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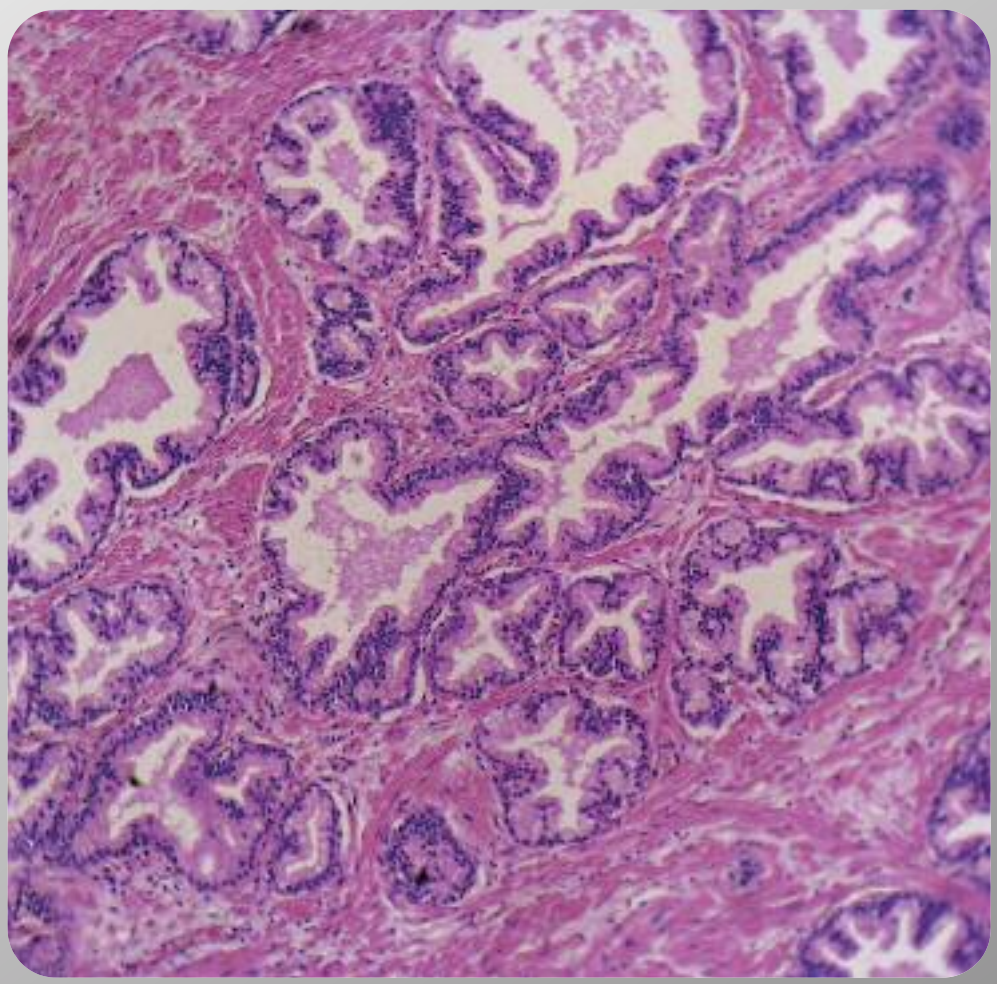


Equivalence, non-inferiority and superiority in clinical trials

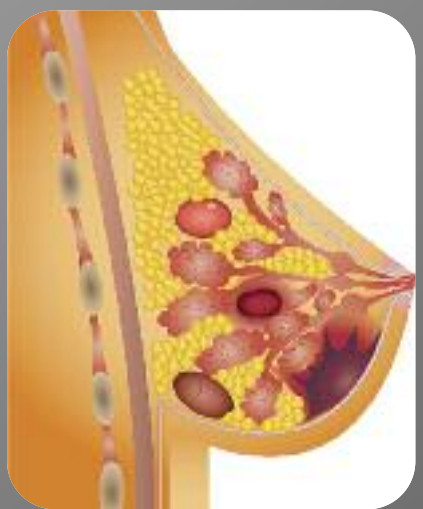
Management of patients with high risk features in radical prostatectomy specimens

EML4 - ALK & Crizotinib: from bench to bedside

Inhibition of angiogenesis in mBC: From Bevacizumab to tyrosine kinase inhibitors

Surgery of neuroendocrine tumors of the gastrointestinal and pancreatic region

Treatment of giant cell tumors of the spine with radiotherapy



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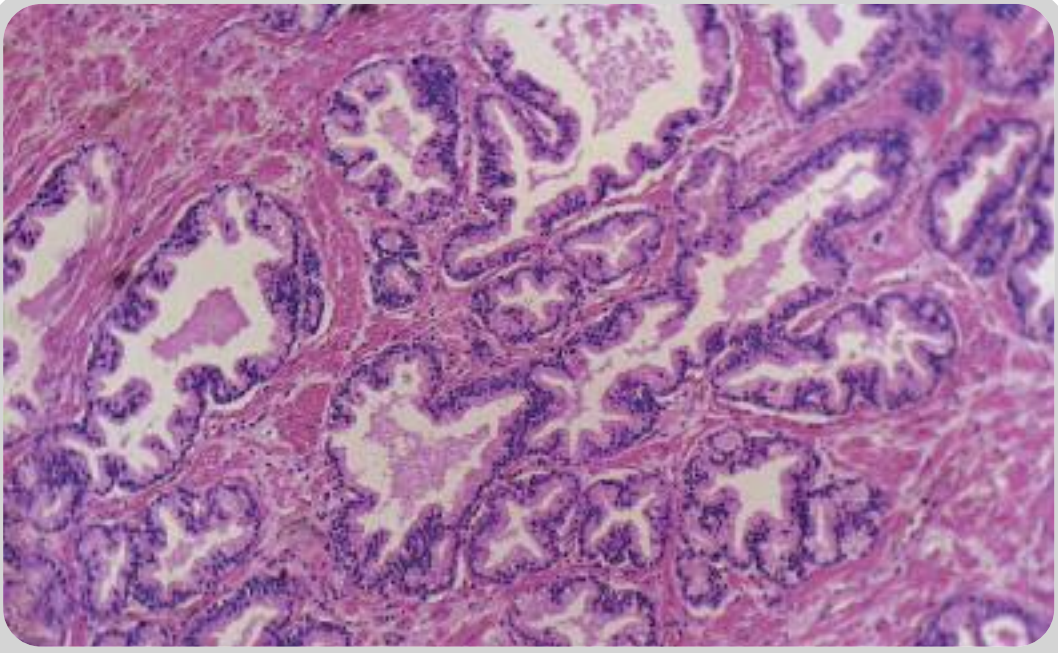

Contents

FCO FORUM of CLINICAL ONCOLOGY
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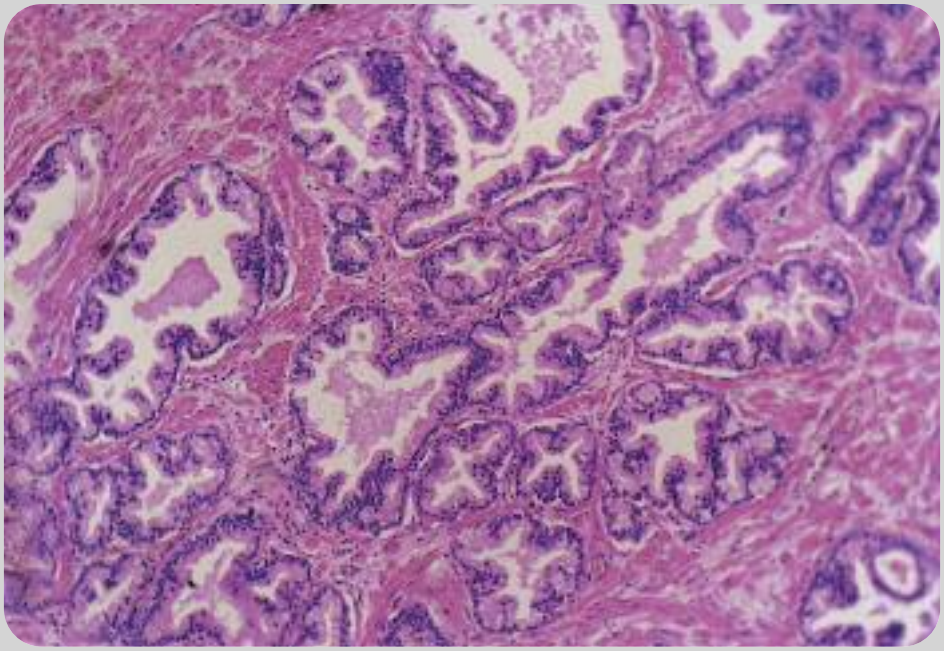
Contents (suite)

Case Report



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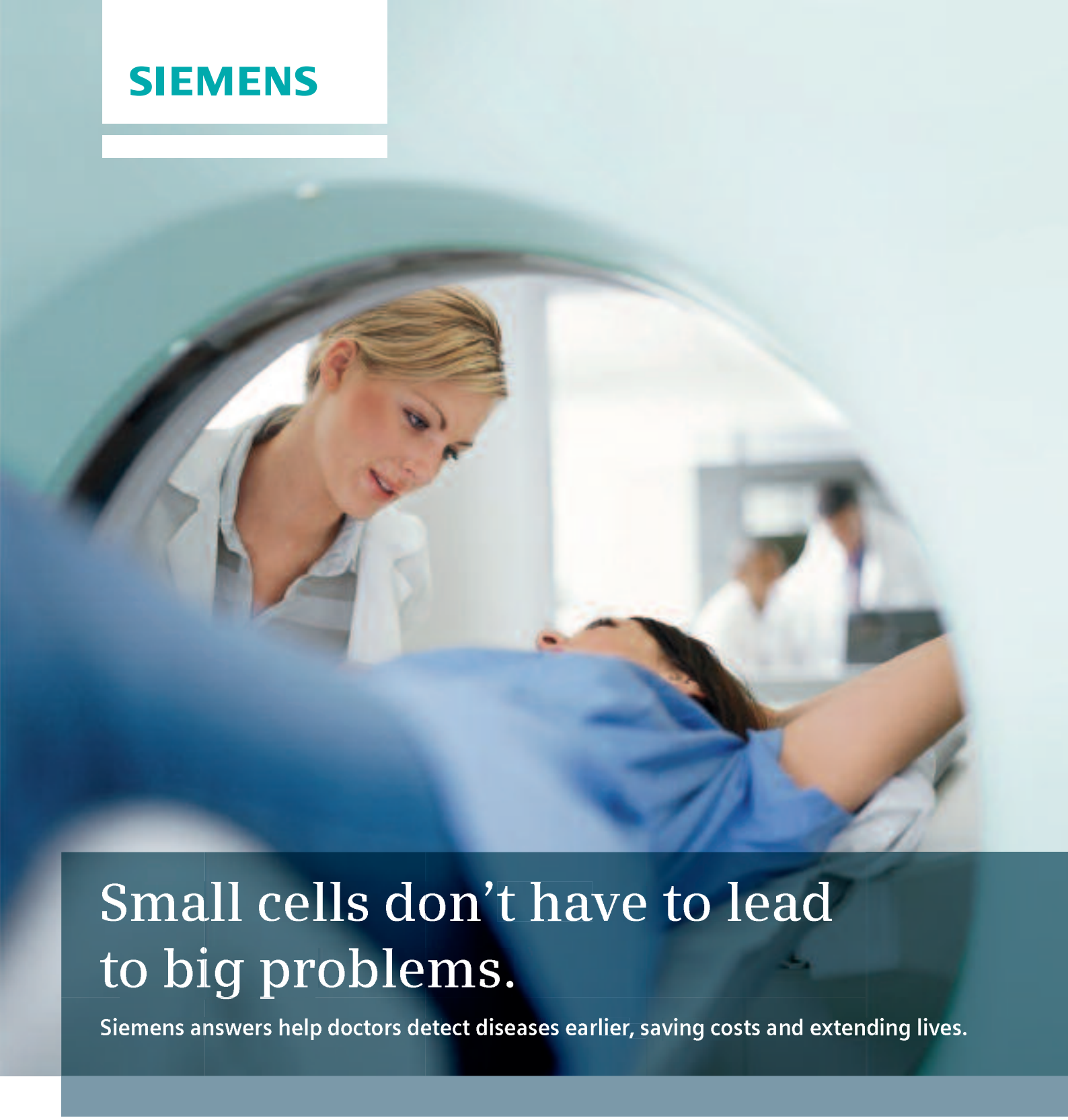

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The fight goes on

Editorial

Vassilios Barbounis

October is breast cancer awareness month; we take this occasion to outline the current developments on that field.

Survival of breast cancer patients has climbed these last years, thanks to the newly developed drugs and to the progress achieved by using state-of-the art technologies in screening, imaging and staging. Developments in breast cancer were also made in surgery and radiotherapy.

Currently, two thirds of women with breast cancer survive the disease more than 20 years, compared to 1900s when barely half did survive; many of the breast cancer survivors die from other causes. As for Greek women, risk of death from breast cancer today is 2%, while the risk for coronary disease is 40%.

Novel pharmaceutical agents were added to our therapeutic armamentarium against breast cancer as well as digital and magnetic mammography, positron emission tomography; the possibility of stereotactic biopsy of non-palpable lesions, a non-invasive technique; and molecular signature identification offer the possibility for individualized therapy for each patient.

Progress has also been made on patient information and psychological support for both the patient and her family in every stage of the disease: from diagnosis to treatment, breast reconstruction and follow-up. Unfortunately Greece is lagging behind in the field of patients psychological support but a lot of effort is being made to cover the gap especially by NGOs, support groups and patients associations.

We should equally thank both prominent and anonymous scientists for their efforts and hard work in the fight against cancer. Their achievements take us closer to the victory against cancer. Last but not least to praise scientific journals –print and electronic– for the support of the work of all scientists by reviewing, communicating, updating and educating the community for all the steps that lead to great breakthroughs.

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ΕΣΠΑ 2007-2013

Equivalence, non-inferiority and superiority in clinical trials; the role of statistics

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ABSTRACT

Randomized controlled trials (RCT) are the best method for evaluating the efficacy and comparing effects of treatments. In oncology, the most common type of RCT is the superiority trial. This type of trial aims at demonstrating that an experimental treatment is superior to the standard control. In addition to that type, there are different trial designs such as equivalence and non-inferiority trials; i.e. trials that aim at demonstrating that a new treatment is not superior but equivalent or non-inferior to the standard treatment. It is important to underline that these different types of trials have different methodological requirements. It is also important to highlight the fact that superiority trials are frequently falsely interpreted as equivalence or non-inferiority. The purpose of the current paper is to review the design, analysis and interpretation of superiority, equivalence and non-inferiority trials.

Key words: equivalence; non-inferiority; superiority; clinical trials.

INTRODUCTION

The development of randomized controlled trials represents one of the most significant scientific advances of the twentieth century [1]. Randomized controlled trials (RCTs) aim at definitively evaluating new available agents and thus protecting patients from the administration of ineffective treatments or even ones with detrimental effects. Different randomization techniques are used to allocate patients to treatment groups and therefore minimize the imbalance of key baseline differences (prognostic and predictive factors) between comparison groups (selection bias).

The development of several new agents in the field of oncology has generated increased interest in RCTs [2]. The majority of these RCTs are the so-called "superiority" trials that aim to show that one treatment arm (experimental) is superior to another (control) in terms of some clinically relevant outcome. The most common outcomes in oncology are overall survival; progression free survival or time to tumor progression; and overall response rate. However, besides superiority trials we, as clinicians, frequently face RCT designs that are called non-inferiority (experimental arm is not inferior to control) or equivalence trials (experimental arm is equivalent to control).

In the current paper, we will try to present the design, analysis and interpretation of superiority, equivalence and non-inferiority trials.

SUPERIORITY TRIAL

This kind of trial aims at demonstrating that an experimental treatment is superior to the standard control. This type of study is the most appropriate in cases where no standard treatment exists (i.e. when the control arm is best supportive care or placebo; e.g. the BR.21 trial of erlotinib vs. placebo [3]), or in cases where the new treatment is incremental in nature (i.e. adding a new agent to the standard cornerstone; e.g. the FLEX trial of chemotherapy vs. chemotherapy plus cetuximab [4]).

As in all clinical studies, the primary endpoint selected in superiority trials should be clinically meaningful and objectively measured. Furthermore, the projected effect size of the experimental treatment should be realistic and based on the current literature. For these trials, the null and alternative hypotheses for sample size calculation, are H_0: $\Delta=0$ and H_A: $\Delta\neq0$, respectively (Δ is the difference between the treatments investigated) [5].

However, when trying to reject the null hypothesis, it should be noted that, like any other biological measurement, treatment effect could be subject to non-systematic random variation (in statistical terms, the magnitude of variation is reported as standard deviation [SD] or S^2) that should be taken into account when designing the study [6]. More specifically, even in cases where the null hypothesis is true and no difference between

experimental and control treatment exists, it is possible that the trial shows a difference. This type of error is called "type I error" or, in words more understandable for clinicians, a "false positive" trial. It is obvious that this type of error could lead to the introduction of an ineffective treatment in clinical practice. Contrarily, there are cases where the alternative hypothesis is true (that is to say, there is indeed a difference between the two treatments) and the trial fails to show a difference. This is called "type II error" or, in other words, a "false negative" trial. This error results in rejecting an active treatment. Ideally, these errors should be near zero; however, this would require clinical trials with enormous numbers of patients, which would not be feasible. In clinical practice the risk of type I error (α) is usually set at 5%. So, in a clinical paper, a type I error risk α means that this trial has a 5% chance of introducing an ineffective therapy as beneficial. The type II error risk (β) is usually specified at 10-20%. The smaller the β, the greater the power of the study (1-β) to demonstrate a difference -if it truly exists.

The projected effect size of the experimental treatment that is of interest to be detected, the S^2, as well as the α and β risks, are used to calculate the number of patients required to participate in the study. The appropriate sample size calculation is of paramount importance because an improper sample size will lead to rejection of potentially active treatments. Furthermore, it should be considered unethical to enroll patients to a study that has little chance of yielding its purported result, not because of lack of efficacy but because of weaknesses in study design and lack of power [7].

Another important issue when evaluating the results of a clinical trial is the confidence interval (CI). There is an inverse correlation between the reliability of the results of a trial and the width of a CI; the narrower the CI, the more reliable the result. The width of CI is based on the sample size; the larger the sample size the narrower the CI. In clinical practice usually 95% CI is estimated. The 95% CI reflects the interval which would include the true difference between the treatments studied in 95 out of 100 similar comparisons [6]. Note that for a superiority trial, the 95% CI should not include $\Delta=0$, in order the trial to demonstrate a significant difference at the 0.05 level ($p<0.05$) [5] (Figure 1).

EQUIVALENCE TRIAL

Another type of trial design is the equivalence. In this case the trial aims at demonstrating that a new treatment (experimental) is equivalent to the standard one (control). The equivalence design is applicable when the new therapy has similar efficacy to the standard one, but is simpler to administrate, less toxic, or less expensive [6].

Complete equivalence would mean that the difference (Δ) between the experimental and control treatment is zero. However, demonstrating that two treatments have equal efficacy is not possible with statistical tests [6, 8]. As a result, equivalence trials aim at demonstrating the lack of significant difference between two treatments and that their true difference lies within a specific interval of $-\Delta$ to $+\Delta$ [5].

In these trials the null and alternative hypotheses for sample size calculation, are H_0: $\Delta>+\Delta_E$ or $\Delta<-\Delta_E$ and H_A: $-\Delta_E\leq\Delta\leq\Delta_E$, respectively. For an equivalence trial to be positive, the CI should lie between the $-\Delta$ and $+\Delta$ interval [9] (Figure 1).

In equivalence trials it is crucial to determine the magnitude of the difference Δ that is acceptable in order to claim that the two treatments are equivalent. The choice of Δ is difficult and is based on the opinion of clinical experts, and a crude rule is that Δ should generally be smaller than half the difference used in a corresponding superiority trial [9].

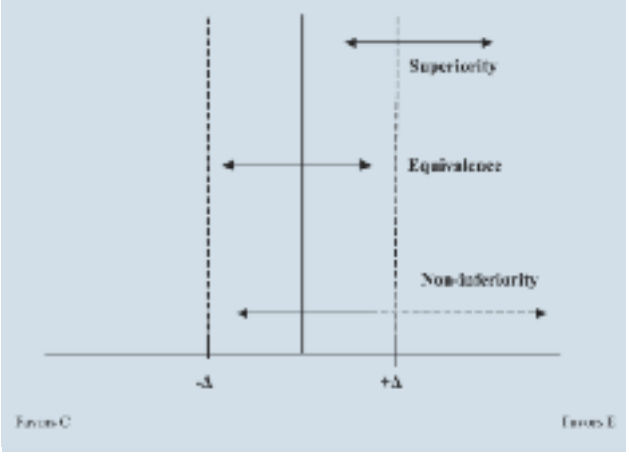
It should be noted that because the Δ differences used for sample size calculation in equivalence trials are smaller than those used in superiority trials, the former needs a substantially larger sample, as compared to the latter.

NON-INFERIORITY TRIAL

A non-inferiority trial aims at demonstrating that a new treatment is not inferior to a standard treatment for a selected clinical outcome. This trial is appropriate in case that a new treatment is not expected to be better than the control treatment in terms of a relevant clinical outcome, but is expected to be less toxic; easier to administer; is cheaper; or associated with better compliance [5]. An example of non-inferiority trial is the INTEREST trial of gefitinib vs. docetaxel as second line treatment for patients with non-small-cell lung cancer (NSCLC) [10].

In non-inferiority trials the Δ difference in treatment effect between the experimental and the standard treatment should be higher than $-\Delta$. The null and alternative hypotheses for sample size calculation are H_0: $\Delta<-\Delta_{NI}$ and H_A: $\Delta\geq-\Delta_{NI}$, respectively. For a non-inferiority trial to be positive, the lower

Figure 1.
95% confidence intervals for superiority, equivalence and non-inferiority trials



bound of CI for the difference in effect between the two treatments should be positioned above –Δ [6] (Figure 1). It should be noted that while in superiority and equivalence trials the significance testing is performed at a two-sided level (0.05), in non-inferiority trials it is performed at a one-sided 0.05 level [5]. For that reason the sample size is smaller compared to a corresponding equivalence trial [6].

The most challenging issue in non-inferiority trials is to determine the non-inferiority boundary. In other words, it should be decided what degree of inferiority is acceptable, in order for the new treatment to be useful in clinical practice. Two approaches have been proposed for the determination of non-inferiority boundaries [11]. The first is based solely on expert clinician opinion and requires clinicians to set the cut-off point [5]. However, this is very difficult, especially in lethal diseases such as cancer and is not used practically. The second approach uses the observed treatment benefit of the control treatment over placebo as a measure to define non-inferiority margin. Let us consider a control treatment that is associated with a Hazard Ratio (HR) for survival of 0.75 (95% CI 0.84 to 0.65) vs. placebo. This means a reduction in the risk of death of 25% with a 95% CI of 16% to 35%. A general rule is to set the lower boundary for non-inferiority to half of the minimal estimated difference of the control treatment vs. placebo. Thus, in that case, the efficacy of the experimental treatment could be no less compared to control treatment than 8% (16%/2=8%) and the HR of experimental over standard treatment could be no more than 1/(1-0.08)=1.087 [2].

TYPE OF ANALYSIS

The most common type of analysis for a superiority trial is the analysis based on intention-to-treat (ITT) population. This means that all patients who were randomized are included in the analysis, irrespectively of whether they were protocol violators; they did not receive any treatment; missed one or more visits; etc. [5]. This type of analysis is used as a control measure, so that when the study is poorly conducted there will be a very small chance that the experimental treatment proves to be more active than the control one.

On the contrary, an ITT analysis may not be appropriate for equivalence or non-inferiority trials. This is because in these trials ITT analysis would be more likely to draw the results of the two treatments compared closer to each other and thus demonstrating equivalence or non-inferiority [5]. Therefore it is recommended to use an analysis based on population treated as per-protocol (i.e. patients who were randomized in the trial and actually received treatment), or to use both types of analyses [5].

INTERPRETING A SUPERIORITY TRIAL AS "NON-INFERIORITY"

Let us take the example of a phase III trial comparing paclitaxel poliglumex vs. docetaxel in the second-line treatment of NSCLC reported by Paz-Ares *et al.* [12]. This trial was designed to show a 1.5-month improvement (30% increase) in median survival from baseline of 6 to 7.5 months in favor of paclitaxel poliglumex. Although designed as a superiority trial, the authors concluded that *"Paclitaxel poliglumex and docetaxel produced similar survival results…"* and stated that the two treatments were equivalent.

An unplanned non-inferiority conclusion is usually drawn in cases of negative superiority trials; however, this conclusion is not justified. First of all, the problem of a non-inferiority conclusion in these cases is that the sample size is calculated on the basis of a superiority rationale and therefore is significantly smaller than the sample required for a non-inferiority or equivalence trial -as already stated [13]. Another weakness is that the conclusions of superiority trials are based on an ITT analysis, which is not the type of analysis suitable to be used alone for non-inferiority or equivalence trials. An assessment of the methodological quality of publications through a MEDLINE search from 1992 to 1996, reported by Greene *et al.*, found that 67% of publications stated equivalence after negative results of a superiority design [14].

Therefore, we as clinicians should keep in mind that negative superiority trials cannot be used to claim equivalence or non-inferiority. Equivalence and non-inferiority trials require a special design and larger patient populations in order to be of high quality and provide reliable and valid results. Also, we should approach with skepticism equivalence and non-inferiority trials that fail to clearly describe the rationale on which the justification of equivalence (or non-inferiority) margin was based and provide a sample size calculation founded on that margin.

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Management of patients with high risk features in radical prostatectomy specimens

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ABSTRACT

Background: Adverse pathological features in radical prostatectomy specimens are detected in 38% to 52% of patients undergoing the procedure. As such, extension beyond the prostate, positive surgical margins or seminal vesicle invasion are associated with a significantly increased risk of cancer recurrence and progression.

Patients & Methods: A PubMed search was performed on the available treatment modalities for patients with locally advanced PCa. Large randomized controlled studies, as well as retrospective non-randomized studies were reviewed and emphasis was given on treatment outcomes that have been demonstrated in these studies.

Results: Based purely on evidence criteria, adjuvant RT has to be considered as the gold standard for patients with high-risk features in radical prostatectomy specimens. Since the determination of such a risk remains difficult, the fundamental question of whether individual patients should be counseled for immediate adjuvant RT based on pathological features or for observation with selective salvage RT or for HT has not yet been answered.

Conclusions: The management of these patients is complex. Although level-1 evidence supports relatively widespread immediate adjuvant radiotherapy, some arguments for a more selective approach are described.

Key words: locally advanced prostate cancer; adjuvant radiotherapy; salvage radiotherapy; positive surgical margins; seminal vesicle invasion.

INTRODUCTION

Prostate cancer (PCa) is considered as one of the most important medical issues affecting male population. The global incidence of PCa has been estimated at 500,000 new cases each year. Between 230,000 to 240,000 men are diagnosed annually with PCa in both Europe and the US [1]. In the former, it is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer and is currently the second most common cause of cancer death in men [2]. Although PCa has a relatively slow progression pattern, patient prognosis and subsequent treatment depends significantly on the degree of tumor differentiation at diagnosis. Thus, in men with low-grade and intermediate-grade tumors, a 10-year cancer-specific survival (CSS) of >90% and >75% respectively has been reported, while there is a significant decline in 10-year CSS among patients with more aggressive high-grade tumors, as would be expected [3]. Over the past 2 decades, PSA screening has allowed detection of PCa at earlier stages, improving patient survival and the chances of cure with definitive local therapy. In the National Prostate Cancer Detection Project Study [4] involving serial screening with PSA, digital rectal examination and transrectal ultrasonography the rate of clinically advanced disease was reduced to less than 9% of all newly diagnosed cancers over a 10-year period, compared with 41% in a survey of 1982 [5].

Despite this favorable stage migration which has led to decreasing mortality rates and concomitant significant improvement of CSS, 15% of patients still present with high-risk tumors that may be characterized by the development of locally advanced disease or distant metastases [6]. Even for patients with early stage tumors, 15-40% still go on to develop progressive disease, despite adequate local treatment [7].

Radical prostatectomy (RP) is an effective treatment for patients with organ-confined disease and has demonstrated to reduce the risk of death from the disease [8]. Approxi-

mately 40% of the patients who choose definitive therapy will undergo RP. RP provides high rates of local control in patients with PCa. However, as soon as the prostate capsule is penetrated, cancer control rates drop significantly [9].

Pathologically advanced disease is detected at RP in 38% to 52% of patients [10]. Each stratum of extraprostatic disease -i.e. pathological extension beyond the prostate; positive surgical margins; or seminal vesicle invasion- is associated with a significantly increased risk of cancer recurrence and progression, measured at the earliest time with a detectable PSA, also known as biochemical failure (BCF) [11]. A large community-based series of men in the US undergoing radical prostatectomy would suggest that about a third will have positive surgical margins [12]. Positive surgical margins have been reported in 11-38% in contemporary series [13, 14]. In addition, histopathological examination reveals seminal vesicle invasion in 1-33.3% of patients undergoing RP [15, 16].

The natural history of PCa with BCF after RP can be variable; however, approximately two thirds of these patients will develop metastatic disease if left untreated and most will die of PCa [17]. The most comprehensive study of the natural history of PCa with BF was conducted in a series of 1997 men who underwent RP [18]. In this cohort BCF occurred in 15% of these men and time from RP to BCF averaged 3.5 years. The 5-year risk of clinical progression ranged from 27 to 60% and correlated with the time interval from RP to BCF, the prostatectomy Gleason score and the PSA doubling time. Median time from BCF to clinical progression was 8 years. Of men with BF, 17% died from prostate cancer.

Monotherapy has been demonstrated to be inadequate for cancer control in this patient population, resulting in a greater likelihood of relapse, and combination therapy regimens are often used to obtain local and systemic control. However, since not all patients benefit equally from secondary treatment modalities and as more aggressive therapy has the risk of greater morbidity, accurate identification of patients with such high-risk PCa is essential. Inaccurate risk characterization could result in inappropriate management, such as indiscriminate application of hormonal or other adjuvant therapeutic modality, as well as excluding certain patients from potentially curative local treatment [19].

DEFINITION OF HIGH-RISK DISEASE

Earlier in the PSA era, patients with high-risk disease often had clinical T_3 disease and were more likely to receive high-dose radiation therapy (RT) in combination with androgen deprivation [20]. Stage migration has increased the number of men diagnosed with clinically localized disease, while the ability to detect high-risk features has improved as well. High-risk PCa has frequently been defined using a single parameter, including clinical stage T_3 [21] Gleason score 8-10 [22] or PSA kinetics [23]. D'Amico *et al* [24] combined these parameters into a widely used risk classification scheme, according to which patients with PSA above 20; or Gleason sum of at least 8; or clinical stage of at least T_{2C} are defined as high-risk. Partin *et al* [25] constructed nomograms using PSA, Gleason score and clinical stage to assist with preoperative prediction of final pathological stage for patients with clinically organ-confined disease. Biopsy Gleason score and the percentage of cores positive for cancer in prostate needle biopsy specimens have been reported by several authors to be strong predictors of tumor stage [26]. Özgür *et al* [27], in a retrospective analysis on 171 patients who underwent RP, suggested that TRUS biopsy Gleason score and percent of cores positive for cancer have been found to be independent variables regarding the prediction of extracapsular extension, while PSA ≥10 and Gleason score were found to be independent variables regarding the prediction of seminal vesicle invasion, positive surgical margins and lymph node involvement.

To date, various risk classifications and a variety of nomograms and predictive models have been published, each with their own combination of variables [28]. However, all these attempts at risk identification and stratification are complicated by the large number of risk definitions that have been devised, as more than 40 risk stratification models have been reported in the literature and there is a lack of studies comparing their relative predicting power [29]. Moreover, all these predictive models seem to work excellently for patients with low-risk disease -however equivalent efficacy in the high-risk population has not been demonstrated [19]. Additionally, as most of these risk models use surrogate end points (e.g. PSA recurrence) for PCa-specific mortality, there is little evidence showing an actual correlation of risk stratification and cancer-specific or overall survival [28].

THE IMPACT OF ADVERSE PATHOLOGICAL FEATURES IN RP SPECIMENS

Positive surgical margins

A positive surgical margin (PSM) has been defined as cancer identified at the inked surgical resection margin of the RP specimen. There are two types of PSM: iatrogenic and non-iatrogenic. In other words, PSM can result from incision into extraprostatic cancer in patients with extracapsular extension (pT_{3a}) or capsular incision into organ-confined tumors (pT_{2+}) [13]. From an oncological point of view, the presence of PSM at the RP specimen indicates theoretically inadequate cancer clearance. Retrospective reports have suggested that PSMs are a risk factor for future BF in all patients with clinically localized disease [30]. Thus PSMs have been associated with increased adverse outcomes in several studies and most investigators consider PSMs as an independent predictor of PCa recurrence after RP [13, 31]. However, some other studies have contested these findings and have not found PSM to be an independent predictor of disease recurrence and progression [32]. Furthermore, data indicates that when adverse pathological features such as

% Gleason grade 4/5, SVI or LNI are accounted for, margin status no longer plays a role in determining clinical outcomes [33]. Thus, the effect of margin status on disease recurrence in patients after RP remains controversial and the debate over whether PSM represents unfavorable tumor biology, technical error or both is still pertinent. It is conceivable that an iatrogenic capsular incision of a low-grade organ-confined cancer (pT_{2+}) provides different prognostic information than a PSM associated with extraprostatic extension of high-grade tumor [34].

Seminal vesicle invasion

SVI is defined as invasion of seminal vesicle muscular wall. SVI is associated with a poor prognosis, as these tumors usually have large volumes; they are poorly differentiated; and tend to have a greater incidence of extracapsular extension [35]. In these patients the results for the pathologic parameters of capsular invasion and surgical margin status have demonstrated controversial results regarding progression after RP. This is exemplified by the demonstration that extraprostatic extension of PCa is associated with a progression rate that is not very different from organ-confined disease, whereas patients with SVI experience tumor recurrence almost universally after surgery [36]. Nevertheless, few studies investigating tumors with isolated SVI have attempted to stratify the prognosis based on the pathological parameter of SVI alone and biochemical progression-free survival rates from 5% to 60% have been reported [37].

MANAGEMENT OF PATIENTS WITH ADVERSE PATHOLOGICAL FEATURES IN RP SPECIMENS

Radical prostatectomy as a sole treatment modality does not cure most men with adverse pathological features in RP specimens. Although retrospective studies have reported encouraging results for this difficult-to-treat patient category, there is no randomized data to suggest that RP is superior to other treatment modalities for this patient population [38]. However, the rationale for RP as first line treatment for this patient population is based on three beneficial effects of surgery: excellent local control of the primary tumor; accurate definition of disease extension, which can guide subsequent therapy; and removal of benign source of PSA, so that failures can be promptly identified and secondary treatment can be initiated in a timely manner [39]. Nevertheless, as the optimal treatment for patients with extraprostatic disease noted after RP is still unknown, considerable attention has focused on evaluating secondary local treatment modalities to improve patient outcomes.

Adjuvant radiation therapy

Even though adjuvant treatment with radiotherapy (RT) after surgery is commonplace in malignancies such as breast cancer, PCa has different treatment options because of the PSA testing, which allows early detection of postoperative recurrence before clinical symptomatic or palpable disease recurrence is found. When used as curative therapy, post-prostatectomy radiation therapy may be classified as: 1) immediate adjuvant; 2) salvage for biochemical failure; or 3) salvage for local recurrence [40]. The primary issue after RP for patients with adverse pathological features in RP specimens is that the possibilities of no therapy, early therapy and delayed or salvage therapy at recurrence all seem feasible depending on individual patient risk.

The term adjuvant is used to indicate that the treatment is given electively for the purpose of improving the outcome by reducing the recurrence rate following RP. In other words, adjuvant radiotherapy may be delivered to a given anatomical region even if the likelihood of residual cancer is relatively low and absolute documentation of such residual tumor is lacking. The tradeoffs of treatment versus observation then relate to the likelihood of residual tumor, effectiveness of the adjuvant therapy in reducing cancer recurrence and treatment risks [41].

Clinical trials of adjuvant RT

Adjuvant RT has been used for more than 4 decades to reduce the risk of disease recurrence, but has also been the subject of considerable debate [42]. Literally hundreds of case series have been published on the subject with authors advocating for and against treatment based on outcomes and side-effects of highly selected series of patients. There is abundant data available from non-randomized studies reporting on the outcome and toxicity of adjuvant RT. Several retrospective series indicated that adjuvant RT may significantly improve the **biochemical no evidence of disease** rate (bNED) and the **disease-free survival** rate, respectively [43-45]. Depending on the individual trial, increases in bNED rates of roughly 20-40% were reported.

The impact of adjuvant RT on overall survival (OS) and cancer-specific survival (CSS) has also been investigated in several retrospective studies. Porter *et al* [46] in a matched case-control study of 118 patients who received adjuvant RT after RP and who were matched with controls that did not receive adjuvant RT after RP, found no statistically significant difference in OS and CSS (10-yr OS rates were 81.1% vs. 75.5% respectively). More recently, Boorjan *et al* [47] evaluated retrospectively a series of 361 patients who received adjuvant RT after RP in the immediate or salvage setting, and compared it to a second cohort of men who did not receive RT. They found a significantly improved 10-yr biochemical recurrence-free survival (68% vs. 45%, $p<0.001$), 10-yr local recurrence free survival (97% vs. 82%, $p<0.001$) and a decreased rate for late hormone therapy (17% vs. 25%, $p=0.002$). However, no significant impact of adjuvant RT on OS was noted either.

Nevertheless, the retrospective nature of all these trials cannot lead to definitive conclusions, as the value of data

definitively increased with the use of PSA testing, more precise staging methods and improved RT techniques.

To address the role of post-prostatectomy RT for patients with pathologically advanced PCa, three prospective, randomized, controlled, multi-institutional trials commenced about 20 years ago. The results of these trials were recently presented either as mature publications (EORTC 22911 and SWOG 8794) [48-53] or as presentations during major conferences (German Intergroup trial number ARO 96-02/AUO AP 09/95) [54-56]. All three trials have prompted an ongoing debate concerning the indications for, and timing of, postoperative RT [57]; nevertheless they have been considered by most authors as the most significant contributions to the urological oncology literature in recent years [58].

The European Organization for the Research and Treatment of Cancer (EORTC) trial 22911 [48-50] is the largest of the three. 1005 patients who underwent RP between 1992 and 2001 were randomized to adjuvant RT; to a dose of 60Gy; or to a "wait and see" policy. Eligibility criteria for the enrolment were pathological evidence of ECE, SVI and PSM, in the absence of known metastatic disease. The original primary endpoint of palpable local recurrence was revised to clinical progression-free survival (cPFS) in 1995 and biochemical progression-free survival (bPFS), defined as an PSA increase of 0.2 ng/ml over the lowest postoperative PSA value, in 2003.

The Southwest Oncology Group (SWOG) 8794 [51-53] was the first randomized controlled trial designed to evaluate the role of adjuvant RT for pathologically advanced PCa. 425 patients treated with RP between 1988 and 1997 were randomized within 16 weeks after RP to immediate RT, to a dose of 60 to 64Gy (in 30 to 32 fractions), versus observation. The eligibility criteria were similar to those of EORTC. However, lymphadenectomy was not mandatory for patients considered to have a low-risk of lymph-node involvement. Furthermore, an undetectable PSA after surgery was not required for study entry and approximately one third of the enrolled patients had a persistently elevated PSA. Distant metastasis-free survival was the pre-specified primary end-point of this trial, and biochemical recurrence was assessed with a PSA cut-point of 0.4 ng/ml. Secondary endpoints included PSA relapse-free survival; recurrence-free survival (excluding PSA relapse); overall survival (OS); and freedom from hormonal treatment.

In 1996, the Arbeitsgemeinschaft Radiologischer Onkologie (ARO) and the Arbeitsgemeinschaft Urologische Onkologie (AUO) of the German Cancer Society initiated a randomized, multicenter, phase III trial (ARO 96-02/AUO AP 09/95) to test the hypothesis that immediate RT after RP improves bNED in patients with pT_3 tumors with undetectable PSA and with high-risk tumor progression. 385 patients with $pT_3N_0M_0$ PCa were randomized 1 week after surgery to the observation group or to receive adjuvant RT. If an undetectable PSA level (<0.1 ng/ml) after RP was subsequently not achieved, patients were excluded from protocol and treated with immediate RT. The primary endpoint of this trial was PFS, with progression defined as two consecutive PSA increases above the detection limit of the assay used; local or distant clinical recurrence; or death.

Median follow-up time for the EORTC trial was 5 years; for the SWOG trial 10.6 years and for the ARO/AUO trial 40/53.6 and 38.5/53.7 months for the RT and the observation group, respectively.

Table 1 shows a design overview of these 3 randomized trials.

Clinical trial results

The overall results of these three clinical trials are consistent, showing an approximate halving of the risk for biochemical relapse with adjuvant RT (Table 2). The bRFS

Table 1.
Overview of the randomized trial designs

	EORTC 22911	SWOG 8794	ARO 96-02/AUO AP 09/95
Time of study	1992-2001	1988-1997	1997-2004
Number of pts	1005	425	388
Adjuvant RT vs. Wait & see or OBS	502/503		
Eligible pts	Extraprostatic extension, pN0, cM0, (+) sm	Extraprostatic extension, pN0, cM0, (+) sm	pT3, pN0, cM0, (+) sm
PSA before RT	Never undetectable 11%	Never undetectable 33%	Never undetectable 21%
RT parameters	60Gy in 6 wk	60-64Gy in 30-32 fractions	60Gy in 30 fractions
Time of RT after RP	90 d	120 d	45-90 d
Endpoints	DRE (+) Clinical progression FS BRFS (0.2ng/ml)	MFS BRFS (0.4ng/ml)	BRFS (0.1ng/ml)

rates in SWOG 8794 were 64% for adjuvant RT vs. 35% for the observation group. The 5-year bRFS rates in the EORTC 22911 and the ARO/AUO trial were 74% for adjuvant RT vs. 52.6% for the observation group and 72% vs. 54%, respectively.

The EORTC trial revealed no significant differences for the distant failure endpoints and the OS rates (distant failure rates for RT group were 6.1% vs. 6.3% for the observation group; OS rates were 92.3% in the RT group vs. 93.1% in the observation group).

Very recently, van Poppel *et al* [69] demonstrated the 10-yr follow-up results of the EORTC trial, during the annual meeting of the European Association of Urology in Vienna (18-22 March 2011). The 10-yr clinical progression-free survival rate was 70.3% and 64.8%, respectively (HR=0.81, P=0.054). With RT, the 10-year cumulative incidence of locoregional failure decreased from 16.6% to 7.3% (P<0.0001). Neither 10-year cumulative incidence of distant metastases (11.0% vs. 10.1% with RT; P>0.1) nor overall survival (10-yr survival rates 76.9% vs. 80.7% with RT, P>0.1) were impacted. Subgroup analyses suggested a significant interaction between patient age (≤70 vs. >70 years) and benefit from immediate RT (interaction P<0.05 for biochemical progression-free survival; clinical progression-free survival; and overall survival). The authors concluded that conventional post-operative RT improves biochemical progression-free survival and local control without significantly impacting distant metastases or overall survival.

In an earlier publication of the SWOG 8794 trial results in 2006, no statistically significant benefits for adjuvant RT in terms of metastasis-free survival and OS were reported [51]. However, in a recent update of the SWOG 8794 trial, with a median follow-up of 12.6 years, significantly improved survival rates were in fact reported; metastasis-free survival was significantly greater with RT (93 of 214 events in the RT arm vs. 114 of 211 events in the observation group, p=0.016) and OS also improved significantly with RT (88 deaths of 214 in the RT arm vs. 110 deaths of 211 in the observation group, p=0.023) [53].

Despite the lack of significant influence on OS and metastasis-free survival, the SWOG trial demonstrated a considerable reduction of PSA relapse rates associated with adjuvant RT. The median PSA relapse-free survival period was 10.3 years in the RT group vs. 3.1 years in the observation group. Moreover, the SWOG trial provided evidence that adjuvant RT notably improved freedom from hormonal treatment.

The subgroup analyses performed within the EORTC and the SWOG trial demonstrated an important treatment effect on bNED rate for all subgroups (ECE, SVI, PSM). However, in a subsequent subset analysis within the EORTC trial, the PSM status risk factor, as assessed by reviewing pathology, was the strongest predictor of prolonged biochemical progression-free survival with adjuvant RT [49].

As the efficacy of adjuvant RT has to be balanced against its side-effects, a treatment toxicity analysis was also performed in all three trials. During the EORTC trial, side-effects were documented prospectively using the World Health Organization (WHO) and the Radiation Therapy Oncology Group (RTOG) criteria for early and late side-effects (Table 3). RT was associated with an increased risk of immediate and late grade 1-2 side-effects; grade 3 side-effect rates were reported in <5% of the patients. In the SWOG trial treatment toxicity was not documented prospectively. A retrospective analysis, however, showed that side-effects were more common in patients undergoing adjuvant RT (23.8% of patients receiving RT vs. 11.9% in the observation group). The preliminary results of the ARO/AUO

Table 2.
Biochemical recurrence-free survival rates in randomized clinical trials

Trial (Arm)	BRFS	Median Follow-Up (y)	Hazard Ratio (95% CI)
SWOG 8794			
Immediate ART	64%	10.9	0.43 (0.31-0.58); P< .001
"Wait and see"	35%		
EORTC 22911			
Immediate ART	74.0%	5	0.48 (0.37-0.62); P< .0001
"Wait and see"	52.6%		
ARO 96-02			
Immediate ART	72%	5	0.53 (0.37-0.79); P= .0015
"Wait and see"	54%		

Abbreviations: ART, adjuvant radiotherapy; BRFS, biochemical recurrence-free survival

trial revealed that serious side-effects were rare (grade 3, genitourinary, acute toxicity in 3% of patients). Late grade 3 genitourinary side-effects were observed in 2% of patients; late grade 2 rectal side-effects occurred in 1%.

In summary, the data from these three randomized controlled trials show that adjuvant RT improves bNED rates and local control in patients with locally advanced PCa after RP and most retrospective studies agree with this conclusion. However, evidence demonstrating a CSS and OS advantage has not been established. These results, which are in accordance with the results obtained in most of the retrospective studies, reflect the highest level of evidence (level=1), so the efficacy of adjuvant RT after RP in order to eradicate microscopic residual tumor-cell deposits should be considered as proven [59].

Salvage radiotherapy

In contrast to the adjuvant RT, salvage RT following RP is a treatment that may be employed after cancer recurrence. Salvage RT for biochemical recurrence after RP is typically curative in intent. This has helped fuel the ongoing debate on whether postoperative RT should be given in the adjuvant or salvage setting [60]. Unfortunately, the aforementioned randomized trials, as well as non-randomized studies, are not able to address the question of adjuvant vs. salvage RT. Non-randomized comparisons between adjuvant and salvage RT are fundamentally flawed by the inherent selection bias. Many patients receiving adjuvant RT will have already been cured by surgery alone, whereas all patients who have received salvage RT, by definition have recurrent disease after surgery. It is, therefore, obvious that the outcome of patients who have received adjuvant RT will be better than that of patients who have received salvage RT [60]. The rationale for immediate adjuvant RT is that the best chance to eradicate cancer in its entirety is when the cancer cells are fewest in number and microscopic for presentation [41]. In this regard, Valiceti *et al* [61] presented their matched-pair analysis of adjuvant (within 12 months) and salvage (median PSA before treatment, 0.6 ng/ml) for locally advanced PCa in 316 patients with initially undetectable postoperative PSA levels. They found a significant improvement in long-term PSA control with early adjuvant RT versus delayed salvage RT. The 5-yr bNED rates were 68% in the adjuvant RT and 42% in the salvage RT group.

Nevertheless, data of non-randomized salvage RT studies are available (and of some value) both in terms of demonstrating that long-term disease control is achievable, as well as in identifying outcome predictors. Stephenson *et al* [62] demonstrated in one of the largest series concerning the efficacy and predictive factors of salvage RT, that the 6-yr progression-free probability after salvage RT was 45%. On multivariate analysis, factors associated with post-salvage RT progression included pre-radiotherapy PSA levels >2 ng/ml (HR 2.3), PSA doubling time of 10 months or less (HR 1.7), margin-negative disease (HR 1.7) and Gleason sum 8-10 (HR 2.3).

This data indicates that patients with a higher pre-radiotherapy PSA level have worse results than those with a lower one and this effect cannot be explained merely by differences in the rate of PSA increase after surgery. Furthermore, Stephenson *et al* [63] in another publication suggested that pre-therapeutic PSA levels <0.6 ng/ml resulted in significantly improved local control rates.

More recently, Trock *et al* [64] reported on a retrospective cohort study of 635 men who underwent RP from 1982 to 2004 and experienced biochemical or local recurrence. Patients were classified according to their choice of treat-

Table 3.
RT incidence of late toxicity by RTOG grade

Toxicity	Grade 2	Grade 3	Grade 4	Any significant >G2
Overall GU toxicity	12.4%	2.3%	1%	15.9%
•Cystitis	4.7	0.5	0	
•Hematuria	4.7	0	0	
•Urinary stricture	4.7	1.3	1	
•Urinary incontinence	4.7	0.5	0	
Overall GI toxicity	9.5%	0.2%	0%	9.8%
•Proctitis	8.2	0	0	
•Chronic diarrhoea	3.7	0	0	
•Small bowel obstruction	0.2	0.2	0	
Leg oedema	1.5%	0%	0%	1.5%
Erectile dysfunction				
Secondary malignancy				

ment. Thus, within the cohort, 397 patients received no salvage treatment; 160 received salvage RT alone; and 78 received salvage RT combined with hormonal treatment. With a median follow-up of 9 years (6 years after recurrence), salvage RT alone was associated with a significant 3-fold increase in CSS versus no salvage therapy (HR 0.32, p<0.001). The addition of hormonal therapy to salvage RT was not associated with a significant increase in CSS. It is interesting to note that the beneficial impact of salvage RT on CSS was most marked in patients with a PSADT shorter than 6 months, who underwent salvage RT within 2 years of biochemical recurrence, regardless of margin status or Gleason score; and in patients with a Gleason score of 8-10.

Finally, in order to compare survival rates between this cohort and the ones in the adjuvant RT trials, an evaluation restricted to patients with pT_3 PCa showed that those who received salvage RT had a 10-yr OS rate of 89%. This compares favorably with the 10-yr OS reported in the SWOG 8794 trial: 74% for patients randomized to adjuvant RT versus 66% for those randomized to initial observation.

Currently, there is an ongoing prospective trial which is hoped to add to the future understanding of the adjuvant versus salvage RT issue. In the United Kingdom and Canada, the Radiotherapy and Androgen Deprivation in Combination After Local Surgery trial (RADICALS, MRC PR10) [65] opened three years ago. Men who have undergone RP may be randomly assigned to either adjuvant or early salvage RT at PSA failure. The aim of this trial is the identification of optimal timing of post-RP RT and the extent of benefit from the addition of hormonal therapy to secondary RT.

In summary, the findings from the non-randomized retrospective studies regarding the efficacy of salvage RT in patients with adverse pathologic features in RP specimens strongly suggest that men with a rising PSA after PSA should receive salvage RT as early as possible and that is not appropriate to wait for the PSA to reach some arbitrary threshold. Pre-RT PSA levels <0.6 ng/ml result in significantly improved local control and disease-free rates. However, in the absence of data from randomized trials demonstrating the superiority of adjuvant radiotherapy over a surveillance strategy (with planned salvage radiotherapy at the earliest evidence of BCR), a shared decision-making between physicians and patients, based on the relative advantages and disadvantages of each approach, has been suggested [66].

Hormonal therapy

Treatment for patients with evidence of clinical progression has historically consisted of androgen ablation. Currently there is no consensus regarding a PSA level that signals the requirement for hormonal therapy (HT) initiation. One option is to delay administration of HT in men with biochemical recurrence until symptoms or radiological evidence of clinical progression. Another option is to administer HT prior to evidence of clinical progression in high-risk patients [28].

The use of HT in symptomatic men with biochemical recurrence and no evidence of metastasis is controversial. Boustead *et al* [67] examined the impact on survival (OS and CSS) of androgen-deprivation therapy in men with locally advanced PCa, using a systematic review of 8 randomized clinical trials comparing early HT with deferred HT. In the primary analysis, the meta-analysis of all-cause mortality of early vs. deferred HT shows a lower relative risk in favor of early HT (0.86%, p<0.001). In the secondary analyses, cancer-specific mortality was assessed and a greater decrease in relative risk with early than with deferred HT was found. The comparison of early versus deferred HT in terms of disease progression and overall progression showed a significant reduction risk in favor of early treatment. Similar were the results concerning local or distant progression.

This systematic review showed that early intervention with HT significantly reduces the risk of overall mortality (relative reduction of 14%, p<0.001). The authors concluded that early initiation of HT should be offered to men at highest risk of disease progression and cancer-related death.

In a more recent meta-analysis of randomized trials, Bria *et al* [68] demonstrated similar beneficial effects of HT in patients with locally advanced PCa. Additionally, they concluded that HT plus RT significantly decreases recurrence and mortality of these patients, without affecting toxicity.

However, as the administration of HT in men with biochemical recurrence is associated with significant side-effects, including decreased libido, erectile dysfunction, gynecomastia, osteoporosis, anemia, increased risk of incident diabetes and coronary heart disease, many authors suggest that use of HT in men at low risk of clinical progression should be cautious -if at all [29].

In summary, there is evidence that an adjuvant HT alone improves long-term outcome for patients with locally advanced PCa after RP. Thus, the decision to complement RT with adjuvant HT can only be made after individual risk assessment.

CONCLUSIONS

Management of high-risk PCa patients with adverse pathological features in RP specimens is complex. Based purely on evidence criteria, adjuvant RT has to be considered as the gold standard for those patients with a reasonably high-risk of local relapse, but with a comparatively low risk of distant metastases. Since the determination of such a risk remains difficult, the fundamental question of whether individual patients should be counseled for immediate adjuvant RT based on pathological features or for observation with selective salvage RT or for HT has not yet been answered. Thus, there is still concern over inadequate therapy versus overtreatment that is associated with unnecessary cost, bother and side-effects. Therefore, identification of new predictive factors and high-quality pathological analyses are of the utmost importance for the future.

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EML4 - ALK & Crizotinib: from bench to bedside

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ABSTRACT

Cytotoxic chemotherapy has been the foundation of Medical Oncology, but over the last decade it has reached a therapeutic plateau. Targeted therapies have been successfully applied and have offered, apart from valuable clinical benefit, a better understanding of cancer biology. Specifically in lung cancer, the connection of EGFR mutations to tyrosine kinase inhibitor clinical response has altered the algorithm of non-small-cell lung cancer treatment, identifying a subgroup of patients with distinct clinical course and response to therapy. Further elucidation of lung cancer biology and identification of EML4-ALK as a driving mutation as well as a target for therapy were achieved over the past few years. The EML4-ALK mutated tumors occur in younger patients, mostly in male non-smokers with adenocarcinoma. Crizotinib, initially designed as a MET inhibitor, is active in almost all patients with the mutation, binding the fusion protein of EML4 and ALK. Crizotinib is actively investigated in the specific subgroup and its role in previously untreated patients and following resistance to chemotherapy is a matter of ongoing clinical research. Identification of the fusion protein is accurate with immunohistochemistry and FISH but the most appropriate method and algorithm are still a subject of debate. Furthermore, these developments offer insight in the biology of lung cancer and promise landscape changes in the field of targeted therapies in lung cancer.

Key words: advanced NSCLC; chemotherapy; EGFR; VEGF; EML4-ALK; Crizotinib; EGFR mutations.

1. INTRODUCTION

NSCLC remains the leading cause of cancer mortality in western countries, as over one million deaths from lung cancer occur each year. The majority of patients present with advanced disease at diagnosis; despite improvements in the detection and treatment of lung cancer, the overall 5-year survival rate is still not higher than 15%. This phenomenon is mainly due to the fact that conventional chemotherapy with platinum-based doublets in various combinations has already reached a therapeutic plateau in terms of efficacy in the past few years, with a median survival of almost one year. Chemotherapy has so far been applied non-selectively to every patient with non-small-cell histology; moderate activity, along with accumulating toxicity, have further burdened the benefit from chemotherapy. Novel therapeutic approaches are needed in order to reach a point of personalized medicine in lung cancer; advances in the molecular characterization of tumors, drug development, and pharmacogenomics have the potential of allowing individualized selection of treatment as determined by specific patient characteristics, as well as the tumor itself [1].

Over the last decade, histology has emerged as a more important and relevant variable in the decision-making process; Scagliotti *et al* showed that the combination of cisplatin with Pemetrexed in the first line setting had higher efficacy in patients with non-squamous histology [2].

Strategies with sequential/maintenance therapy had been evaluated in many clinical trials; in the Ciuleanu *et al* study, sequential Pemetrexed following platinum doublet regimens obtained a significant improvement in progression-free survival (PFS) [3]. The SATURN study evaluated sequential therapy with Erlotinib in patients with no evidence of progression after 4 cycles of standard chemotherapy [4]. Inhibition of the VEGF pathway with Bevacizumab has demonstrated prolonged survival in patients with advanced NSCLC; two randomized trials (ECOG 4599 and AVAIL) [5, 6] showed that the combination of Bevacizumab with chemotherapy produced better outcomes than chemotherapy alone in chemo-naïve patients with non-squamous cell carcinoma tumors.

EGFR, a member of the human epidermal receptor family, is overexpressed in 50%-80% of NSCLC patients. Additionally, tyrosine kinase-based therapeutics have assumed an increasingly important role, particularly in genetically defined subsets of patients; at present, there is clear evidence to indicate that in patients with advanced NSCLC, activating mutations in the EGFR gene confers hypersensitivity to the tyrosine kinase inhibitors, Erlotinib and Gefitinib (IPASS phase III study) [7]. Cetuximab is the second principal strategy designed to inhibit the EGFR pathway. In the FLEX trial [8], an increase in overall survival (OS) was observed with the addition of Cetuximab to platinum-based chemotherapy in patients with EGFR-positive tumors, while in the BMS 099 trial there was no significant improvement of PFS in the Cetuximab arm [9].

The EML4-ALK is a novel oncogene, which represents one of the newest molecular targets in NSCLC. Oncogenic fusion genes consisting of echinoderm microtubule-associated protein-like the 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene are present in a small subgroup of NSCLCs, representing 2-7% of such tumors. Since 2007, a small molecule inhibitor of the ALK tyrosine kinase (PF-02341066) named Crizotinib is being evaluated in clinical trials, which explore the therapeutic efficacy of inhibiting ALK. Recent data suggests that the inhibition of ALK in lung tumors with the ALK rearrangements resulted in tumor shrinkage or stable disease in most patients.

In this review, we discuss the biological, molecular and clinical feature of EML4-ALK NSCLC patients and highlight the potential future use of ALK inhibitor Crizotinib as therapy for said patient population.

2. CLINICAL AND MOLECULAR FEATURES FOR EML4-ALK NSCLC

Historically, the histological appearance of lung cancer has been used to guide treatment decisions and strategies. A recent shift from squamous to adenocarcinoma as a predominant histology has been attributed to changes in cigarette manufacturing. Over the past five years, distinct genomic changes of adenocarcinomas allow their further classification into clinically relevant molecular subtypes; the two proto-oncogenes that are most commonly mutated in pulmonary adenocarcinomas are K-RAS and EGFR. Nearly 90% of lung cancer-specific EGFR mutations comprise a leucine-to-arginine substitution at position 858 (L858R) and deletion mutants in exon 19 that affect the conserved sequence LREA. These mutations cause constitutive activation of the tyrosine kinase of the EGFR ('driver' mutations or 'growth drivers', that contribute to tumor progression). This phenomenon offers sensitivity to the Gefitinib and Erlotinib tyrosine kinase inhibitors. Conversely, tumors with somatic mutations in K-RAS, which encodes a GTPase downstream of EGFR, display primary resistance to tyrosine kinase inhibitors.

Although known mutations correlate well with responsiveness and tumor-free survival, almost all NSCLCs that respond initially to tyrosine kinase inhibitors eventually relapse and resist further treatment. In 2007, Soda *et al* [10] identified another potential driver mutation in NSCLC; a small inversion within chromosome 2p results in the formation of a fusion oncogene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene in NSCLC cells. EML4 is composed of an N-terminal basic region, a hydrophobic domain and WD repeats, while ALK was first identified as a fusion partner of nucleophosmin in anaplastic large-cell lymphoma with a t (2;5) chromosome rearrangement. Other chromosome translocations involving the ALK locus were subsequently identified in the same lymphoma subtype as well as in inflammatory myofibroblastic tumors. EML4-ALK possesses potent oncogenic activity both *in vitro* and *in vivo* [11].

2.1. EML4-ALK variants and NSCLC

This inversion on chromosome 2p, leading to the formation of the EML4-ALK fusion oncogene, is most commonly found in lung cancer patients as well as in lung cancer cell lines. In the original report, five out of 75 lung tumors demonstrated expression of the fusion transcript (at a frequency of almost 6.7%), while in subsequent studies that primarily involved Asian patients with early-stage resectable disease, EML4-ALK has been detected at a lower percentage (1-4.9%) suggesting that EML4-ALK rearrangement is a relatively rare event in unselected NSCLC populations. EML4-ALK has been identified also in other cancers such as breast and colorectal carcinoma, according to sporadic reports [12].

Usually, in NSCLC patients EML4 is disrupted at a position of exon 13 and is ligated to a position of exon 20 of ALK, giving rise to the EML4-ALK (variant 1) fusion gene (both the ALK gene and the EML4 gene map to chromosome 2p, but have opposite orientations) [11, 12]. However, the chromosomal inversion does not always occur in the same location and multiple variants of EML4-ALK have been identified, all involving the intracellular tyrosine kinase domain of ALK beginning at the portion encoded by exon 20. In addition, two other non-exclusive fusion partners of ALK have been reported from NSCLC tumor samples; TFG and KIF5B, two proteins which also fuse with intracellular domain of ALK.

2.2. Epidemiological - demographic features, smoking history and morphological profile

There is still a debate on whether ALK rearrangements do represent a brand new molecular target in NSCLC and define a specific molecular subset of lung cancer with distinct clinical characteristics. Yet, it is unknown whether this chromosomal rearrangement shares similar outcomes with other genetically defined subsets of NSCLC, particularly in the advanced or metastatic setting.

Shaw *et al* studied the prevalence of EML4-ALK fusion oncogene in selected patients according to clinical characteristics such as female sex; Asian ethnicity; little or never smokers; and adenocarcinoma histology [13]. Low frequency of EML4-ALK that has ranged from 1.5% to 6.7% in unselected population was reported, while in a select subpopulation of predominantly white patients, the majority of whom had metastatic NSCLC, the frequency of EML4-ALK was significantly higher than that reported for unselected patients. Additionally, in patients with NSCLC who had clinical characteristics associated with EGFR mutation but who had negative EGFR screening test, 1 in 3 may harbor EML4-ALK. A significantly greater percentage of men as compared to women were positive for EML4-ALK (23 vs. 9%) and EML4-ALK patients were also significantly younger (difference in median age: 10 years). Interestingly, several other cancers such as anaplastic large-cell lymphomas, inflammatory myofibroblastic tumors, and neuroblastomas are also associated with younger age and are most common in children and young adults.

Although the EML4-ALK fusion oncogene was initially identified in a smoking person who had lung cancer, data accumulation reveals that this specific genetic alteration is more common in never- or former- or lighter-smokers (<10 packs per year) with NSCLC (frequency of 9.4 vs. 2.9% in current heavy smokers). In this clinical population of never- or former-light smokers, EGFR mutations still account for the vast majority of patients, while a minority contains either K-RAS or ERBB2 mutations.

Multiple histological subtypes of NSCLC have been tested, but adenocarcinomas seem to be the major NSCLC cell type harboring EML4-ALK fusions. EML4-ALK fusions have been associated with adenocarcinomas with acinar histology (ranging from well-differentiated tubulopapillary and cribriform patterns) apart from lack of EGFR or K-RAS mutations and younger age. From the variety of histological features, mostly signet-ring call nests with mucin production has been reported. The acinar pattern is mainly associated with Asian populations, whereas signet-ring with Western patients. The majority of them exhibited tumor cells with a solid or sheet-like pattern, easily distinguishable from the acinar, papillary or bronchioalveolar patterns. Other histological types such as squamous or mucoepidermoid carcinomas only rarely contain EML4-ALK translocations [14, 15].

2.3. Identification, diagnosis and screening for EML4-ALK

There is currently no standard method for detecting EML4-ALK NSCLC. Among several methods, three are the most reliable that are still being evaluated: reverse transcriptase polymerase chain reaction (RT-PCR); immunohistochemistry (IHC); and fluorescence in situ hybridization (FISH). None of these assays have proven to be easily adopted by diagnostic molecular pathology laboratories. ALK antibodies seem to give variable results. RT-PCR is a potentially rapid diagnostic method with an extreme sensitivity for detecting mutant transcript, IHC analysis of formalin-fixed paraffin embedded (FFPE) tissue specimens remains the mainstay of routine surgical pathology practice, and FISH-based methods for the identification of EML4-ALK can achieve more specific detection of ALK rearrangements of commercially available probes flanking the ALK breakpoint with tumor cell nuclei [14]. In Shaw's and Kwak's studies, ALK rearrangements have been identified by FISH, which was performed in FFPE tumors by using a break-apart probe to ALK. All FISH-positive occurrences (defined as >15% of tumor cells with split signals) were confirmed by IHC, using a mouse monoclonal antibody against ALK. A subset of FISH-positives occurrences was also confirmed by RT-PCR, while EGFR and K-RAS mutations were determined by direct DNA sequencing [13, 16]. Although the FISH assay for molecular testing is well established for other targets as well (such as HER2 in breast cancer) the clinical utility of this assay for new targets is not immediately transferable. The variability of positive-testing tumors in the literature is likely to be the result of different detection methods used in various studies. It becomes obvious that future efforts are needed in order to determine the optimal method for everyday routine diagnostic detection of ALK fusions in lung cancer [17-19].

The non-randomized European study by Rosell *et al* [1, 20] shows the feasibility of large-scale screening for EGFR mutations in patients with advanced NSCLC for selection for therapy with the Erlotinib tyrosine kinase inhibitor (TKI). The survival curves of patients treated with Erlotinib were relatively high compared with the arm that was treated with chemotherapeutic regimens. In the study by Mok *et al* [1, 7], responses to Gefitinib were almost entirely limited to the mutation-positive group of East Asian patients with adenocarcinoma who had little or no exposure to tobacco smoke, whereas mutation-negative patients benefited from chemotherapy. These two studies suggest that first-line treatment with a TKI should be considered for carefully selected groups of patients of Asian and non-East Asian origin with NSCLC.

Likewise, a major issue nowadays is whether it is necessary to screen and find the appropriate NSCLC population that may harbor ALK rearrangements and could possibly benefit from an analogous inhibitor agent. Using clinical criteria alone, in order to enrich the potential responders, might be one acceptable, albeit potentially misleading way; the first EML4-ALK fusion was found in a former smoker and not a light/never smoker; although K-RAS mutations are associated with smoking, 15% or more of never smokers have tumors that harbor mutant K-RAS. Ideally, neoplasms could simultaneously be tested for the three most common lesions to-date –K-RAS, EGFR and ALK fusions. For example, Sun *et al* [21] studied 52 resected lung adenocarcinomas from East Asian never smokers at a single institution and analyzed them concurrently for major

recurrent oncogenic mutations in EGFR, K-RAS, N-RAS, H-RAS, HER2, BRAF, ALK, PIK3CA, TP53, and LKB1; the prospective mutation testing could successfully assign the appropriate targeted therapy in the majority of patients.

An alternative approach -suggested by Leora Horn and William Pao in 2009 [15]- should also be considered: an algorithm that shows the potential future steps in the treatment strategy for selected patients with lung adenocarcinomas; test for K-RAS mutations first, as 15% to 30% of tumors harbor such alterations; if the tumor is negative, it should be tested for EGFR mutations (approximately 10% of tumors); if again negative, ALK translocations should be assessed in the tumor for an ALK inhibitor to be included in the treatment, regarding a positive result. The triple negative tumors should then be considered for analysis of rarer mutations, such as in BRAF, AKT1, MEK1 or PIK3AC.

3. ALK-TARGETED THERAPY IN NSCLC

The basis for selective response to tyrosine kinase inhibitors in patients with NSCLC was known. Several TKIs have been shown to have pronounced therapeutic activity in patients with cancer. As it has already been mentioned, for instance Imatinib mesylate and Gefitinib, tyrosine kinase inhibitors for the c-abl oncogene 1 non receptor tyrosine kinase (ABL) and epidermal growth factor receptor (EGFR), improve the outcome for patients who have chronic myeloid leukemia positive for the BCR-ABL fusion kinase and patients with NSCLC that is associated with EGFR activation, respectively.

In preclinical analyses of more than 600 cell lines from human carcinomas, an investigational selective ALK inhibitor reduced cell proliferation, specifically in those cancer cells with proven genetic alterations in ALK, supporting the role of ALK in the malignant proliferation and as a future drug target. Cell lines underwent downregulation of critical survival signaling pathways and apoptosis after treatment with an ALK kinase inhibitor. Furthermore, transgenic mice expressing EML4-ALK in the lung epithelium developed numerous lung adenocarcinomas, again demonstrating the oncogenic nature of this fusion gene [10, 11, 16, 22].

Currently, although several agents have been examined in preclinical models, clinical trials are investigating only one agent, Crizotinib (PF-02341066), an oral inhibitor of the tyrosine kinase activity of both ALK and the met proto-oncogene (MET), for the treatment of EML4-ALK positive NSCLC. The phase I study of this agent by Kwak *et al* [16] started in May 2006; the dose expansion cohorts included patients with either genomic alterations in MET (amplifications and/or mutations) or ALK. 5.5% of patients with NSCLC were identified with advanced ALK-positive (but MET-negative) disease, who had already received at least one previous line of chemotherapy. Most of them were non-smokers, had adenocarcinomas and tended to be younger than those without the rearrangements. The initial findings were presented in ASCO 2009; a remarkable 57% response rate to Crizotinib was observed according to RECIST criteria and a disease control rate (partial response and stable disease) of 79%-87% at 8 weeks. Although there was no control group in the study, the results compared favorably with the 10% response with second-line chemotherapy. At a mean treatment duration of 6.4 months, 27 patients (33%) had stable disease; 46 had a partial response; and 1 had a complete response. A total of 63 of 82 patients (77%) were continuing to receive Crizotinib at the time of data cutoff, and the estimated probability of 6-month progression-free survival was 72% (95% CI, 61 to 83), with no median for the study reached; follow-up is ongoing. Grade 1 nausea and diarrhea were the most commonly adverse events reported by 34 patients (41%), while grade 3 elevations in alanine transaminase (ALT) and aspartate transaminase (AST) were observed in 4 patients (5%), which reversed on cessation of Crizotinib.

These results led to the design of other two clinical trials; the first (PROFILE 1007) is a randomized phase III trial of Crizotinib 250 mg/BID administered on a continuous dosing schedule vs. standard chemotherapy (Pemetrexed 500 mg/m^2 or Docetaxel 75 mg/m^2) on day 1 of a 21-day (three weekly) schedule in patients with EML4-ALK NSCLC as second line therapy after prior platinum-based chemotherapy; and the second one (PROFILE 1005) is a phase II trial of single agent Crizotinib 250mg/bid in patients not eligible for the phase III trial or those randomized to platinum-based chemotherapy who develop progression disease [14].

Next future step in the research and clinical trial field will be the efficacy of Crizotinib with equally strong clinical responses as first line therapy alone or in combination with conventional chemotherapeutic agents or monoclonal antibodies or anti-angiogenic regimens. In addition, as with other TKIs and the resistance to them from the start of treatment or after the initial respond, other possible mutations in EML4-ALK which confer resistance to the drug must be discovered [23]. It is obvious that the appearance of Crizotinib-resistance mutations indicate that additional ALK inhibitors will be required in order to target EML4-ALK mutants that are insensitive to Crizotinib in the clinical setting.

4. CONCLUSIONS

Recent progress in the identification of the EML4-ALK mutation as a driving force in NSCLC represents a major progress both in understanding the biology and advancing lung cancer therapy. Identification of the EML4-ALK mutated lung cancer as a distinct group follows the landscape changes regarding the EGFR mutations and the selective activity of erlotinib and gefitinib and creates hope for further elucidation of the biology and development of an algorithm that successfully seeks mutations for the majority of patients with NSCLC. Precise and reproducible demonstration of the fusion protein is achieved with both IHC and FISH, but the

optimal method is yet to be found. Clinical activity has been demonstrated objective response to Crizotinib for the vast majority of patients carrying the fusion protein and ongoing studies will define the role either as first line or following cytotoxic chemotherapy. Even before Crizotinib becomes commercially available, the momentum for incorporating the diagnostic test in a substantial number of patients and the development of a new algorithm is a reality.

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Inhibition of angiogenesis in metastatic breast cancer (mBC): From Bevacizumab to tyrosine kinase inhibitors

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ABSTRACT

Angiogenesis, a process involving endothelial cell proliferation, migration, reorganization of extracellular matrix and vessel formation, has been recognized as an essential component of cancer growth, invasion and metastasis. Inhibition of angiogenesis is an attractive strategy for cancer treatment. The most studied antiangiogenic agent is Bevacizumab, a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). Bevacizumab has been paired with conventional chemotherapeutic agents and approved for the treatment of various malignancies. Several small molecule inhibitors of VEGF receptors with promising activity in preclinical tumor models are under clinical investigation. However, the current antiangiogenic regimen is far from optimal and the clinical benefits are modest. The following review describes the therapeutic approach of angiogenesis inhibition in the context of metastatic breast cancer and highlights several questions, such as choice of drug combinations; optimal duration and resistance to therapy; and patient selection criteria, which remain unanswered.

Key words: breast cancer; angiogenesis; Bevacizumab; tyrosine kinase inhibitors.

INTRODUCTION

Angiogenesis, the growth of new vessels from preexisting vasculature, is a critical step in carcinogenesis and tumor progression, as it connects the proliferating tumor cells with the host circulation. Newly-arising tumors or micrometastatic foci usually stop expanding at a microscopic size and remain in a non-angiogenic, dormant condition. Incipient micrometastatic deposits will not grow beyond the size of approximately 1-2mm unless they can develop a blood vessel supply to provide the necessary oxygen and nutrients [1].

The ability of a tumor to induce the formation of a tumor vasculature has been termed the "angiogenic switch" and is initiated when the homeostatic balance between pro-angiogenic and anti-angiogenic stimuli is disrupted in favor of the former, resulting in activation of angiogenic signaling pathways [2]. The pro-angiogenic growth factors may be over-expressed because of genetic alterations of oncogenes and tumor suppressor genes, or in response to the reduced availability of oxygen. Rapid tumor cell growth creates intracellular hypoxia, which initiates a series of cell signaling events that promote angiogenesis. Hypoxia-inducible factor (HIF) is the major transcription factor that responds to changes of intracellular oxygen concentration. In addition to hypoxia, PI3K and Ras pathways can increase HIF expression by promoting HIF translation [3]. Under typical oxygen levels, HIF is hydroxylated and acetylated, modifications that facilitate its association with von Hippel-Lindau factor and ubiquitination-driven degradation. During hypoxia, HIF accumulates and is transported to the nucleus where it induces the expression of a wide variety of target gene products, including proteins important for tumor angiogenesis (Figure 1). Growth factors induce signaling pathways that result in endothelial cell proliferation, increased vascular permeability and cell migration. Extracellular matrix proteases and regulators induce tissue matrix remodeling in preparation for migration of endothelial cells from existing vessels.

A crucial factor involved in angiogenesis in nearly all human tumors is a protein identified as vascular endothelial growth factor (VEGF) [4]. The VEGF family consists of five members in mammals: VEGF-A, VEGF-B, VEGF-C,

VEGF-D, and placental growth factor (PlGF) [5]. The term VEGF typically refers to the VEGF-A isoform, the main mediator of tumor angiogenesis. When VEGF is secreted from tumor cells, it interacts and activates three structurally similar tyrosine kinase receptors (VEGFR 1, 2 and 3) located on endothelial and bone marrow-derived cells. Among these receptors, VEGFR-2 is believed to mediate the majority of the angiogenic effects of VEGF-A, whereas the role of VEGFR-1 is complex and not fully understood. The VEGFR-3 is involved in lymphangiogenesis and does not bind VEGF-A [6].

VEGF SIGNALING IN BREAST CANCER

High VEGF protein levels are related to microvessel density and pathologically aggressive phenotype in ductal in situ carcinoma [7]. VEGF protein content is also increased in invasive breast cancer and its overexpression has prognostic significance for both relapse-free and overall survival [8]. Additionally, up-regulation of VEGFR-2 mRNA was found earlier in invasive primary and metastatic breast cancers [9] and increased levels of VEGF and/or VEGFR-2 are predictive of a poor response to both tamoxifen and chemotherapy in patients with metastatic breast cancer [10].

CLINICAL RELEVANCE OF TARGETING ANGIOGENESIS IN BREAST CANCER

Research in angiogenesis inhibition as a therapeutic strategy against cancer started in the early 1970s, when Folkman postulated that tumor growth is dependent on angiogenesis [11] and that involved molecules in angiogenesis signaling pathway could serve as targets for biological therapies. Several drugs that target VEGF ligands (monoclonal antibody) or receptors (tyrosine kinase inhibitors) have now emerged into the clinic. In general, although the use of angiogenesis inhibitors as single-agent therapy did not demonstrate any remarkable activity [12], their combination with conventional chemotherapy has been proved particularly effective, as it improved substantially -at least- overall response rate (ORR) and progression-free survival (PFS) in patients with advanced breast cancer. One question that has been raised is how angiogenesis inhibitors enhance the efficacy of chemotherapy. One theory is that the presence of the drug during the break period between each successive cycle of chemotherapy slows down tumor repopulation by inhibiting angiogenesis. The presence of antiangiogenic drugs during these breaks may also improve tumor-cell kill, possibly by improving endothelial-cell kill as well [13]. Another theory involves a concept known as "vessel normalization". It is based on the idea that the dysfunctional and abnormal newly-formed blood vessels in tumors can be pruned by antiangiogenic agents. The vessel normalization process may cause a reduction in interstitial fluid pressures within tumors and transiently increase blood flow. In theory, giving chemotherapy during this normalization window can improve drug delivery, resulting in a more uniform distribution of chemotherapy within antiangiogenic drug-treated tumors and thus increase tumor response [14].

Figure 1.
Simplified angiogenesis cascade

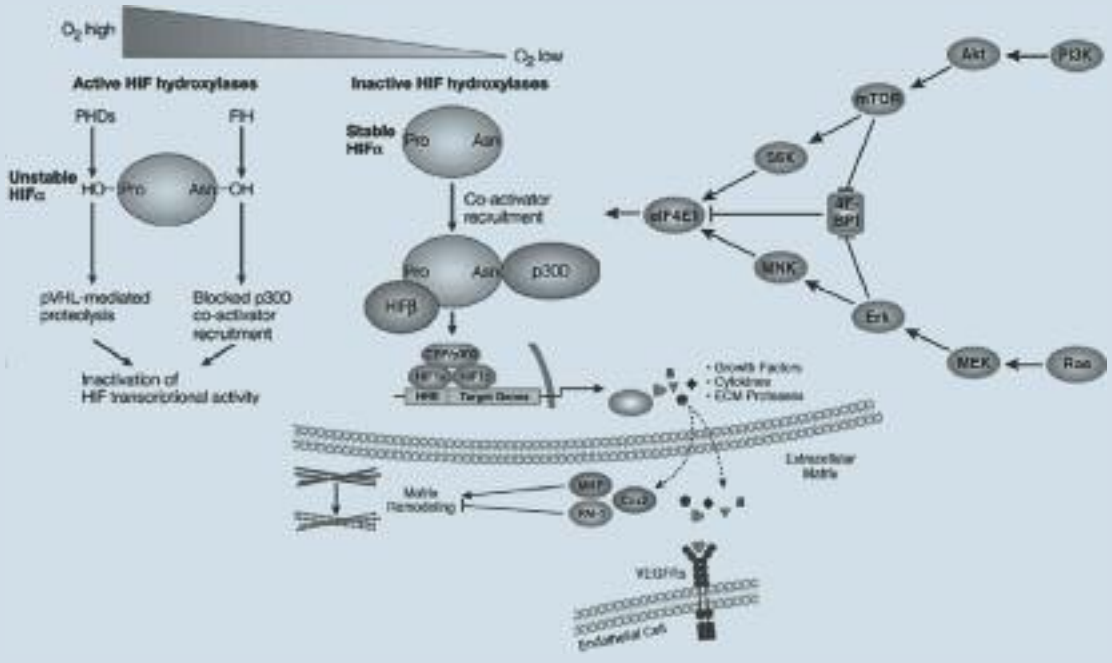
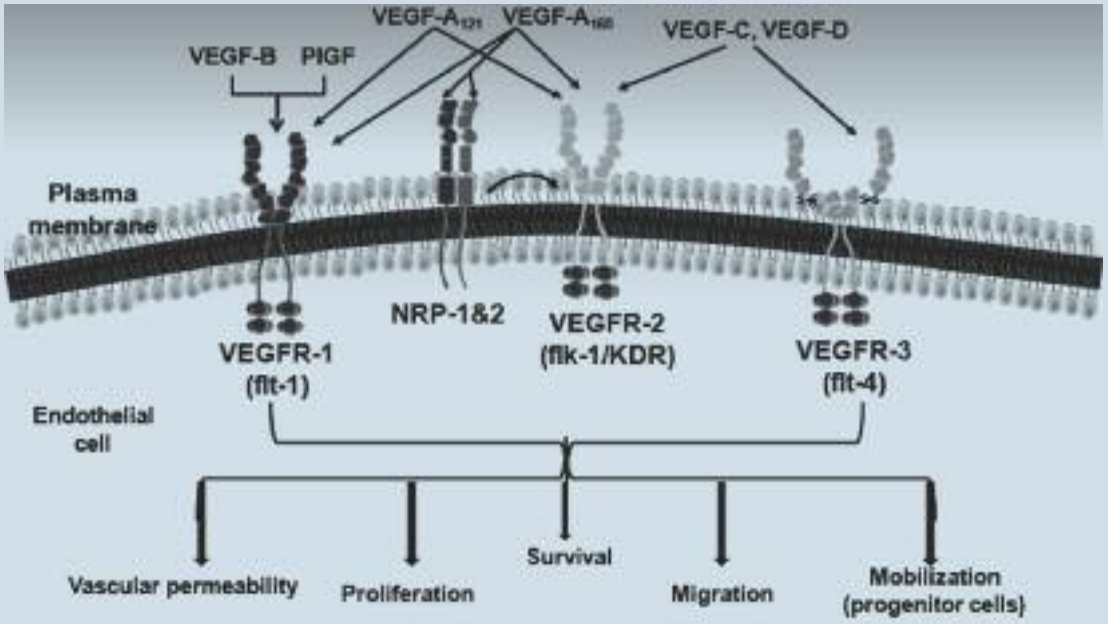


Figure 2.
Vascular endothelial growth factor receptors (VEGFRs) signaling



BEVACIZUMAB IN METASTATIC BREAST CANCER

The most studied antiangiogenic agent in metastatic breast cancer (MBC) is Bevacizumab, a humanized monoclonal antibody that binds to VEGF-A, preventing it from binding to receptors and activating signaling cascades that lead to angiogenesis. Different phase II studies have evaluated the feasibility of combining cytotoxic agents with Bevacizumab. All of these studies led to the conclusion that Bevacizumab could be combined safely with a variety of cytotoxic drugs and that the increased ORR suggested some additional benefit from their combined use. Three multicenter, randomized phase III trials have been reported in patients with HER-2 negative MBC receiving first-line chemotherapy with or without Bevacizumab (Table 1).

In the E2100 study, paclitaxel was given at 90mg/m^2 weekly [15]. In the combination arm, patients without disease progression could continue Bevacizumab after discontinuing paclitaxel. In total, 722 patients were randomized. The addition of Bevacizumab improved median progression-free survival from 5.9 to 11.8 months. Grade 3-4 hypertension, proteinuria, arterial thromboembolic events, bleeding, congestive heart failure and gastrointestinal perforations were increased by the addition of Bevacizumab. No difference in OS was observed, even though combined therapy increased 1-year survival rate (81.2 vs. 73.4%, p=0.01).

The AVADO study was a controlled, three-arm, international phase III trial, randomizing patients with HER-2 negative advanced breast cancer to docetaxel 100mg/m^2 every 3 weeks with either placebo, or combined with Bevacizumab at 7.5 or 15mg/kg, as their first-line chemotherapy treatment [16]. The study was designed to detect a 30% reduction in the risk of disease progression or death as the primary endpoint. At progression, the patients in the single-agent docetaxel arm could be crossed over to Bevacizumab in combination with a number of other agents. The primary endpoint was improved from 8.1 months to 9.0 and 10.1 months for the low and high dose Bevacizumab arms, respectively. For the 15mg/kg Bevacizumab arm the hazard ratio (HR) for PFS was 0.67. The response rate (RR) improved from 46.4 to 55.2% (p=0.074) and 64.1% (p=0.0003), but similar to the E2100 study, the addition of Bevacizumab failed to improve OS.

The RIBBON1 study is also a randomized, placebo-controlled, double-blind phase III trial exploring the efficacy and safety of Bevacizumab in combination with capecitabine-, taxane- or anthracycline-based chemotherapy as first-line treatment for advanced HER-2 negative breast cancer [17]. This study enrolled 1237 patients, with a two-to-one randomization to receive either placebo or Bevacizumab at 15mg/kg every 3 weeks. As in AVADO, patients with progression of disease were eligible for switching to Bevacizumab in combination with second-line chemotherapy. In this study, the median PFS improved by adding Bevacizumab with a HR of 0.69 for capecitabine, and in the taxane/anthracycline cohort the HR was 0.64. Similarly to the E2100 and AVADO studies, the RR improved by 11.8% in capecitabine arm and 12% and 15% in the anthracycline and taxane arms, respectively.

A meta-analysis was performed using complete survival data

for 2447 patients from these three trials and the results were reported at the 2010 ASCO annual meeting [18]. As presented by O'Shaughnessy, the trials met their primary endpoints by demonstrating significantly improved PFS favoring the addition of Bevacizumab to chemotherapy over chemotherapy alone, regardless of hormone receptor status; site of metastases; disease-free interval; or prior adjuvant taxane use. The ORR of patients with measurable disease for the Bevacizumab-containing group was 49% compared with 32% in the chemotherapy only group. Although the 1-year survival rate did demonstrate superiority favoring the Bevacizumab-containing arm (control: 77%; Bevacizumab plus chemotherapy: 82%; p=0.003), OS was not significantly improved. In the pooled population, median OS was 26.7 months with Bevacizumab and 26.4 months with chemotherapy alone (HR 0.97; p=0.56). Based on the aforementioned results, the U.S. Food and Drug Administration concluded that Bevacizumab does not improve OS and patients treated with it are at greater risk for adverse effects, such as bowel perforation, and finally decided to revoke the indication for Bevacizumab in metastatic breast cancer.

A plausible reason for the lack of OS benefit in this pooled analysis is the high duration of survival post-progression (SPP). In general, there is a higher probability of demonstrating an OS benefit in populations with short SPP. In the aforementioned trials the median SPP was 20 months. Additionally, in mBC first-line therapies have difficulty demonstrating OS benefit because of the highly biologically heterogeneous populations studied. Another reason could be the fact that at least two thirds of patients received additional regimens once they progressed, and about half of the patients in the non-Bevacizumab group received Bevacizumab upon progression.

A different explanation for the obtained results could be the assumption that antiangiogenic drugs constitute a means by which tumors become more aggressive over time [19]. One way this could occur, is by elevated levels of the HIF-1 transcription factor, which in turn is known to induce a number of genes, such as *c-met* [20] and *twist* [21], which are involved in tumor cell motility and invasion. Subsequently, the degree of the obtained initial benefit (increased tumor responses and PFS) could be partially reversed by the onset of more aggressive tumor growth after the end of therapy. As has been shown, temporary or permanent termination of Bevacizumab therapy might result in subsequent acceleration in the growth rate of tumors such as liver metastases in colorectal cancer patients [22]. Such observations have an impact also on the debate over the duration of antiangiogenic treatments, and whether such treatments should be continued beyond tumor progression. Retrospective analysis of the observational BRiTE study in patients with metastatic colorectal cancer, suggested that continued VEGF inhibition beyond initial progression could play a role in improving the survival of patients [23]. However, the retrospective nature of this analysis requires caution in the interpretation of the results, which should be evaluated in appropriately designed prospective trials. Currently, the randomized SWOG 0600 study is evaluating this hypothesis and may elucidate the role of Bevacizumab continuation after disease progression.

COMBINATIONS OF BEVACIZUMAB WITH OTHER BIOLOGICAL AGENTS

The cross-talk interaction between HER-2 and VEGF suggests that VEGF is a downstream target of HER-2 activation [24]. The combined treatment with Bevacizumab

Table 1.
First-line phase III studies in metastatic breast cancer with Bevacizumab and chemotherapy

	E2100	AVADO	RIBBON1
Number of patients	673	736	1237
Randomized	Yes	Yes	Yes
Placebo	No	Yes	Yes
Bevacizumab dose	10 mg/kg/2W	7.5/15 mg/kg/3W	15 mg/kg/3W
Randomization ratio	1 : 1	1 : 1 : 1	1 : 2
Bevacizumab crossover	No	Yes	Yes
Chemotherapy	Paclitaxel 90mg/m^2/W	Docetaxel 100mg/m^2/3W	Capecitabine, Docetaxel/nab-Paclitaxel Doxorubicin/Epirubicin
Primary endpoint	PFS	PFS	PFS
RR (%)	21.2 vs 36.9	45.9 vs 64.1	33.0 vs 45.9
PFS (months)	5.8 vs 11.3	7.9 vs 8.8	6.8 vs 8.9
PFS (HR)	0.48, p<0.0001	0.62, p=0.0003	0.66, p=0.0001
OS (months)	-	8.0 vs 7.7 vs 7.5	5.6 vs 6.7

and trastuzumab confirms the predicted synergism of preclinical models [25]. A phase II study enrolled 50 chemotherapy-naïve patients, with HER-2 positive advanced breast cancer [26]. Objective clinical responses were documented in 24 patients (48%) with 6 patients (12%) having stable disease that lasted >6 months (12%) and a clinical benefit rate of 60%. The median TTP was 9.2 months and the median OS was 43.8 months. These remarkable results formed the clinical basis for the AVEREL randomized phase III study, which evaluates the incorporation of Bevacizumab into first-line treatment with docetaxel and trastuzumab of HER2-positive advanced breast cancer. The E1105 study of the Eastern Cooperative Oncology Group investigates the added value of Bevacizumab to docetaxel/trastuzumab with or without carboplatin. Preliminary results of a phase II study of Bevacizumab combined with lapatinib in heavily pretreated patients with HER2-positive metastatic breast cancer demonstrated promising results and acceptable toxicity [27].

Laboratory models have suggested that simultaneous targeting of the VEGF ligand and the intracellular kinase domain of its receptor VEGFR2 can result in enhanced antitumor efficacy. Based on this hypothesis, in a phase II study sunitinib, a potent inhibitor of VEGFR-2 tyrosine kinase, was combined with paclitaxel and Bevacizumab [28]. Patients receiving the three-drug regimen exhibited an unacceptably high level of drug-related toxicity and authors concluded that adding sunitinib to standard doses of Bevacizumab plus paclitaxel for metastatic breast cancer is not feasible.

BEVACIZUMAB IN HORMONE RECEPTOR-POSITIVE BREAST CANCER

The human VEGF gene contains functional estrogen and progesterone responsive elements. Progesterone and estrogen affect transcription and post-transcriptional modification of VEGF as well as VEGFR expression in breast cancer cell lines [29]. Multiple points of interaction between the ER and the VEGF pathways suggest that overexpression or over-activation of the VEGF pathway results in resistance to endocrine treatment. Clinical studies have shown that tumors with high levels of VEGF fail to respond to hormone therapy [30]. In a phase II study, 43 patients received letrozole and Bevacizumab 15mg/kg every 3 weeks [31]. Although 84% of patients had at least stable disease on a non-steroidal aromatase inhibitor, confounding efficacy results, partial responses were seen in 9% and stable disease ≥6 months was noted in 67% of patients. Safety analysis suggested an increased incidence of hypertension and proteinuria with this combination, compared to other studies with Bevacizumab. Nonetheless, a median PFS of 17 months remains impressive. Phase III proof-of-efficacy trials of endocrine therapy plus Bevacizumab are in progress (Cancer and Leukemia Group B 40503 study and GEICAM group 2006-11 study).

Another recurring theme is whether Bevacizumab in combination with anti-estrogens is able to improve disease control in patients having progression after treatment with an aromatase inhibitor. A single-stage phase II study of fulvestrant and Bevacizumab was conducted with these objectives, but failed to meet the specified endpoint [32].

METRONOMIC REGIMENS AND BEVACIZUMAB

Metronomic chemotherapy refers to the frequent, regular administration of relatively low doses of an agent over long periods of time with no prolonged drug-free interruptions. One mechanism of action to account for the anti-tumor effects of metronomic chemotherapy is through inhibition of angiogenesis. This can occur either by targeting the activated and dividing endothelial cells in newly-formed tumor-associated blood vessels [33], or by targeting circulating endothelial progenitor cells [34].

This type of approach has been applied in the clinic with low-dose combinations of methotrexate and cyclophosphamide. In preclinical models, the addition of VEGFR-2 antibodies resulted in enhanced tumor regression. In a phase II study, Spanish investigators applied a 2-week schedule consisting of Bevacizumab 10mg/kg and methotrexate 1mg/kg on day 1 combined with cyclophosphamide 50mg daily [35]. In 22 evaluable, pretreated patients, this regimen resulted in an overall RR of 31.8%, with stable disease (>6 months) amounting to 31.8%, and a combined clinical benefit rate of 63.6%. In another phase II clinical trial from the European Institute of Oncology, 46 patients with advanced breast cancer received metronomic capecitabine (500mg thrice daily) and cyclophosphamide (50mg daily) plus Bevacizumab (10mg/kg every 2 weeks) [36]. Treatment was proved extremely promising both in terms of efficacy (overall clinical benefit rate 68%; median PFS 10.5 months) and minimal host-associated toxicity.

TYROSINE-KINASE INHIBITORS IN THE TREATMENT OF ADVANCED BREAST CANCER

Stimulation of VEGFRs and other tyrosine kinase receptors, such as PDGFRs and FGFRs, causes massive activation of signaling pathways in endothelial cells. Tyrosine kinase inhibitors (TKIs) are small molecules able to pass through the cell membrane and block the activation of various downstream signaling pathways intracellularly. Most of them compete with ATP at the ATP-binding site of a tyrosine kinase. There are three types of TKIs. Type I recognizes the active conformation of a kinase. An example of a type I TKI is sunitinib, which demonstrates competitive inhibition to ATP against VEGFR-2, PDGFR-β, VEGFR-1 and -3, PDGFR-a, KIT, FLT3, CSF-1R and RET [37]. In contrast to type I, type II kinase inhibitors recognize the inactive conformation of a kinase. Sorafenib is a type II kinase inhibitor and blocks the phosphorylation of VEGFR-2 and 3, PDGFR-β, Raf, and KIT by using a hydrophobic pocket to compete with ATP [38]. A third class of kinase inhibitors covalently and irreversibly binds to cysteine at specific sites of the kinase. Examples of

covalent tyrosine kinase inhibitors are quinazoline-based inhibitors such as vandetanib, which, in addition to targeting VEGFR, inhibits EGFR [39].

Sunitinib is the most studied TKI in MBC. A phase III study of sunitinib plus paclitaxel versus Bevacizumab plus paclitaxel as first-line therapy (NCT00373256) has been terminated prematurely as it would not meet its primary goal (the primary endpoint being PFS). Furthermore, two randomized phase III studies investigating the addition of sunitinib to docetaxel [40] and capecitabine [41], respectively, did not meet their primary endpoint of prolongation of PFS, despite a significantly increased ORR (51% versus 39%) in the docetaxel study. Finally, a study comparing capecitabine with sunitinib in MBC has been halted because of futility [42].

Sorafenib in a randomized phase IIb study (229 MBC patients) comparing capecitabine plus sorafenib with capecitabine plus placebo has shown significantly increased PFS [43]. In addition, a randomized phase IIb study comparing paclitaxel plus sorafenib with paclitaxel plus placebo as first-line therapy in 237 MBC patients demonstrated significant improvements in time to progression and ORR. However, the primary endpoint (PFS) was not significantly increased (HR 0.788, p=0.0857) [44]. Many others TKIs are in pre-clinical and clinical development.

Despite the promising activity of TKIs in preclinical tumor models, targeting VEGFR signaling appears to be insufficient to permanently inhibit angiogenesis and tumor growth. The reason for the lack of effect is probably multifactorial. One explanation could be insufficient dose intensity due to toxicity and subsequent drug-free breaks, which can sometimes result in acceleration of tumor regrowth. Preclinical studies have shown that, although treatment of tumors in mice with a TKI can result in rapid reduction of tumor vascularity, there is a very quick rebound in tumor revascularization which occurs within one week, if drug treatment is stopped [45].

MODES OF RESISTANCE TO ANTI-ANGIOGENIC THERAPY

Clinical experience has shown that, similar to other drugs, there are two modes of resistance in response to antiangiogenic therapy: adaptive evasion and intrinsic non-responsiveness. Adaptive or evasive resistance refers to the ability of a tumor, after an initial response phase, to adapt so as to evade the therapeutic blockade by inducing mechanisms that enable neovascularization despite the therapeutic blockade, or reduce dependence on angiogenesis by other means, leading to renewed tumor growth and progression. By contrast, intrinsic non-responsiveness is a pre-existing condition defined by the absence of any beneficial effect of an antiangiogenic therapy. Consequently, tumors grow and progress unabated during the course of antiangiogenic therapy.

Evasive resistance to VEGF pathway inhibitors involves a number of distinct and interrelated mechanisms that may be variably important. Activation and/or upregulation of other pro-angiogenic signaling pathways, including those involving members of the fibroblast growth factor (FGF), ephrin and angiopoietin families [46], placental growth factor (PGF) [47] and notch ligand/receptor system [48] can circumvent the antiangiogenic therapy and provoke neovascularization and subsequent tumor relapse.

Hypoxia caused by vessel regression during the course of antiangiogenic therapy, acting in part through HIF-1α and its targets (stromal cell-derived factor-1α and VEGF) can attract a heterogeneous population of bone marrow-derived cells consisting of vascular progenitors and pro-angiogenic monocytic cells (tumor-associated macrophages, and immature monocytic cells, such as $TIE2^+$ monocytes, $VEGFR1^+$ hemangiocytes and $CD11b^+$ myeloid cells) [49]. Endothelial and pericyte progenitors are incorporated as components of new vessels to directly build new blood vessels. Pro-angiogenic monocytes fuel the tumors with pro-angiogenic cytokines, growth factors and proteases, all of which facilitate neovascularization.

Although inhibition of VEGF signaling pathways can lead to vessel regression, a few 'functional' vessels remain; these vessels are densely and tightly covered with pericytes, and are markedly distinct from the vessels that are seen in untreated tumors, which are typically dilated, tortuous and irregularly shaped, and variably covered with less closely associated pericytes. Such coating by pericytes helps the tumor endothelium to survive and function, and thereby enables tumors to grow during the course of an antiangiogenic therapeutic regimen [50].

Finally, when tumors are not able to adequately reinitiate angiogenesis, cancer cells may invade adjacent normal tissue to achieve vascular sufficiency in a dispersed fashion. Tumor cells can migrate along the outside of blood vessels (perivascular invasion), using them as conduits into normal tissue, or infiltrate through the extracellular matrix to achieve vascular sufficiency [46].

In addition to the aforementioned mechanisms of acquired resistance, there are a number of other possible mechanisms. These include rapid vascular remodeling or maturation during or after antiangiogenic therapy, thus resulting in vessels with a more mature phenotype; such vessels tend to be less- or non-responsive to antiangiogenic drugs compared to immature, growing vessel capillaries [51]. Selection and overgrowth of tumor cell subpopulation that can survive under more hypoxic conditions, as a result of various genetic mutations, may be another mechanism of acquired resistance [52].

Although intrinsic resistance could reflect rapid adaptation and onset of evasive resistance, there is evidence that occasionally tumors have already activated one or more of resistance mechanisms, not in response to therapy but rather in response to the selective pressures of their microenvironment during premalignant development and malignant progression. An analysis of human breast cancer biopsies revealed that late-stage breast cancers expressed

a plethora of pro-angiogenic factors, including FGF2, in contrast to earlier stage lesions, which preferentially expressed VEGF [53]. The pre-existence of FGF2 in these tumors could enable continuing angiogenesis in the face of Bevacizumab therapy, such that inhibition of VEGF signaling does not affect angiogenesis. Other tumor types, such as pancreatic ductal adenocarcinoma, survive and prosper in the hypoxic microenvironment of a massive (largely avascular) desmoplastic stroma. These tumors in 75% of cases carry inactivating mutations in the p53 tumor suppressor gene, loss of which has been shown to improve survival in hypoxic conditions, including ones induced by angiogenesis inhibition [54].

BIOMARKERS OF ANGIOGENESIS AND PREDICTION OF RESPONSE

All antiangiogenic agents demonstrate clear therapeutic heterogeneity in that they are active in some patients but inactive and toxic in others. A biomarker to predict which patients might experience the most benefit and least toxicity would be of clinical and scientific value.

Many biomarkers of angiogenesis have been proposed as predictors of response, but none has yet been identified. An obvious candidate would be elevated VEGF expression, detected either within tumors, or systemically in the circulation. Pre-treatment plasma levels of VEGF are indicative of poor prognosis, but do not predict response to antiangiogenic therapy, including Bevacizumab. Considerable research has been conducted to test the possibility that single-nucleotide polymorphisms in the germ-line involving angiogenesis-related genes influence the natural history of the disease and its response to treatment. Recently, in a retrospective analysis of E2100 study, an association between the VEGF genotype and median OS and severe hypertension has been demonstrated in MBC patients receiving Bevacizumab and paclitaxel [55].

SUMMARY AND CONCLUSIONS

A large number of angiogenesis inhibitors has been described and many have proved to be valuable clinical adjuncts to conventional chemotherapy, by reducing tumor loads and, in certain tumors, prolonging survival. However, angiogenesis is a fundamental biological process, essential for the survival of the organism and, as such, is likely to be initiated by the combined activation of multiple pathways. These compensatory mechanisms may be what ultimately limits the therapeutic potential of antiangiogenic therapies, because blocking a single pathway may induce compensation by other proangiogenic pathways. Consequently, resistance to antiangiogenic drugs can develop quickly through multiple mechanisms, diminishing the initial positive impact of antiangiogenic therapies in the clinical course of disease. Improvements in therapeutic outcomes may emerge from several different strategies, including the use of antiangiogenic drugs in combination with other therapies, such as metronomic therapy, or other kinds of targeted agents, such as epidermal growth factor receptor inhibitors, drugs that target HER2, or hormonal-based therapies. A final and important strategy for improving therapeutic outcomes will be to identify patients who are more likely to benefit from antiangiogenic drugs, for example, on the basis of predictive biomarkers.

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Surgery of neuroendocrine tumors of the gastrointestinal and pancreatic region

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ABSTRACT

The natural history of NETs and PETs is highly variable. The role of surgery in themanagement of these rare tumors is crucial because patients with completely resected tumors generally have a good prognosis. Also the surgery may play an important role in advanced disease, in which debulking or cytoreductive resectionmay also prolong survival. Surgical strategy, such as timing; extent of the resection; and the use of laparoscopic procedures are currently under debate.

Key words: surgery; carcinoid tumors; pancreatic neuroendocrine tumors.

INTRODUCTION

Gastrointestinal carcinoid tumors, now termed as neuroendocrine tumors (NETs), and pancreatic endocrine tumors (PETs) are uncommon malignancies with an annual incidence of 3-5 cases per 100,000 individuals [1, 2, 3].

The prognosis of these tumors compares favorably with other types of intra-abdominal digestive or other location malignancies and prolonged survival is sometimes observed even in the presence of metastatic diseases [2, 3, 4, 5].

NETs occur most commonly in the appendix and small intestine in the majority of cases and stomach, colon and rectum in a smaller number of cases [1, 2].

PETs represent a subnet of pancreatic neoplasms accounting for 2-4% of all clinically detected pancreatic tumors, and are rare yet fascinating tumors functional which specific endocrine syndromes or non functional PETs (nf PETs) with symptoms similar to pancreatic carcinomas [5, 6].

In this review we discuss the current surgical strategies for treating these tumors.

1. GASTROINTESTINAL NEUROENDOCRINE TUMORS (NETS)

The most important statement in the management of such tumors is **"patients with NETs, including functional adenomas or carcinomas, should be considered for definitive resection"** [7]. The carcinoid tumors arise from argentaffin cells located in the foregut, midgut and hindgut.

Sixty-six percent of carcinoid tumors arise in the midgut, with the small bowel being the most common site, followed by the appendix. The predominance of midgut tumors may be related to the incidental finding of carcinoid tumors in appendices removed for appendicitis or prophylactically excised during gynecology operations. On the other hand, carcinoid tumors associated with MEN 1 arise in the foregut (pancreas and proximal small intestine).

50% of patients with malignant carcinoid tumors will live 5 years or more after initial diagnosis [8].

NETs can secrete various hormones with the carcinoid syndrome as the classical manifestation such as episodic cutaneous flushing, abdominal cramps and diarrhea related to the secretion of serotonin, histamine or tachykinins into the systemic circulation [9]. One third of patients with carcinoid syndrome develop valvular cardiac complications, especially tricuspid regurgitation or pulmonary stenosis.

1.1. Treatment of NETs

Depending on the results obtained from diagnostic evaluation workup, the disease is classified as locoregional or metastatic. Surgical resection of all neoplastic tissue should be performed for localized disease. However, the extent of surgical resection depends on tumor location; its size; patient

stage performance status; and hospital volume regarding the management of such tumors [10].

Small intestine carcinoids

Surgical resection is recommended with clear margins over 5cm.

In duodenal lesions, endoscopic resection procedures may be used if indicated. Together with intestine resection, a prophylactic cholecystectomy should be considered, as possible subsequent treatment with octreotide may be needed in the future, and this management increases the risk of developing gallstone [11].

Appendiceal carcinoids

For tumors <2cm and confined to the appendix, a laparoscopic appendectomy is sufficient [12]. If the tumor is larger than 2cm in diameter, surgical resection is a right hemicolectomy. If the finding is presented in postoperative histology of incidental appendectomy, re-exploration is required after carefully evaluating the presence of locoregional spread to lymph nodes or adjacent structures, with abdominal/pelvic CT or MRI scans.

Colon carcinoids

Rare tumors for which surgical resection is the typical therapeutic approach. The type of operation depends on tumor localization.

Rectal carcinoids

The treatment of rectal NETs is based on the size of the primary tumor. If the lesion is less than 2cm, endoscopic or transanal resection is recommended -if possible. For tumors larger than 2cm, low anterior resection or abdominoperineal resection should be considered [13].

Gastric carcinoids

The most important factor in the management and prognosis of these tumors is whether they are associated with hypergastrinemia or not.

Patients with **normal gastrin levels** have an aggressive **potential malignant course** [14]. In these cases, total gastrectomy with D2 lymph node resection is recommended.

For patients with hypergastrinemia, tumor size is the key factor when deciding about resection. For tumors smaller than 2cm, endoscopic resection with biopsy is recommended; the follow-up is observation and octreotide administration for patients with Zollinger–Ellison syndrome.

For tumors larger than 2cm, endoscopic resection (if possible) or gastrectomy is indicated, and in the latter, the role of D1 or D2 lymph node dissection is controversial.

1.2. Surgical treatment of metastatic NETs

The clinical course of patients with metastatic NETs is often highly variable. Some patients with indolent tumors remain symptom-free for years, even without treatment. Others have symptomatic progressive metastatic disease, either from tumor bulk or biochemical hypersecretion and should be treated.

The most favorable organs to develop NETs metastasis are the liver, the lungs, the bones and the mesenteric lymph nodes. **The management** of patients with metastatic NETs is focused on symptoms **palliation** and on **the prevention** of further disease-related complications.

Hepatic metastases management comprises hepatectomy or RFA procedures in order to debulk tumor mass, and is successful in 50-60% of cases with a 5-year survival in 35-50% [15, 16].

In cases of wide-spread of diffuse metastatic disease within the liver, palliative procedures such as chemoembolization; radionuclide therapy; or cryotherapy are recommended [17]. Lately, many liver surgeons suggest lobectomy in the site of bulk disease and multiple wedge resections or RFA in the other site.

Liver transplantation may be an alternative method but is not indicated.

Mesenteric mass metastases must be debulked due to the risk of developing gastrointestinal obstruction or ischemia. Complete relief of obstructive symptoms was noted in all patients in which tumor mass was debulked. In cases of unresectable mesenteric mass, intestinal bypass is indicated as palliative surgical procedure.

Aggressive surgical intervention is highly effective in patients with metastatic NETs not only as palliative management but also as cytoreductive effect, in order to help the adjuvant hormonal or targeted systemic treatments [19].

The most difficult problem in metastatic NETs is bone metastases. If painful bone metastases are present or weight-bearing bones are involved, recommended options include radiotherapy (with or without bisphosphonates) or targeted therapies that may play a palliative and therapeutic role.

2. SURGICAL MANAGEMENT OF PETS

The endocrine pancreas contains at least five types of cells that produce characteristic polypeptides. Malignant pancreatic endocrine tumors account approximately for 1% of pancreatic cancers by incidence and 10% by prevalence [20].

Up to 50% of PETs are non-functional with 90% being malignant and the remainder able to manifest with hormonal symptoms.

Fifty percent of these are insulinomas, 90% of which are benign; approximately 50% are gastrinomas, with 60-90% of them being malignant. The remaining 2-4% may be glucagonoma, VIPoma, somatostatinoma or PPoma [21].

Islet cell tumors or PETs occurring in patients with MEN 1 or MEN 2 are typically multiple, as compared to sporadic PETs that are usually solitary.

Surgical resection is the optimal treatment for PETs but it is highly important to treat any symptoms of hormonal excess prior to resection.

The relief of gastrinoma symptoms is sufficient to inhibit gastrin secretion with H2-receptors or, better yet, with proton pump-inhibitors (PP1). In the case of insulinomas, glucose levels must be stabilized using diet and medication.

In glucagonoma or VIPoma patients it is crucial to stabilize fluid and electrolyte abnormalities with octreotide and fluid administrations. Zinc supplementation is also helpful in cases of skin rash.

Another factor that may be evaluated during the preoperative period of glucagonoma patients is the high risk of postoperative pulmonary embolism, so it is necessary to consider them as candidates for vena cava filter and continuous anticoagulation treatment.

In cases that might require splenectomy, a trivalent vaccine is indicated before or immediately after the operation [11, 22].

The majority of glucagonomas are located in the tail of the pancreas, and calcified with malignant behavior and positive lymph nodes.

The approach for pancreatic gastrinomas usually depends on the results of preoperative localization and exploratory laparotomy findings. There are three possibilities:

- Occult gastrinomas: observation or enucleation of tumors if identified.
- Gastrinomas ≤5cm: either non-invasive enucleation or resection.
- Gastrinomas ≥5cm: Whipple procedure or resection with LN dissection.

Laparoscopic surgery can be considered in patients with benign insulinomas and non-functional tumors located in the body and tail of the pancreas.

Laparoscopic surgery must be reserved for tumors less than 2cm located on, or near the surface of the pancreas, and not in contact with splenic vessels, the portal vein or the main pancreatic duct. If these criteria are not met, open surgery might be the preferred choice.

For head of pancreas tumors, Whipple procedure with dissection of peripancreatic nodes is indicated.

2.1. Management of metastatic or locoregional recurrent PETs

Patients with malignant neuroendocrine tumors of the pancreas frequently present with liver metastases, or locoregional recurrences. Repeated resections for resectable recurrences or metastases are thought to be indicated in order to improve survival [23].

If an aggressive approach is adopted, potentially curative resections and overall 5-year survival rates up to 60% can be achieved.

In studies with hepatic metastases from PETs treated by surgical resection, there was an average operative mortality of 3% and a 5-year survival rate which ranges from 64 to 72% [23]. These results are very encouraging when compared with historical controls, where patients with liver PETs metastases remained untreated and had a 5-year survival rate of only 25-40% [24]. Orthotopic liver transplantation should be an alternative treatment but only to be considered in select young patients with metastases limited to the liver and those with recently resected primary PETs who require relief from hormonal or tumor symptoms.

Other options for more advanced diseases include regional therapies, such as arterial embolization; radioembolization; chemoembolization; RFA; cryotherapy; while microwaves provide effective liver metastases cytoreduction [25].

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Treatment of giant cell tumors of the spine with radiotherapy: a case report and literature review

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ABSTRACT

Introduction: Giant cell tumors are rare, primary, histologically benign bone tumors which are most frequently located in the long bones and rarely in the spine. Management of giant cell tumors localized in the spinal column presents a challenge due to their anatomical location.

Case presentation: A 44-year-old female presented with backache and paraplegia progressing over a period of three months. Magnetic resonance imaging (MRI) demonstrated diffuse enhancement of the T6 vertebral body with associated spinal cord compression. The patient underwent surgical decompression but the lesion could not be radically resected due to its anatomical location. Histopathological examination revealed a giant cell tumor. The patient was subsequently treated with radiotherapy and experienced significant clinical response regarding pain and neurological symptoms and long disease progression-free survival.

Conclusion: Radiotherapy is an effective adjuvant treatment modality in patients with incompletely resected giant cell tumors.

Key words: giant cell tumors; spinal column; radiotherapy.

Abbreviations

CT: computed tomography
IMRT: intensity-modulated radiation therapy
MRI: magnetic resonance imaging
PET: positron emission tomography

INTRODUCTION

Giant cell tumors of the bone are rare tumors which, although histologically benign, can be locally invasive and potentially metastatic [1]. They are most commonly found in the long bones and rarely occur in the spine.

Management of vertebral giant cell tumors is a difficult issue because of their anatomical location that can lead in some cases to spinal cord compression.

CASE PRESENTATION

A 44-year old female was admitted to the Emergency Department of our Hospital with backache and paraplegia which were gradually progressing over a period of three months. Physical examination revealed hyperreflexia and hyposensitivity of the right lower limb. MRI of the vertebral column revealed diffuse enhancement of the T6 vertebral body with an expansile mass causing a compression deformity of the spinal cord, suggestive of either a primary or secondary bone tumor (Figure 1).

Surgical decompression was performed but the anatomical location of the lesion rendered a radical resection of the tumor impossible. Biopsy revealed a tumor composed of numerous giant cells with scant stroma. The giant cells were multinucleated and the stromal cells displaced mild to moderate atypia while atypical mitoses were rare. Surgical borders where difficult to be assessed due to fragmentation of the specimen.

The patient had an uneventful postoperative recovery and was discharged with the diagnosis of giant cell tumor of the T6 vertebral body. Three weeks after surgery, and due to the fact that the tumor was incompletely resected, the patient was referred to our Department.

Two-dimensional (2D) treatment planning was performed. The target volume was determined by careful review of the CT and MRI. The patient was treated with a direct posterior field in a prone position using a 6MV

Figure 1.
Contrast-enhanced sagittal T1-weighted magnetic resonance image showing the tumor with heterogeneous enhancement. Tumoral mass involves the T6 vertebral body and extends into the spinal canal (arrow)

Figure 2.
Sagittal PET image showing increased FDG uptake of the T6 vertebral body (arrow). FDG: fludeoxyglucose

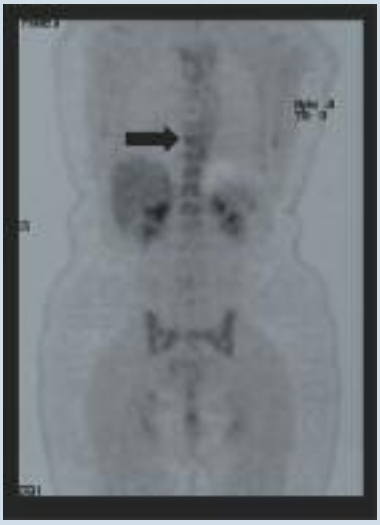
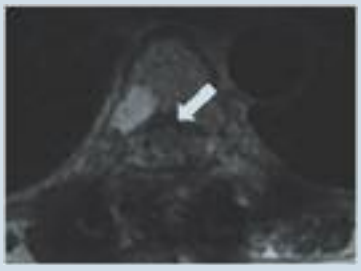


Figure 3.
Contrast-enhanced transverse T2-weighted magnetic resonance image after radiotherapy, showing that the tumor mass is not extending into the spinal canal (arrow)



linear accelerator, receiving adjuvant radiotherapy of 45Gy in 22 fractions. Treatment fields covered the tumor bed with a margin of 3cm.

Shortly after the initiation of radiotherapy the patient reported pain relief, and regular clinical examination showed significant neurological improvement. The response to radiotherapy was assessed clinically and radiologically with MRI, by analyzing the T6 vertebral body signal intensity; the enhancing pattern; the presence or absence of spinal canal involvement; and spinal cord compression.

MRI at one month after completion of radiotherapy revealed contrast enhancement of the T6 vertebral body, however the expansile mass that was compressing the spinal cord was not apparent. In order to assess the response to radiotherapy in terms of local control and possible presence of remainder tumor, the patient underwent further diagnostic work-up with a PET CT scan that showed moderate hypermetabolism (SUVmax = 2.5) of the T6 vertebral body that was, however, not relevant with a remainder tumor but rather with the effect of radiation on the thoracic vertebrae (Figure 2). Three months later the patient underwent a repeat MRI that showed further radiological response, with no contrast enhancement of the T6 vertebral body, and no extension of the tumor mass into the spinal canal (Figure 3).

The patient remains asymptomatic and neurologically intact 2 years after surgical decompression of the tumor, followed by adjuvant radiotherapy, while there is no evidence of recurrent disease on serial imaging.

DISCUSSION

Giant cell tumors of the bone were first reported by Cooper and Travers in 1818 [2]. They are very rare primary bone tumors with benign histology but show a tendency for significant bone destruction, local recurrence, and occasionally metastasize to the lung. Metastases to the lung occur in two to nine percent of the cases [3].

A female predominance is reported in the literature, especially in women between the ages 20 to 40 [4, 5]. Giant cell tumors have a predilection for epiphyseal areas surrounding the knee joint and only two to three percent are originated in the spine [4]. In a literature review by Shankman *et al.*, only 2.7% of the 1,277 giant cell tumors reported were located in the spine [6], data which is in agreement with Hunter *et al.* [7]. Sanjay *et al.* [8] reported that from 1955 to 1990 there were only 24 patients with giant cell tumors of the spine at the Mayo Clinic.

Giant cell tumors have a distinctive microscopic appearance. Histologically, they consist of two main cell types, stromal and giant cells. The stromal cells are mononuclear cells that exhibit true cytological atypia and are the only proliferating element within the lesion [9]. Giant cells are large and have more than 20 to 30 nuclei, mostly in a pericentral location.

Patients with giant cell tumor of the spine most commonly present with localized pain and a subset of these patients may also report varying degrees of paraplegia due to spinal cord compression. Our patient presented with pain as well as hyperreflexia, which suggested spinal cord compression.

Radiographically, giant cell tumor manifests as a destructive, osteolytic lesion on plain films. The CT and MRI studies provide information for the extent of bone involvement and the degree of marrow and surrounding tissue involvement. In our patient, MRI demonstrated diffuse enhancement of the T6 vertebral body with an associated expansile mass that was causing spinal cord compression.

Many treatment strategies have been developed for giant cell tumors, including surgery, radiotherapy, embolization, cryosurgery and cementation, however optimal management still remains complete tumor resection with wide margins -if possible.

Whereas tumor radical resection with wide margins is feasible in long bones, this approach can cause substantial functional deficits when tumors occur in the axial skeleton. In these patients radiotherapy has been used alone or in combination with limited surgical resection as an adjuvant therapy -like in our patient. Regarding the literature, in the series by Miszczyk *et al.* [10] it is suggested that giant cell tumors may be radiosensitive and that radiotherapy with a total dose of 40-45Gy seems to be highly effective. Contrary to that, Caudell *et al.* [11] could not demonstrate a dose-response relationship; the median dose in their series was 46Gy. But as illustrated in the series of Caudell *et al.*, dose-limiting structures, like the spinal cord, also often preclude dose escalation. Other studies have noticed the importance of hypofractionation and suggested that doses of 35-45Gy may be delivered in 15-20 fractions [12].

Although there is no 'gold standard' treatment algorithm for giant cell tumors, treatment should be focused in tumor removal; reduction of the likelihood of local recurrence; preservation of spinal neural function; and spinal stability restoration or maintenance.

Radiotherapy is strongly considered in cases of macroscopically or microscopically incomplete tumor resection as an adjuvant therapy; in cases of giant cell tumors that are unresectable, or in which excision would result in serious functional deficits; or as a palliative treatment of postoperative recurrences.

Modern radiotherapy techniques (IMRT, stereotactic radiotherapy) could be effective in such tumors due to the fact that they can deliver a high dose to the tumor with low dose to the normal surrounding tissues.

CONCLUSIONS

Giant cell tumor of the spinal column is an extremely unpredictable, rare bone tumor. Although radical resection is the treatment of choice, it is often difficult to be achieved due to its anatomical site and the increased risk of causing functional disability. In such cases, radiotherapy with a total dose of 40-45Gy appears to be a safe and effective adjuvant treatment modality in achieving local control and pain relief.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

None

Authors' contributions

Both authors have made a significant contribution to the execution of the work described and assume responsibility for the content of the entire paper.

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