Useful known and unknown views of the father of modern medicine, Hippocrates and his teacher Democritus

**Abstract**

Hippocrates is considered to be the father of modern medicine because in his books, which are more than 70. He described in a scientific manner, many diseases and their treatment after detailed observation. He lived about 2400 years ago. He was born in the island of Kos and died at the outskirts of Larissa at the age of 104. Hippocrates taught and wrote under the shade of a big plane tree, its descendant now is believed to be 500 years old, the oldest tree in Europe –platanus orientalis Hippocratus– with a diameter of 15 meters. Hippocrates saved Athens from a plague epidemic and for that was highly honored by the Athenians. He considered Democritus –the father of the atomic theory– to be his teacher and after visiting him as a physician to look after his health, he accepted no money for this visit. Some of his important aphorisms were: “As to diseases, make a habit of two things –to help or at least to do no harm”. Also: “Those by nature over weight, die earlier than the slim”, also, “In the wounds there are miasmata causing disease if entered the body”. He used as a pain relief, the abstract from a tree containing what he called “salycasia”, like aspirin. He described for the first time epilepsy not as a sacred disease, as was considered at those times, but as a hereditary disease of the brain and added: “Do not cut the temporal place, because spasms shall occur on the opposite area”. According to Hippocrates, people on those times had either one or two meals (lunch and dinner). He also suggested: “...little exercise ...and walk ...do not eat to saturation”. Also he declared: “Physician must convert or insert wisdom to medicine and medicine to wisdom”. If all scientists followed this aphorism we declared: “Physician must convert or insert wisdom to medicine and medicine to wisdom”. If all scientists followed this aphorism we would have more happiness on earth.

**Keywords:** Father of modern medicine – Democritus – Surgery – Athens plague – Philosophy

Hippocrates greatly contributed to modern medicine by declaring that medicine should stand on detailed observation, reason and experience in order to establish diagnosis, prognosis and treatment. After Hippocrates, medicine no longer a mixture of superstition, magic, religion views and empirical treatment, excersised by priests-physicians, but became a real science with accumulating experience.

Hippocrates was born in Astypalaia the ancient capital of the island of Kos in 460 BC [1]. Kos is the second largest island in the Dodecanese, next in size to Rhodes. His father was an Asklepiad physician [1]. His mother was a descendant from the hero and semi-god Hercules, who returning from his labors at Troy, sojourned in Kos and established a dynasty of Hippocrates. Democritus was a contemporary of Hippocrates and one of his teachers. Democritus lived in Avdira, in Thrace. Democritus was a scientific pillar of modern physics because he believed that there exists a multiple universe and that the universe is immortal and unfading. The universe as a whole and everything exciting in it i.e. to óv’ in Greek, consists of atoms which could not split any further. Atoms can not be sensed by us but are considered to exist by reason. Larger and heavier parts or atoms are pushed inside and the lighter at the outside portion of any existing part of the universe. Similar atoms adjust to each other and are gravitated by other similar atoms. Today we know that the heavier particles, neutrons and protons are inside and the electrons at the periphery of the mol-
ecule [3]. Sometime before his death, Democritus chose to live outside the city of Avdría studying birds and other animals and often laughing with his own thoughts. His co-citizens thought he was crazy and invited Hippocrates to examine him. Hippocrates came from Kos and after meeting with Democritus he said to the citizens of Avdría, that Democritus was his teacher and he was healthy and sound more than many other people in Avdría. Hippocrates refused to be paid for examining his teacher [2].

The views of Hippocrates about treatment relied on the power of Nature and were directed to the patient as a unique physical, mental and spiritual entity [1]. In agreement with Plato and Aristotle, Hippocrates believed that the soul of every man is a kind of energy coming out from his body.

In his book: “The Aphorisms”, the first aphorism reads: “Life is short and the art long, the occasion fleeting, experience fallacious and judgment difficult. The physician must not only be prepared to do what is right... but also to make the patient, the attendants and externals, cooperate”. A fragment of the Hippocratic Oath on a papyrus dating from the third century is kept in the Wellcome Library, London [4].

In a dialogue between Socrates and Crito about the Oath of Hippocrates, Socrates says [5]: “In the marketplace, physicians charge a large fee. They claim good will and unselfishness, but at the table I have never met a more misanthropic crowd.” “Doesn’t the Oath impose an impossible code of behavior on the weak of spirit?” Crito: “That is not so. Homer and the tragedians tell us that those who struggle are admired, even if they fail. The Hippocratic art can never become obsolete so long as its followers strive to be virtuous as well as skillful.”

Hippocrates also pledged never to participate in euthanasia and abortion. In his treatise: “On the Epidemics”, book 1(5) he stated the axiom “…as to disease, make a habit of two things –to do good, or at least to do no harm” [6].

Many diseases were described by Hippocrates exactly as they would have been described by a contemporary physician. In acute hepatitis Hippocrates in his book “About Diseases” described: “Acute jaundice rapidly spreading...urine has a red sentiment....high fever, uneasiness and cnidoses. The patient dies within 4 to 10 days.” [7]. He also described askitis: “Liquid collection... around the abdomen becomes...” [8]. He also described acute cholangitis: “Hard and painful hypochoondria, jaundice....bile in the urine...fever...bile in the blood.” [9].

In “The Aphorisms” part II, Hippocrates wrote: “those by nature over weight, die earlier than the slim.” [10].

Hippocrates was asked to find out why Scythian had male impotence. He noticed that the wealthier Skythians who were able to buy horses, had impotence because they passed a great part of their lives riding on horses, thus harming their genitalia. On the contrary the poor were unable to buy horses, had impotence because they passed a great part of their lives riding on horses, thus harming their genitalia. On the contrary the poor were unable to buy and ride horses and they were sexually competent [2].

For surgery and for treating wounds, Hippocrates in his book: “About the Physician” advised: “clean clothes or othernia-a word still used in Greece to day...and old wine as antiseptic...” We know that old wine is richer than recently prepared wine, in alcohol. Also Hippocrates in his books: “Of Surgery in the Clinic” and “About the Clinician” wrote: “...the nails of the surgeon should be cut in a certain manner, there should be proper light coming from the proper direction ...skilled assistants are necessary...and they should be silent...” [11].

Hippocrates knew that “in the wounds there are miasma-ta causing disease if entered the body...” Miasma or miasma in single tense, is a word still used in Greece and meaning “something dirty” [12]. Twenty three ages later, Pasteur will describe with his microscope the microbes, a word meaning in Greek: “small living”.

Hippocrates described plectrodactelia (fingers like plictron in Greek) in cradiopathies and in lung cancer [13]. For the treatment of anaemia he suggested solutions of iron dissolved in wine [13].

For pain confront he suggested extract of “salyasia” a tree between acacia and leului. This is the so called today salix tree or aspen or willow. Only on 1829 Leroux isolated salycin. On 1899 Felix Hoffman produced synthetic acetylsalicylic acid -aspirin from the word aspen [13].

In psychiatry, Hippocrates anticipated Freud by diagnosing that the cause of melancholy of the son of King Perdica II of Macedonia was that Perdica was secretly in love with his father’s mistress [2].

Hippocrates in his book: “On the Sacred Disease” described for the first time epilepsy not as a sacred disease as was considered at those times, but as a hereditary disease of the brain and added: “do not cut this (temporal) place, because spasms (on the opposite area) do attach the man who is cut” [6, 11].

Statue found in the Odeon of Cos, probably representing Hippocrates (4th century B.C.)
He declared that all feelings have a seat in the brain, not in the diaphragm, as Homer had said before him [2]. From this belief of Homer’s, the nerve of the diaphragm is still called “frenic nerve”, frenes, meaning the soul.

For brain concussions he suggested operation by an iron drill, to take place early, within the first 3 days, in order to avoid infection [6, 11].

In his book: “On the Articulations” Hippocrates described the tubercular spine which is to day called: “Potteian illness” [11].

In his book: “On Haemorrhoids” he treated them by stypptic suppositories, by operation or by cautereization. He used the first proctoscope or hodoscope which he called “katopter” meaning: to investigate downwards [11].

According to Hippocrates, people had either one or two meals (lunch and dinner) every day. He suggested that these habits should be strictly followed…in order to give time to digest…[14]. Today we take several meals every day which according to what was mentioned before, “does not give proper time to digest”. Hippocrates also suggested: “…little exercise…and walk…do not eat to saturation” [6].

In order to increase the natural internal temperature of our body and to better adjust ourselves to cold weather, Hippocrates advised healthy men: “to cool their body during the winter by taking cold baths or by any other means…of long duration…” [15]. This is what the winter swimmers do today.

All the above indicate that Hippocrates observed and learned from Nature itself. As his teacher Dimocretus had said: “We must rather think a lot than learn a lot”. Galen, after about 500 years said, that Hippocrates considered Nature as: “the teacher of all teachers” [2].

In his book “Mochilkon-Instruments of Reduction” Hippocrates uses the word “apoptosis” to indicate tissue death, detachment and fall from the body [17]. Recently in 1972, Kerr JFP et al re-used the same word “apoptosis” [18].

In “Decorum” (5) Hippocrates declares that: “when the physician is also a philosopher he is equal to God. Between the two there is no big difference. “Physician must convert or insert wisdom to medicine and medicine to wisdom” [6, 15].

If it was for the reviewers of this paper to choose the best of Hippocrates aphorisms (doctrines), we would choose the last one mentioned above, because if all scientists behaved in wisdom, we might have more happiness in our world.

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**Bibliography**

News related to Nuclear Medicine

Fotis Kalafatos, president of the European Research Council. Fotis Kalafatos was born in Crete in 1940. He was highly successful in all his pre- and post-doctoral education. He was appointed a full professor at the University of Harvard at the age of 28. The University of Athens invited him to take a part time professorship. In Athens he established a Research Department in Genetics. Following that he went to Crete where he stayed from 1982 to 1993 and founded the Institute of Molecular Biology and Biotechnology. Then he went to Heidelberg, Germany in the Molecular Biology Laboratory, where he became Director General for twelve years. In 2005 he was appointed professor of immuno-genomics at the Imperial College of London, UK and holds this chair until now. In 2005 he was one of 400 nominations who applied to be a member of the Scientific Research Council of Europe. Twenty two of these candidates including Fotis Kalafatos were selected to serve at this Council. Fotis Kalafatos was elected by the other 21 members as their president. Since December 2005 Fotis Kalafatos is the President of the European Research Council. The Scientific Research Council of Europe has a budget of 7.5 billion euros for 2007-2013. Around 300 applicants have been awarded grants of 1-1.5 billion euros each, to continue and complete their research.

The Lancet in its issue of February 2, 2008 on page 379, described the profile of Fotis Kalafatos as written by James Butcher.

Post traumatic stress disorder (PTSD). According to a letter to the editor written by C. Psarros, C. Theleritis, S. Martinakis and I.D. Vergiannakis and published in The Lancet 2008; 371: January 24, p301, 19 of the 102 firefighters who were interviewed and were long involved facing the wildfires in Peloponnesus in August 2007, had PTSD. Twelve of whom were seasonably employed. The above authors suggest that those who are going to be involved in extinguishing fires for a long period of time, should not be young in age, should have sufficient experience and should not have an irritable character.

Related to PTSD, I was told that some policemen in North Africa, after shooting and killing villains, suffered from PTSD. This disorder made them insufficient in exercising their duties in the future. In fact, they were unable to shoot at any human target. Police authorities in order to avoid similar disorders of their policemen, used in the educational program of police officers, a “target” which in its very center did not show a dot as usual, but a human face. It was expected that this change would familiarize police officers to shoot on human subjects when necessary.

Nuclear Medicine shows interest in the brain scan of patients with functional neurologic disorders like PTSD.

The Editor
The role of PET in head and neck cancer

Abstract

PET and PET/CT are the procedures of choice for molecular imaging in the head and neck area. The current data of the literature show, that functional imaging with fluorine-18-deoxyglucose (18F-FDG) provides the possibility to obtain information about the viability of malignant lesions. The use of hybrid systems, PET/CT, enables physicians to assess both, morphology and function, and achieve a high diagnostic accuracy exceeding 90%. PET with 18F-FDG is the most sensitive method to detect tumor recurrence. However, false positive results must be considered due to unspecific changes following treatment, especially radiotherapy. The use of quantitative PET scans as well as the application of a second tracer, enhance the capability of PET to assess questionable masses more accurately. Follow up examinations with PET and 18F-FDG provide data about early changes in the tumor metabolism due to chemotherapeutic treatment. Studies in patients undergoing surgery and radiotherapy demonstrated, that PET with 18F-FDG can be used for the prediction of individual survival.

Introduction

Tumors of the oral cavity and the oropharynx are number six in the list of the most common cancer types for men in Germany [1]. The standardized mortality rate increased continuously from 1950 to 1992, followed by a 26% decrease until 2005. Oropharynx cancer is age dependent with a maximum for 60-64 years. Besides the common squamous cell carcinoma, which accounts for about 95% of tumors in the head and neck area, a variety of other histologies exist, including sarcomas and even endocrine tumors.

Like in other tumors, accurate methods are needed for tumor staging to guide the patient to the appropriate therapy: surgery, chemotherapy, and/or radiotherapy. Besides endoscopic evaluation, including histological assessment of the primary tumor, morphological methods are used to assess the primary tumor according to size, location, and infiltration of the surrounding structures as well as for the detection of metastatic lesions in the lymph nodes and other tissues. Magnetic resonance imaging (MRI) and contrast enhanced axial computerized tomography (CT) are established procedures for the assessment of a head and neck tumor. However, morphology based methods always demand changes in the tissue structure, which do not necessarily exist in the initial phase of a malignant lesion. Lymph nodes may be infiltrated by the malignant tumor while they appear with normal size in CT. This is why functional methods can provide additional information for staging purposes.

Results

Tumor diagnostics

Ultrasound (US) and CT have improved the diagnosis and staging of head and neck tumors in the past. MRI and contrast enhanced CT are established procedures for the assessment of a head and neck tumor. Within the last ten years MRI has gained increasing interest due to the possibility to obtain non-invasively high contrast images of morphological structures. Leslie et al. evaluated CT and MRI for T-and N-staging of squamous cell carcinoma of the oral cavity and oropharynx in patients with primary or recurrent disease [2]. Interestingly, the accuracy for the staging of primary tumors was 77% for MRI and 67% for CT. The authors note that despite the fact that the T-stage results were comparable for MRI and CT, the delineation of a tumor was better with MRI. In contrast to the staging results, the detection of recurrent tumors was improved with an accuracy of 89% for MRI and 100% for CT [2]. The main problem with both imaging modalities was the N-staging, because the procedures failed to identify small metastases. Considering a node size exceeding 10 mm as malignant, MRI had a sensitivity of 75% and specificity of 63%, while CT had a sensitivity of 35% and...
a specificity of 100% [2]. Others compared CT, MRI, US, and single photon emission tomography (SPET) for the detection of cervical lymph nodes in patients with squamous cell carcinoma [3]. The highest sensitivity was achieved for MRI (85.7%), followed by CT (77.7%), SPET (75.6%), and US (70.7%). However, the accuracy of all methods did not exceed 70% in this study. The authors conclude that despite high specificity rates, none of these imaging methods is reliable in evaluating occult regional metastases [3]. The data demonstrate that other methods are needed to improve the staging accuracy, especially for N-staging.

Functional methods are primarily based on nuclear medicine procedures. Basically, a radiopharmaceutical is used to generate functional images. A radiopharmaceutical is generally containing two major parts: the isotope, which is needed to obtain a signal outside the body and the pharmaceutical, which determines the functional information achieved by the examination. In the last fifteen years positron emission tomography (PET) has found increasing attention for oncological examinations. PET is based on the application of radiopharmaceuticals labeled with positron emitting isotopes, primarily fluorine-18 (18F). These isotopes have the advantage to annihilate with a high energy radiation of 511 keV. Furthermore, the radiation is emitted with an angle of 180 degrees, providing the use of the so called coincidence technique. Thus, the spatial resolution of PET is higher by a factor of 3-5 as compared to conventional nuclear medicine procedures based on single photon emitting isotopes.

One of the most common radiopharmaceuticals for PET is 18F-labeled deoxyglucose (FDG), which has found widespread use for oncological studies [4]. FDG is transported like glucose into the cells, also phosphorylated by hexokinases, but not further metabolized. The dephosphorylation rate is generally low in most of the malignant tumors for at least one hour. One of the initial studies performed by Minn et al. (1988), compared the 18F-FDG data with flow cytometry in head and neck tumors [5]. The authors found no correlation with the histologic grade of the tumors, but a correlation was noted for the 18F-FDG uptake ratio and the proliferating cells as measured by flow cytometry [5]. We compared the tumor perfusion using 15O-water and 18F-FDG uptake with flow cytometry data in 35 patients with head and neck tumors [6]. Interestingly, the tissue perfusion data did not correlate neither to the 18F-FDG uptake nor to the flow cytometry results. The 18F-FDG data revealed two subgroups with a significant correlation of the 18F-FDG surface uptake values (SUVs) in each subgroup with the proliferative index [6]. It was assumed that the difference between the two uptake groups was related to a different expression of oncogenes. The data demonstrate, that functional methods like PET with 18F-FDG are closely related to molecular biological processes and may therefore be helpful to assess a malignant lesion in more detail. Thus, the initial diagnosis and staging of a lesion may be improved and further information can be obtained, which is helpful for the individual therapy management.

Several studies have focused on the aspect of diagnostic accuracy of PET in head and neck tumors. Gambhir et al. (2001) performed a meta analysis of data about the use of PET in oncology [7]. Their evaluation of studies concerning head and neck tumors comprise 298 patients and 580 lesions assessed for tumor diagnostics and 591 patients with 2113 lesions evaluated for tumor staging [7]. PET and CT results were compared and an average sensitivity and specificity of 93%, 70% for PET and 66%, 56% for CT respectively were calculated from the literature data for primary tumor diagnostics. The data were comparable for tumor staging except for a higher specificity of PET and CT as compared to the diagnostic studies (PET: sensitivity 87%, specificity 89%; CT: sensitivity 62%, specificity 72%). The clinical situation however is usually associated with a certain prevalence of disease prior to any diagnostic procedure. Then diagnostic methods are applied and it is expected that the gain in information will enhance the probability or suggest the absence of disease. This is the classical application for the Bayesian statistics [8]. The data from Gambhir et al. (2001) can be analyzed using the Bayesian approach. Figure 1 demonstrates the association of prior probability of disease and the posterior probability for a true positive and a false negative result. Overall, PET provides a higher gain in information as compared to CT. Especially the rate of false negative results with PET is significantly lower as compared to CT. The differences between the probability curves reflect the gain in information obtained with a diagnostic procedure (Fig. 2). PET provides more information than CT for all prior probability levels. The advantage of combining a morphological method, CT, with a functional procedure, PET, is also assessed by using the literature data and the predicted gain in information is calculated. The results show, that especially in patients with a low prior probability of disease the combination of PET and CT will be helpful.

The recent development of hybrid systems, combining PET and CT, is a major step forward to achieve the most accurate correlation between morphology and function. Due to
the sequential acquisition of CT and PET data the misalignment between CT and PET is kept to a minimum and the images can be reviewed side by side or as fusion images. Figure 3 demonstrates a patient with a head and neck tumor and lymph node metastases. The combined assessment of both, CT and PET, as well as the fusion images are helpful to delineate and locate the metastases (Fig. 3). Others compared PET/CT with PET and CT as individual modalities in patients with head and neck tumors [9]. Again, the lowest accuracy was noted for CT (74%), while PET (90%) and PET/CT (94%) were significantly more accurate. When Bayesian statistics are applied to the data, the highest gain in information is obtained with PET/CT. The intra-observer variation and the accuracy of the correct anatomical association of PET findings was evaluated by others [10]. As expected, PET/CT was the most accurate procedure to limit the intra-observer variation and achieve reproducible diagnostic results. The advantages of PET/CT are also reported by others [11]. These authors are among the first who have used PET/CT in patients and they emphasize that PET and CT are matching with a few millimeters difference. Therefore, the combined use of these imaging modalities improves the presurgical staging by providing both the anatomical location based on CT and the high lesion detectability of PET with $^{18}$F-FDG.

The metabolically active tracer $^{18}$F-FDG provides generally a high sensitivity for the detection of abnormalities. Therefore, generally false negative results are less likely than false positive results when $^{18}$F-FDG is used for tumor diagnostics. However, little is reported about false positive results. Others assessed the clinical usefulness of $^{18}$F-FDG-PET in recurrent nasopharyngeal carcinomas and compared the results to those of the MRI studies [12]. The overall sensitivity of PET, comprising the primary tumor site and the lymph node metastases, was 89.5%, while the specificity was only 55.6% [12]. One limitation of PET with $^{18}$F-FDG was the number of false positive results obtained in these patients. However, the patients had received radiotherapy and also chemotherapy had
been given to most of the patients. Therefore, there is a higher likelihood of an enhanced, reactive metabolic activity in tissue, according to therapy.

The problem of $^{18}$F-FDG uptake in both, malignant tumors as well as in inflammatory tissue, is a general problem in PET studies. False positive results are mainly based on the enhanced $^{18}$F-FDG transport into leukocytes. To limit false positive results, generally two approaches are possible: the use of more sophisticated quantification methods to assess the $^{18}$F-FDG kinetics or the application of a second radiopharmaceutical. Besides $^{18}$F-FDG, we have investigated a synthetic amino acid, $^{11}$C-aminoisobutyric acid (AIB), which is a marker for the A-type transport of amino acids into the tissue, in patients with sarcomas and other tumor types [13]. Interestingly, the A-type transport of amino acids was lower in inflammatory lesions, when we compared 36 tumors and 5 inflammatory lesions, examined with both $^{18}$F-FDG and AIB (Fig. 5a-c). Therefore, AIB may be used in addition to $^{18}$F-FDG if inflammatory changes are to be considered.

One of the promising tracers in oncology is 3′-deoxy-3′- $^{18}$F-fluorothymidine ($^{18}$F-FLT). This tracer is a substrate for the thymidine kinase and associated with the proliferation rate of tumors. However, initial results demonstrate, that $^{18}$F-FLT is not helpful to differentiate between reactive and metastatic lymph node metastases [14]. One reason, as discussed by the authors, may be the B-lymphocyte proliferation in reactive lymph nodes. Another reason may be the dependency of $^{18}$F-FLT kinetics on the extracellular adenosine triphosphatase (ATP) concentration, which has an impact on the structure and the performance of thymidine kinase.

Another new tracer is $^{18}$F-galacto-RGD, the pentapeptide cyclo(-Arg-Gly-Asp-D-Phe-Val-), which binds preferentially to the αvβ3 receptor [15]. Integrins are an important group of genes, related to tumor growth, invasiveness and likelihood of metastases. Initial studies suggest the use of this tracer in patients with head and neck tumors, however further studies must be performed to assess the value of this tracer for the diagnostics or therapy management.

Other tracers like $^{18}$F labeled tyrosine or the SSTR2 (so-
matostatin receptor 2) binding $^{68}$Ga-DOTATOC ([1,4,7,10-tetraazacy-clododecane-N,N',N'-tetraacetic-acid-D-Phe1-Tyr3]-octreotide) have found limited use. A high $^{18}$F-FDG uptake is noted in the abscess, while no enhanced A-type amino acid transport is present.

Figure 5a. Double tracer examination with $^{18}$F-FDG (left) and $^{11}$C-AIB (right) of a patient with an abscess. A high $^{18}$F-FDG uptake is noted in the abscess, while no enhanced A-type amino acid transport is present.

Figure 5b. Results obtained in 36 tumors and 5 inflammatory lesions. Significant overlap of the $^{18}$F-FDG SUV for both groups.

Figure 5c. The overlap of tumors and benign, inflammatory lesions is significantly lower as compared to FDG. C-11-AIB can be helpful to differentiate between tumor and inflammation due to the low uptake in benign lesions.

PET $^{18}$F-FDG studies are usually performed for therapy monitoring to assess changes in tumor metabolism following therapy. The evaluation of 169 patients demonstrated a sensitivity of 84% and specificity of 95% for the assessment of therapy related changes in the tumor [7]. Again, PET was superior to CT (60% sensitivity, 39% specificity), because usually functional changes precede changes in tumor volume. Gambhir et al. (2001) noted a correlation of tracer kinetics and growth rates and report about a 33% change in therapy management due to PET results [7].

The prognostic value of PET with $^{18}$F-FDG was investigated in a few studies. Based on the results obtained by others [5, 6], it can be expected that the quantitative evaluation of the $^{18}$F-FDG uptake may be helpful to assess the proliferative aspect of tumors. Others evaluated the association of $^{18}$F-FDG uptake, as measured by the SUV, and therapy outcome [17]. The authors performed $^{18}$F-FDG studies in 73 patients prior to therapy (surgery and radiotherapy). An SUV of 10 was used for Kaplan-Meier analysis and revealed a highly significant difference in survival [17]. Therefore, the quantitative data of the initial $^{18}$F-FDG uptake prior to therapy are predictive for therapy outcome. We investigated the correlation of changes in $^{18}$F-FDG uptake and tumor growth rates in patients with head and neck tumors, receiving a cisplatinum based chemotherapy [18]. Dynamic PET studies were performed prior and after one chemotherapeutic cycle and the changes in tracer uptake were compared to the changes in tumor volume, as calculated from CT images. The growth rates and the changes in $^{18}$F-FDG uptake (SUV) were correlated for both tumors ($r=0.98$) and lymph node metastases ($r=0.94$). Interestingly, the growth rates were different for the same changes in the $^{18}$F-FDG uptake. Overall, tumors were more sensitive to therapy than lymph node metastases [18].

Future aspects

The recent developments in quantitative PET imaging direct to a better understanding of tracer kinetics by associating PET data with molecular biological data [19]. $^{18}$F-FDG transport and phosphorylation is not only correlated to glucose transporters and hexokinases, but modulated by many other processes like angiogenesis, apoptosis, and proliferation. Thus, results obtained from dynamic PET data can be used to predict changes in gene expression patterns. However, in head and neck tumors more data are needed, correlating gene

Therapy management

One major aim of new diagnostic methods besides improvements of tumor diagnostics is the individualization and optimization of therapy management. PET with $^{18}$F-FDG is actually an established procedure for the follow up of oncological patients since several years [4]. In head and neck tumors one important topic is the improved detection of a recurrent tumor. Based on the data from Gambhir et al. (2001), who included 426 patients in the meta analysis, the sensitivity of $^{18}$F-FDG-PET on a patient based analysis, is 93% and the specificity, 83% (CT has a 54% sensitivity and a 74% specificity) for the detection of recurrent head and neck tumors [7]. These data are comparable to those obtained for tumor diagnostics.

The recent developments in quantitative PET imaging direct to a better understanding of tracer kinetics by associating PET data with molecular biological data [19]. $^{18}$F-FDG transport and phosphorylation is not only correlated to glucose transporters and hexokinases, but modulated by many other processes like angiogenesis, apoptosis, and proliferation. Thus, results obtained from dynamic PET data can be used to predict changes in gene expression patterns. However, in head and neck tumors more data are needed, correlating gene
expression with PET tracer kinetics in order to achieve a higher accuracy of both tumor staging and therapy management.

Besides $^{18}$F-FDG, receptor targeting agents are getting more and more attention. Currently, $^{68}$Ga-DOTATOC has found use in endocrine tumors [20]. The SSTR2 binding tracer can also be used to assess receptor positive tumors in the head and neck area, especially endocrine tumors or paragangliomas. Other receptor active tracers are under development. A few studies were performed with $^{68}$Ga-bombesin, mainly in gastrointestinal stroma tumors (GIST) [21]. This tracer binds to three receptors, the gastrin releasing protein receptor, the bombesin-3 receptor, and the neuromedin-B. Besides GIST, some studies have been performed in prostate cancer (bombesin-3 receptor) and astrocytomas (neuromedin-B receptor). The value of the above studies in head and neck tumors has not been shown. Further tracers are in development at our center and will focus in future on aspects like angiogenesis, e.g. the VEGF (vascular endothelial growth factor) receptors. Due to the increasing availability of gene expression data, other differentially expressed receptors (tumor/reference tissue) will be identified and docking-ligand experiments will help to design new radiopharmaceuticals.

**Five-year view**

Current state-of-the-art systems, based on PET/CT hybrid systems, provide the best approach to assess a tumor in the head and neck area most accurately with an overall accuracy exceeding 90%. PET/MRI is visible at the horizon, but some years of development are needed to get systems for routine use. Further developments are also needed to provide other tracers besides $^{18}$F-FDG to gain additional information for the differentiation of tumor and inflammation. Today and within the next years, receptor binding pharmaceuticals will find more frequent use to assess specific properties of a lesion. This will be especially helpful for patients treated with new chemotherapeutic drugs targeting dedicated receptors in the tumor.

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