleading. In general chronic rather than transient hypoxia is the dominant component. Chronic hypoxia is probably due to a large distance between tumor cells and blood vessels. Transient hypoxia may be due to blood flow variations [33,34].

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CHEMOTHERAPY

Advantages of Chemotherapy

With wide infection rates and very few cures, cancer is slowly becoming one of the biggest killers of our population's history.

History of Chemotherapy

Chemotherapy is a type of cancer treatment that attempts to destroy the malignant cells within the body through exposing them to toxic substances. Gemcitabine has been widely administered as the first-line drug against pancreatic cancer in clinical practice. Gemcitabine was administered at a dose of 1000 mgm^{-2} in a 30-min intravenous infusion on days 1, 8 and 15 in 4-week cycles. In 2005, combination therapy with gemcitabine and S-1 was introduced at our institution. As we reported previously, gemcitabine was administered at a dose of 1000 mgm^{-2} in a 30-min intravenous infusion on days 1 and 15 and S-1 was administered orally at a dose of 40 mgm^{-2} twice daily for the first 14 consecutive days, followed by a 14-day rest in 4-week cycles. Initial dose reduction in gemcitabine monotherapy was allowed at the discretion of the physician, according to age or comorbidity. In contrast, initial dose modification was not performed in combination chemotherapy with gemcitabine and S-1 because combination therapy was administered only to fit patients with less comorbidity.

THE CLASSIC PHASE I TRIAL

Standard Design

The standard Phase I design is a Dose acceleration trial in which successive small groups of patients (Called "cohorts") are given successively higher doses of the treatment until some of the patients in a cohort experience unacceptable side effects. In most Phase I trials there are 3-6 patients in each cohort. The first cohort of patients in the trial typically get a rather low dose. If unacceptable side effects are not seen in the first cohort, the next cohort gets a higher dose. This continues until a dose is reached which is too toxic for a set fraction of patients, say one in three. Then the previous dose level is considered to be the Maximum Tolerated Dose (MTD). It's important to realize that individual patients are only treated at a single dose level, although they may receive several treatments at that dose level. It's also important to understand that the few patients who are treated at a dose above the MTD may not have serious problems. Even those patients who have dose limiting toxicity often are not permanently harmed although the treatment has to be stopped due to the side effects. Also at any given dose level, some patients will have milder side effects than others and some will not experience severe side effects even at doses above the MTD. It was treated in a Phase I trial at a dose level 50% greater than what was later selected as the MTD yet it will be actually tolerated the treatment better than most of the patients who were treated at the MTD.

Phase I Trials of Brand New Drugs

The patients in the first dose cohort of a Phase I trial of a new drug are the first humans ever to get that drug. Such a trial as close as you can get to the stereotype of a truly experimental treatment. Before any new drug can be given to humans, it must go through extensive pre-clinical testing in animals. The likely nature of the side effects and required effective dose can be extrapolated from the animal results, but there can still be surprises since animals are quite different from people. Because of this uncertainty, they typically start the trial with a very low dose, often one which is far too low to be effective even if the drug is later found to be active.

Phase I Trials of Combinations

Cancer treatment often consist of a cocktail of several drugs, and many Phase I trials test a new combination of drugs rather than a new drug. Perhaps a drug is being added to a standard treatment already known to have some effectiveness, or perhaps two active drugs are being tested in combination in the hopes that the results will be superior to those with either drug alone. Combinations in Phase I trials can involve drugs which are not yet approved for general use. Phase I trials of combinations are still dose escalation studies but because the side effects of the individual drugs are known the investigators have a better idea what doses are likely to be tolerable what the side effects are likely to be what doses may be required for efficacy.

Phase I Trials: Variations

Phase I trials often involve more than just the "dose" of the drug when and how it's given figure into the trial design as well. If a drug was previously given by 15 minute IV infusion five days a week, a new dose schedule involving continuous infusion with a portable pump will require a new Phase I trial. If this is a promising drug which is not yet approved such a trial could be a relatively good especially if you don't qualify for a Phase II trial involving this drug. More biologically targeted drugs may have a different endpoint for their Phase I trials than the MTD. Instead the trial may strive to achieve. If a drug has a specific molecular target which is unique to cancer cells, enough drug to completely saturate the target should achieve the maximum possible effect against the tumor and this dose may or may not cause significant side effects. Beyond the maximum saturation point, more will not be better, but it may be more toxic! If the effect on the molecular target can be measured during the trial, it may not be necessary to drive the dose to the level that side effects become limiting. Of course in this situation, it is still true that the MTD could turn out to be less than the maximum biologic dose. In addition, when a particular molecular defect is targeted, eligibility criteria may include proof that your tumor has the defect in question even in Phase I.

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Fig. 1. Feature role of imaging in cancer management

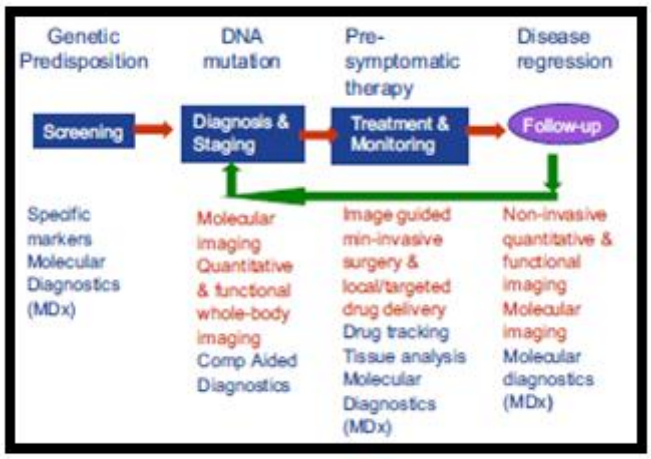
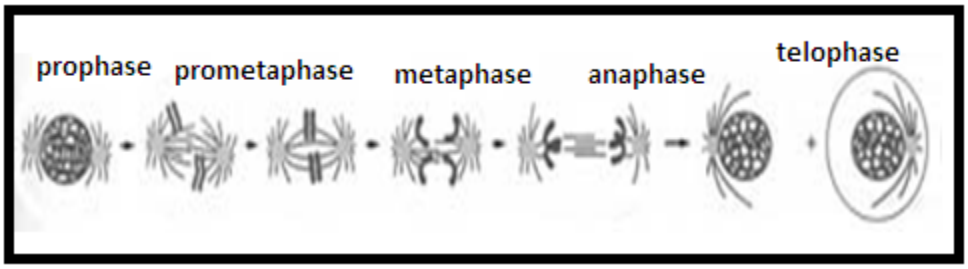


Fig. 2. Separation of cytokinesis



Phase I/II Trials

Phase I/II trials combine a Phase I and a Phase II trial of the same treatment into a single protocol. First the Phase I part of the trial is done to determine the MTD. Then more patients are treated at the MTD in the Phase II part, which follows immediately afterwards. The Phase I and Phase II parts are basically ordinary Phase I or Phase II trials, so you can analyze the trial as either a simple Phase I or Phase II trial, depending whether they've reached the Phase II part of the trial or are still in the Phase I part. The only way to find out is to talk to the investigators.

APPLICATIONS IN CANCER

Nuclear medicine systems are one of the mainstays of cancer centers both for imaging and therapy delivery. Nuclear medicine imaging has been used for over three decades in the diagnosis, treatment planning, and the evaluation of response to treatment in patients with cancer. Patient management is one of the most important applications of nuclear medicine in oncology in terms of staging of new cancer patients, restaging for treatment planning and the prediction of therapy response. Nuclear medicine can non-invasively indicate treatment response and disease recurrence so studies can be repeated because of low side effects and the low radiation absorbed doses. It is also possible to correlate nuclear medicine results with analytical laboratory data.

Advantages

The greatest advantage to chemotherapy is its control over the spread of cancer since it is delivered throughout the body in the bloodstream. It is even more effective when combined with surgery or radiation therapy.

Disadvantages

The worst disadvantage of chemotherapy is the unpleasant side effects such as nausea, hair loss and extreme discomfort. A second disadvantage is that chemicals must be carefully selected depending on the type and stage of the cancer.

REGULATION OF THE CELL CYCLE AND CANCER

Definition:

The cell cycle is an ordered series of events that culminate in the growth of a single cell and its division to produce two daughter cells.

Mitosis and Meiosis:

The physical events that occur during cell division are readily visible through the microscope.
In the case of mitosis (normal cell division) you can see over 2-4 hrs:
1. Breakdown of the nuclear envelope (prophase)
2. Condensation of the chromosomes (prometaphase)
3. Chromosomes assemble on the spindle in the centre of the cell (metaphase)
4. Separation of each complete set of chromosomes to opposite ends of the cell (anaphase)
5. Reformation of a nuclear envelope around each set of chromosomes (telophase)
6. Separation of the two daughter cells (cytokinesis).

Variations on the length of the cell cycle

In most adult tissues, one round of cell division takes 22-24 hours. In certain tissues such as varies between different cell types. Embryonic tissues, stimulated B lymphocytes or cancer cells the cell cycle can be <8 hours. G1 phase is reduced. Some yeast cells have no G2 phase. The first 10 nuclear divisions in fruit fly embryos have no G1 or G2 phases.
Phase I studies are primarily designed to determine the tolerability and toxicity profile of a new agent or a new combination of drugs. Characteristic for oncological phase I trials are the small number of patients participating, the uncertainty of toxicity and effectiveness, the study strain for the participants due to the large logistic commitment and multiple safety control visits. Patients participating within these studies are vulnerable patients with advanced cancer who have been through all available standard therapies. The question whether or not to offer a specific patient the chance to participate in a phase I trial is not easy to answer. In order to ensure safety and to minimize risk, the widely accepted inclusion [46].

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Staging systems used to define the prognosis of a particular disease are useful tools to guide treatment options. They are also essential for the selection of patients in clinical trials and for the adequate stratification of the population of interest for randomization. Overall survival (OS) in patients with hepatocellular carcinoma (HCC) is generally predicted using one of the four classical staging systems developed over the last two decades. The Okuda classification system was the first to consider both tumors factors and liver function and the other scores, namely: the Cancer of the Liver Italian Program (CLIP) score, the Barcelona Clinic Liver Cancer (BCLC) system. Treatment in carcinoma hepatic cellular classification was developed thereafter. While BCLC is used successfully in clinical practice to help select the most appropriate treatment option ranging from transplantation to palliative care no consensus has been reached concerning the best tool to be used when considering patients in the palliative setting. This setting nevertheless represents about 70% of all HCC patients and is the main target for clinical trials. Previous studies comparing these classifications have reported controversial results. Several explanations can be proposed. It is widely accepted that the prognosis of HCC patients depends on tumors factors and liver function. The presence and the causes of cirrhosis lead to a wide heterogeneity in the disease and in the population on which the prognostic classifications are applied. Moreover, the statistical analyses used to evaluate score performance were not always appropriate. In particular, only an association between variables and OS was analyses statistically by 'information criterion' or 'measure of gradient' [47,48].

METHODS

1) Patients analysis and data collection:

Dutch patients who participated in eight different phase I studies between July 2004 and August 2008 at the Radboud University Nijmegen. Medical Centre was identified. All patients fulfilled the study specific selection criteria and had objective progressive disease prior to study entry. In each case we recorded the following patient characteristics: age, gender, cancer type, cancer histology, number of metastatic sites, number of previous treatments, performance status, weight loss prior to start, albumin, hemoglobin (Hb), leucocytes, lymphocytes, thrombocytes, LDH, C-reactive protein (CRP), sodium, potassium, calcium, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (AF). The duration of survival, PFS and participation duration were documented. Also 90-d mortality was documented. To determine severe toxicity, we recorded the presence of serious adverse events and treatment related deaths [39].

2) Statistical considerations

First existing prognostic scores as identified in the literature were validated in our dataset on OS, and participation duration using a Cox regression model and on 90-d mortality using a logistic regression model. Only those scores composed of variables available in our data set were tested. Scores using more than two risk groups were modified since the goal was to achieve a simple and objective test able to advise whether or not a patient should be advised to

participate. The potential prognostic factors, mentioned previously, were identified from the literature. Only those that were significant in the univariate analysis in our dataset and had clear clinical relevance were considered for our prognostic score. Those 13 factors were: Hb, albumin, LDH, age, performance status, number of metastatic sites, sodium, potassium, AF, ALAT, calcium and leucocytes. To prevent over-fitting i.e. non-general ability of the fitted model to other datasets, we reduced the number of factors in such a way that the maximum number of factors was one tenth of the number of events. Those factors were selected on the basis of clinical relevance and statistical significance in the univariate Cox regression. The degree of clinical relevance was determined by professionals with extensive experience. Statistical analysis regarding only patients with complete information on study variables was included in the analysis.

The primary end-point was overall survival (OS), defined as the time between the date of randomization and the date of death, or the last date of follow-up for censored patients. In order to describe the impact of baseline characteristics on OS, survival curves were drawn with the Kaplan–Meier product limit method. Statistical analysis was performed by using the Cox proportional hazards model, stratified by trial, including age (older than 70 versus younger), gender (male versus female), PS (1 versus 0; 2 versus 0), histology (squamous versus adeno carcinoma; other histology versus adeno carcinoma) tumor stage type of first-line (platinum based versus other) and objective response to first-line as covariates. The proportional hazard assumption was tested using graphical methods and was adequately met for all analyses. Results are reported as hazard ratio (HR) of death with 95% confidence intervals (CI). Two-tailed p values were determined with the use of a likelihood-ratio test and values less than 0.05 were considered statistically significant. Survival (cancer-specific) analysis was carried out using the Cox -proportional hazard model. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding P-value had to be greater than 0.10. Fisher's exact tests were used to test the effects of GPS on clinic-pathological factors. We investigated whether other prognostic scores had an additional value in predicting OS, while using our prognostic score as follows. We performed a multivariate Cox regression including our prognostic score and the additional score as the only two predictors. Therefore, we modified the outcome of the existing scores into: high and low risk. If the additional score was statistically significant, it had additional value survival (cancer-specific) analysis was carried out using the Cox proportional hazard model. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival [37,40].

3) Analysis

Survival (cancer-specific) analysis was carried out using the Cox proportional hazard model. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival.

Validated non-anatomical prognostic factors

It was historically regarded as a single entity that expressed many possible histological appearances. And now more accurately recognized as a family of cancers resulting from distinct genetic abnormalities with unique morphological features, but a common derivation from the renal tubular epithelium. Aside from the known anatomical prognostic variables, numerous histological as well as clinical criteria have been shown to impact prognosis in patients with it.

Nuclear grade

Nearly all histo pathological tumor grading systems have shown independent prognostic value in studies that included grade as a variable. Developed a four-tier grading system based on nuclear, nuclear size, shape and contents. Nuclear grade has been shown to correlate with tumor stage, tumor size, metastases, lymph node involvement, vascular involvement and peri renal fat involvement Unfortunately, controversy exists concerning the inter observer reproducibility of grading and relevant breakpoints [37,38].

CONCLUSION

The goal of this study was to develop a rapid objective, clinically applicable and simple prognostic score. We decided to incorporate a maximum of three prognostic factors in our prognostic score, using hyponaetremia, anemia and elevated LDH. Hyponaetremia is a well known complication of cancer, caused by several mechanisms including the paraneoplastic production of anti-diuretic hormone, pituitary dysfunction, treatment-related hyponaetremia, sodium depletion and decreases in effective circulating blood volume. This is caused by several factors including tumor grade and severity, response to therapy, patient compliance and secondary organ function. In the study we investigated the prognostic value of the WHO PS and also have developed and validated on two independent samples a score specifically designed for the 70% of HCC patients non-eligible for curative treatments. Eight variables were selected to define the new prognostic score number and size of tumors, resence of US portal vein obstruction and metastasis, three clinical variables.

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