2.1 SUMMARY

As the applications of metabolic imaging are expanding, radiolabeled amino acids might gain increased clinical interest. This review describes first the basic aspects of amino acid metabolism, continues with basic aspects of radiolabeled amino acids and finally describes clinical applications, with an emphasis on diagnostic value. A special focus is on $^{11}$C-methionine, $^{11}$C-tyrosine and $^{131}$I-iodo-methyl-tyrosine studies.

The theoretical and preclinical background of amino acid imaging is quite sound, and supports clinical applications. Amino acid imaging is less influenced by inflammation, which may be advantageous in comparison with FDG PET imaging although tumor specificity is not perfect. In brain tumor imaging, the use of radiolabeled amino acids is quite established, the diagnostic accuracy of amino acid imaging seems adequate, and the diagnostic value advantageous. The general feasibility of amino acid imaging in other tumor types has sufficiently been demonstrated, but more research is required, in larger patient series and in well defined clinical settings.
2.2 INTRODUCTION.

Over the last years clinical interest in metabolic imaging of cancer is growing. The most prominent example is the increasing application of $^{18}$F-fluoro-2-deoxy-D-glucose (FDG) and positron emission tomography (PET). FDG PET is now successfully used in many types of cancer, both in staging and restaging of patients, but also to better differentiate between malignant and benign lesions. Increased anaerobic glycolysis, present in nearly all cancer cells, is the target for uptake of FDG (1).

Another interesting target for metabolic tumor imaging is the increased protein metabolism in cancer cells, for which radiolabeled amino acids can be applied. It is expected that with the increasing clinical applications of FDG, clinical interest in imaging protein metabolism through radiolabeled amino acids, will also increase. It is suggested that these amino acid tracers may help in areas where FDG imaging has its limitations, such as in brain imaging due to high background FDG uptake, or in differentiation of tumorous from inflammatory lesions (e.g. after radiotherapy) due to high FDG uptake in macrophages.

In this review, we give a short overview of amino acid metabolism, describe the basic aspects of radiolabeled amino acids and review published clinical applications in various types of cancer with a special emphasis on diagnostic value. We will especially focus on radiolabeled methionine (L-[methyl-$^{11}$C]-methionine, abbreviated as MET) as this is mostly used, and on tyrosine (L-1-$^{[14]}$C]-tyrosine, TYR) and L-3-$^{[2]}$Iodo-alpha-methyl-tyrosine (IMT) because of local experience.

2.3 AMINO ACID AND PROTEIN METABOLISM

Proteins play crucial roles in virtually all biological processes. Nearly all chemical reactions in biological systems are catalyzed by enzymes, and nearly all enzymes are proteins. Many small molecules are transported and stored through specific proteins. Proteins are the major component of muscles, they are important in mechanical support (collagen), in immune protection (antibodies), nerve impulse transmission (receptors) and in control of growth and differentiation (growth factors, DNA control proteins etc)(2).

Proteins are built from a set of 20 amino acids, characterized by an amino- and a carboxyl-group and twenty kinds of side chains, varying in size, shape, charge, hydrogen-bonding capacity and chemical reactivity. Polypeptide chains (proteins) are formed by linking amino acids through peptide bonds. Of the basic set of 20 amino acids, 11 are synthesized from intermediates of the citric acid cycle and other major metabolic pathways, whereas the other 9 must be obtained from dietary sources (‘essential’ amino acids), because humans are unable to synthesize them. Amino acid
biosynthesis is generally regulated through feedback inhibition mechanisms. The rate of synthesis depends mainly on the amounts of biosynthetic enzymes and their activity, processes that are in themselves also subject to complex regulations (3).

Genes specify the unique amino acid sequence of proteins. After DNA transcription to mRNA in the cell nucleus, protein synthesis (‘translation’ of mRNA) starts at the cytoplasmatic ribosomes. Cells regulate which specific proteins are synthesized and also the total amount of protein synthesis (4). The process of protein synthesis is a coordinated interplay of more than hundred macromolecules and subject to very complex regulation, involving factors such as ribosome synthesis, transport and dissociation rates, mRNA synthesis and degradation rates, transfer RNA supply and binding properties, amino acid supply and many more (5). Amino acids either enter the cell from outside, or are derived from intracellular protein recycling.

Besides being the building block of proteins, amino acids are precursors for a great many other biomolecules, such as the DNA or RNA precursors adenine and cytosine, sphingosine (derived from serine), histamine (derived from histidine), thyroxine, adrenaline and melanine (all derived from tyrosine), and serotonin (derived from typtophan) (3). In addition to being metabolic precursors, amino acids can be crucial in metabolic cycles. For example, the amino acid methionine, derived from the diet, is part of the activated methyl cycle. In this important metabolic cycle, S-adenosylmethionine serves as a methyl group donor in many biosynthetic steps (3).

Amino acid degradation and recycling is a constant and dynamic process that contains two elements. Internal recycling represents reutilization of amino acids within the same cell, external recycling represents the exchange of amino acids between various tissues. In degradation, the alpha amino groups are removed and usually converted into urea. The resulting molecule is converted into metabolic intermediates that may be transformed in fatty acids, ketone bodies or glucose (6). In the same way, surplus amino acids are used as metabolic fuel, since they cannot be stored. Both in internal and external recycling amino acids must cross cell membranes. With radiolabeled amino acids in mind, this transmembrane transport is an important factor in protein metabolism.

**Amino acid transport across cell membranes.**

Although all amino acids can diffuse into cells, the main movement of amino acids into cells occurs via carrier-mediated processes (7,8). Two groups of carriers can be designated. First, many carriers require sodium for maximal activity. The driving forces that energize amino acid transport are provided by the sodium chemical gradient as well as the membrane electric potential. This gradient is maintained by the energy requiring sodium/potassium adenosine triphosphatase ion transporter (Na⁺/K⁺ ATPase). Secondly, sodium independent transport mechanisms exist. In general, amino acid movements
depend on the relative concentrations of the amino acid inside and outside the cell, but frequently transport is associated with countertransport of a second amino acid, whose gradient has been established by one or more of the sodium-dependent carriers. Transport kinetics can be characterized through Michaelis Menten kinetics, and thus depend on transporter affinity (Km) and the number of active transporters in the cell membrane (Vmax).

Few of the membrane transporter proteins have been identified, so investigators have relied on kinetic and competitive-inhibition analyses to define and characterize individual systems. Some 20 systems have been identified; they are designated by letters. Among the main sodium dependent systems, found in all tissues of nearly all species, are system A, system ASC and system Gly (7-11). These systems usually transport short, polar or linear side chains such as alanine, serine and glycine. The most important and ubiquitously found sodium independent system is system L, but other systems such as system B0,+ system y+ also exist. Sodium independent systems are usually responsible for uptake of branched chain and aromatic amino acids, such as leucine, valine, tyrosine and phenylalanine. In addition, some transport systems have only been found in specific tissues, such as system T, that specifically transports tyrosine, phenylalanine and tryptophan into erythrocytes (7). Amino acid transport kinetics can be studied in cultured cells, regional perfusion models or membrane vesicles. The contribution of individual transport systems to the transport of a single amino acid may vary somewhat between different types of cells and species (7,8,10).

Regulation of amino acid transport is complex (8,12). Effects of nutrients are important: cells respond to changes in nutrient availability by regulating individual transport systems. For example, in starvation, system A activity is increased by increasing the number of active A carriers, whereas system ASC appears unchanged (12,13). Apart from these adaptive responses to amino acid availability, hormones and cytokines regulate transport. For example, system A has been found to be very sensitive to glucocorticoids, glucagon and insulin. Growth factors, such as human growth hormone or epidermal growth factor, but also cell volume changes (e.g. cell swelling in hypotonicity) were shown to be involved in transport regulation (14-16). Changes in the amino acid transporter proteins themselves require de novo RNA and protein synthesis. Interestingly, some transporter proteins may have a role as retrovirus receptor, and may be used by virus to gain entry in cells (17).

**Amino acid metabolism in malignancy**

Amino acid transport is generally increased in malignant transformation (18,19). This increase in transport may be associated with specific cell surface changes in transformed cells (20). For example, amino acid transport system A is one of the few identified transport systems that is expressed strongly in
transformed and malignant cells and appears to be a target of proto-oncogene and oncogene action (21). In general, however, the process of malignant transformation requires that cells acquire and use nutrients efficiently for energy, protein synthesis, and cell division. Therefore, it is most likely that increased transport of amino acids is mainly an aspecific net result of increased demand of amino acids. Of the two major steps in protein metabolism, amino acid uptake and protein synthesis, the increased transport rate of amino acids may be more increased than protein synthesis.

Biochemical cellular processes as transamination and transmethylation (3), the specific role of methionine in initiation of protein synthesis, but also important use of amino acid (such as glutamine for energy (22) or as precursors of non-proteins contribute to amino acid transport rather than to protein synthesis.

2.4 RADIOLABELED AMINO ACIDS - PRECLINICAL DATA.

Nearly all amino acids have been radiolabeled to study potential imaging characteristics, usually for PET, since the replacement of a carbon atom by $^{11}$C, does not chemically change the molecule (23). These radiolabeled amino acids differ with regards to the ease of synthesis, biodistribution and formation of radiolabeled metabolites in vivo. For these reasons, mainly $[^{11}$C-methyl]-methionine and tyrosine have been studied clinically. More recently, artificial amino acids such as L-3-[$^{123}$I]iodo-alpha-methyl-tyrosine (IMT) or L-3-$[^{18}$F]fluoro-alpha-methyl-tyrosine (FMT)(24), O-2-$[^{18}$F]fluoroethyl-L-tyrosine (FET) (25), $[^{18}$F]fluoro-L-phenylalanine (26), $[^{18}$F]fluoro-L-proline (27) and (11C-methyl)-alpha-aminoisobutyric acid (28) have been studied.

$^{11}$C-Methionine

The most frequently used radiolabeled amino acid is L-[methyl-$^{11}$C]-methionine. The main reason is the convenient radiochemical production, that allows rapid synthesis with high radiochemical yield without the need for complex purification steps (29). However, this tracer has a considerable non-protein metabolism (see above, role in activated methyl cycle) and generates substantial amounts of non-protein metabolites (30,31). Attempts to develop a metabolic model in muscle have been published, in which usually these alternative pathways are neglected (32,33). In tumors, metabolism may be even more complicated, making correct quantification of protein synthesis rather difficult.

As most clinical applications of MET have focused on brain tumors, studies of the uptake mechanisms have frequently used the same tissues and models. The accumulation rate of radiolabeled methionine, both in normal human brain tissue and in gliomas without disruption of the blood-brain barrier,
decreased by 35% after infusion of branched chain amino acids. In addition, radiolabeled L-methionine accumulated 2.4 times as much as D-methionine (34). These findings by Bergstrom et al. indicate specific carrier mediated uptake as an important factor governing MET uptake. However, O'Tuama et al. could not confirm these results using phenylalanine overload in patients, although the total amount of unlabeled MET in the brain did decrease (35). The importance of blood flow in tumor MET uptake was demonstrated by Roelcke et al., which suggests that at least part of MET uptake may result from passive diffusion, possibly in areas with damaged blood-brain barrier (36). In cell uptake studies, MET transport is usually mediated through the L transport system, with minor contributions of A and ASC (11).

Preclinical studies validating possible use of MET in evaluation of chemotherapy or radiotherapy, generally demonstrate that MET uptake is rapidly reduced, more rapid than FDG, but less rapid and less severe than DNA/RNA tracers such as [18F]fluoro-deoxyuridine (FuDR) (37,38). Autoradiography confirmed MET uptake predominantly in viable tumor cells, with low uptake in macrophages and other cells. In agreement, Minn et al. found that MET uptake correlated better with tumor proliferative activity in squamous cell head and neck cancer cell lines than FDG (39).

Despite these findings that suggest MET uptake to be a good marker for tumor viability after chemotherapy or radiotherapy, other studies have reached opposite conclusions. For example, Higashi et al. and Schaider et al. found increased MET uptake after irradiation and chemotherapy in ovarian carcinoma cells and colon carcinoma cells, respectively (40, 41). Apparently, in vitro studies do not result in a consistent view regarding the background of MET uptake for evaluation of therapies. In vivo data will have to provide the answer.

11C-tyrosine.
In search of a radiolabeled amino acid to quantify protein synthesis, L-[1-11C]-tyrosine was studied (23,42-44). Although radiosynthesis of this amino acid is more difficult, a reliable automated synthesis system was developed and a metabolic model to quantify the protein synthesis rate was described and validated (45,46). TYR is largely incorporated in protein, and generates only a small amount of labeled tissue metabolites on the time scale of 11C PET studies (31,44,46). On the other hand, plasma metabolites (labeled proteins, labeled CO2 acid soluble metabolites such as 11C-L-DOPA) rise to 50% approximately 1 hr after injection, requiring arterial sampling and metabolite correction for quantitative protein synthesis rate (PSR) determinations.

Preclinical studies validating the application of TYR have been published in the early 1990's. In a rat rhabdomyosarcoma model, Daemen et al. found good agreement between tumor growth rate and TYR uptake, better than for FDG (43). Heat-induced inhibition of TYR uptake correlated well with tumor regression (47), but irradiation combined with hyperthermia did not result in
uptake reduction (48). Avid uptake of TYR in prolactinomas indicating protein incorporation, has been described (49).

\[ {^{123}}I\text{-ido-methyl-tyrosine} \]

The artificial amino acid IMT has generated much interest, after the demonstration by Langen et al., that the \[ {^{123}}I \] label did not interfere with recognition by amino acid transport systems in the blood-brain barrier (50). In addition, its relative ease of preparation and its applicability for SPECT are of clinical interest (51). In fact, after application of \[ {^{75}}\text{Se} \]selenium-methionine in the 1970's and 1980's, it is the first radiolabeled amino acid for tumor imaging to be used for SPECT. The large applicability of SPECT tracers is advantageous, although the lower resolution is a disadvantage. Therefore, PET analogues FMT and especially FET are now also being studied (24,52).

IMT is rapidly taken up in brain tumor cells, but also in normal brain tissue (53). Uptake peaks around 15-30 min after injection. It is not incorporated in protein and slowly washes out of the tumors (~30% at 1 hr p.i.)(53,54). Tumor to background ratios are generally between 1.5 - 2.5. When patients were infused with a mixture of naturally occurring amino acids, absolute IMT uptake decreased by 53% in gliomas, by 24% in two meningiomas and one metastasis and by 45% in normal brain tissue (50). This study by Langen et al. is now frequently cited as proof that IMT, despite its artificial nature including a large iodine atom, is still substrate for the specific amino acid carriers in the blood-brain barrier. Similar findings were published by Kawai et al., who found IMT uptake in the canine brain to closely coincide with a 2-compartment model of cerebral amino acid transport (55). IMT is metabolically stable, and is only subject to minor deiodination (53-55).

Although these observations were originally believed to be only valid for brain tumors, Jager et al. found very similar kinetics in a variety of extra cranial tumors, such as breast cancer, lung cancer, soft-tissue sarcoma and lymphoma (54). Apparently IMT transport in tumors is similar to transport through the blood-brain barrier. These findings have widened the scope for clinical studies.

The main amino acid transport system involved in IMT uptake appears to be the L system, as found by three independent studies on IMT kinetics in glioma and lung cancer cell lines (56-58). Dependent on the applied methodology, various but minor contributions of other transport systems were described. IMT uptake seems to follow the same uptake route as the native amino acid TYR (58). In contradiction with these findings, Carnochan and Deehan found IMT and TYR uptake to be mainly governed by blood flow and diffusion in a rat sarcoma model, and suggested tumor growth status not to be related to amino acid uptake (59,60). Apart from being contradictory to cell line studies, this finding also contrasts with findings in human sarcoma patients where IMT uptake significantly correlated with tumor proliferation indexes (Ki-67, mitoses), and was not related to microvessel count (61).
**Figure 1.** Whole body IMT scintigrams in normal person, 30 min after injection with anterior view (left) and posterior view (right), showing low grade brain, liver and spleen uptake and intense uptake in the kidneys and urinary system.

**Other amino acids**
Metabolic behavior of IMT and its fluorinated PET variants FMT and FET appear similar (24,52,62). Both FMT and FET rapidly accumulate (within 30 min) both in normal brain tissue and in brain tumors. Although FMT had minor uptake in the lipid-, RNA/DNA- and protein fractions of mice bearing a human colorectal carcinoma, FMT slowly diffused back into blood. Tumor uptake in mice was higher than for FDG, with tumor-to-muscle ratios around 3 and uptake significantly decreased after administration of large neutral amino acids (63).
FET, that can be produced with high radiochemical yields, also specifically and rapidly accumulated in SW707 colon carcinoma cells. Like IMT and TYR, this tracer seems to use the L amino acid transport system for entry into cells, and most likely shows passive back diffusion out of cells (25,52).

An Iodine-123 labeled variant of IMT, [$^{123}$I]iodo-O-methyl-alpha-methyl-L-tyrosine (OMIMT), appeared to share the distribution pattern of IMT and MET, but due to significantly lower tumor-background ratios, appears less usable in clinical practice (64).

The tryptophan metabolite carbon-11 labeled 5-hydroxy-tryptophan has been used to study carcinoid tumors (65). Uptake in neuroendocrine tumors appears to be irreversible and specific.

**Normal distribution and image acquisition.**
A detailed description of normal and variant uptake of MET has recently been published (66). In brief, low grade uptake is found in the brain, somewhat higher uptake in salivary glands, the lacrimal glands, bone marrow and occasionally in the myocardium. Abdominal uptake in the liver and the pancreas can frequently be seen, as well as intestinal uptake of varying degree. IMT, as it is renally excreted, demonstrates very high uptake in the
kidneys and bladder but is otherwise similar to other amino acids (54) (Figures 1,2). In contrast with IMT, uptake of MET and TYR in the pituitary gland and pancreas is generally high. MET and TYR may only give moderate cortical renal uptake.

Images in amino acid studies are usually acquired within the first hr after tracer administration, as uptake and equilibration with tumor washout is usually rapid. For example, IMT washout is estimated as 35% within the first hr. For clinical purposes the assumption of steady state within the first 45 min is reasonable (53,54). Patients are usually studied after in fasting condition, since extracellular amino acid concentration in vitro clearly influences transport (7-9). In vivo evidence for studying fasting patients is limited to a small study by Lindholm, who found decreased MET uptake after food ingestion in 5 patients (67). However, due to differential influence on various tissues the impact of the nutrition state is rather complex. Lower uptake both in normal brain and in gliomas will result in unchanged tumor-background ratios, but image quality may decrease (50). In other tumor types (meningioma, metastases) however, unchanged tumor uptake and lower background will cause higher ratios. For these reasons, it is preferable to study patients in fasting conditions.

**Amino acid transport or protein synthesis markers?**

Originally it was believed that radiolabeled amino acids that enter protein synthesis (such as TYR, partly MET) are more specifically taken up in malignancy compared to amino acids that are only transported into the cell (such as IMT, partly MET, FMT, FET, and 11C-amino-isobutyric acid). This idea is based on the increased proliferation rate of malignant cells, that requires increased protein synthesis. As a consequence, however, amino acid transport is increased as well in malignancy, and not all amino acids taken up are shuttled into protein synthesis (3,19,20). For example, the activity of the activated methyl cycle may be increased in malignant cells, cells may use amino acid intermediary metabolites for ‘metabolic fuel’, and some tumors produce secretory products out of amino acids (3,22). For example, carcinoid tumors have presumably increased their L transport systems, in order to obtain tryptophan for serotonin synthesis (68). This upregulation presumably also causes increased uptake of IMT that enters the cell through the same carrier (69). All these processes contribute to increased transport rather than to increased protein synthesis.

The importance of transport is further supported by studies by Daemen and Ishiwata, who reported significant MET uptake in murine tumors (in the non-protein fraction) despite inhibition of protein synthesis (70,71). These authors suggested that partial protein synthesis tracers such as MET may also reflect repair mechanisms, whereas pure transport tracers (such as 11C-amino-isobutyric acid) better show tumor viability. Also in vivo studies using IMT (e.g. in soft-tissue sarcoma and gliomas) have demonstrated significant correlations between tracer uptake (amino acid transport) and proliferation (56,61,72). For
these reasons it appears that amino acid transport tracers can be at least equally valuable in clinical applications.

**Specificity of amino acids.**

It is frequently suggested that amino acids are less troubled by interfering uptake in inflammatory tissues such as FDG, making them more tumor specific (73). This is based on the fact that inflammatory cells have lower protein metabolism, as compared to glucose metabolism. Indeed, several reports (especially in vitro studies) exist in which interfering uptake in inflammatory tissue is reported to be smaller than for FDG (74-76). However, the list of non-tumoral uptake of all radiolabeled amino acids is also quite long, and includes ischemic brain areas, infarction, scar tissue, abscess, sarcoidosis, irradiated areas, haemangioma and many other benign processes (54,76-84) (Figure 3).

It seems most likely to conclude that the tumor specificity of amino acids is not an on-off phenomenon, but a more gradual process. Active inflammatory tissue will also exhibit some degree of increased amino acid demand to perform its functions. The increased perfusion of infections may even further contribute to uptake of amino acids. Therefore, the tumor specific nature of amino acids is probably better than for FDG, but surely not perfect.

*Figure 3. Planar IMT image obtained 1 week after 60 Gy radiotherapy in a patient with a non-small cell lung carcinoma in the right middle lobe. Aspecific increased uptake is present in the irradiated field (arrows).*
2.5 CLINICAL APPLICATIONS.

In analyzing the clinical value of diagnostic methods in general, one should keep in mind the five levels of diagnostic performance (Table 1)(85,86). The first level are technical possibilities and feasibility studies. The second level is determination of diagnostic accuracy, where sensitivity and specificity are determined in comparison with a perfect gold standard. In the third level the diagnostic value of the method is studied, in comparison with other diagnostic methods for the same problem. Level four studies the therapeutic value, in other words does the new diagnostic information results in better treatment for patients, and finally in level five the value for individual patients and society is studied: does the diagnostic information and the resulting improvement of treatment result in better survival and quality of life for patients, and at acceptable cost for society?

Analyzing radiolabeled amino acid studies in this way, it seems clear that most of the studies mentioned above, can be assigned to level 1, as they provide preclinical evidence on possible applications in human cancer. In the following section, describing clinical applications, we will see that studies on the use of radiolabeled amino acids usually address level 2. Although some studies compare radiolabeled amino acids with other methods, these other methods are usually other tracer studies using PET or SPECT.

<table>
<thead>
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<td>application possible/feasible?</td>
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<tr>
<td>2</td>
<td>accuracy</td>
<td>sensitivity, specificity?</td>
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<tr>
<td>3</td>
<td>diagnostic value</td>
<td>performance in relation to other tests?</td>
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<tr>
<td>4</td>
<td>therapeutic value</td>
<td>results in better treatment?</td>
</tr>
<tr>
<td>5</td>
<td>patient/society value</td>
<td>results in better survival, quality of life, at acceptable cost?</td>
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*) Slightly adapted from refs 85 and 86.
Brain tumors

The vast majority of amino acid studies has been performed in brain tumors. In contrary to the high FDG metabolism, background uptake or amino acids in normal brain tissue is low, because of low cortical protein metabolism. This provides adequate contrast with tumors. The majority of brain tumor studies has been performed with MET in combination with PET. However, the amount of studies using the SPECT tracer IMT is rapidly increasing, since the first application in 1989 [87]. Also $^{11}$C-labeled tyrosine and 2-[F]$^{18}$fluoro-tyrosine have been applied to some extent [88].

In brain tumor management nuclear medicine techniques might supplement the excellent anatomic imaging modalities like CT and MRI. For example, information on tumor grade, optimal biopsy locations, visualization of the degree of intracerebral infiltration, recurrence detection provided by PET or SPECT methods are likely to be clinically helpful [89,90].

In general good sensitivities are reported in the detection of tumors. For example, Ogawa et al. found an excellent 97% sensitivity of MET PET in 32 high grade tumor patients but considerably lower (61%) in low grade tumors [91]. Mosskin et al. found a patient-based sensitivity of 84% (n=38), in a study comprising multiple stereotactic biopsies from tumor and normal areas. In 5 cases biopsies demonstrated MET uptake in non-tumor tissue and in 5 other cases no radioactivity was found in tumor tissue, indicating that tumor specificity of MET is not perfect [92].

Experience with TYR is more limited. Pruim et al. used TYR PET in both primary and recurrent brain tumors, and found 20 of 22 positive (91%) An example is presented in Figure 4. Also metastases and cerebral lymphomas were visualized [78]. Wienhard et al. studied another tyrosine based tracer, 2-[F]$^{18}$-fluoro-tyrosine (n=15) and found increased tumor uptake and transport rates in brain tumors. Uptake appeared more related to amino acid transport than to protein synthesis [88].

Also the SPECT tracer IMT is taken up in nearly all brain tumors, both astrocytomas and oligodendrocytomas, but also in lymphoma and metastases, as evidenced by many studies now. Reported sensitivities in detection of malignancy are generally in the range of 85 - 100% (Table 2).

Grading

Nearly all studies on tumor detection also addressed the feasibility of tumor characterization and grading, comparing uptake both between benign and malignant processes and between various grades of malignancy. This clinically useful aspect was supported by various in vitro studies, where MET uptake was shown to correlate with the proliferation marker PCNA (proliferating cell nuclear antigen) in human gliomas, and with NOR (nuclear organizing regions) and Ki-67 proliferation markers in meningioma [101,102]. Likewise, a relation
### Table 2. Clinical studies using IMT in brain tumors.

<table>
<thead>
<tr>
<th>Author (ref)</th>
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<th>#pat</th>
<th>purpose</th>
<th>sensitivity</th>
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<td>Biersack(87)</td>
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<td>first study</td>
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<tr>
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<td>1990</td>
<td>32</td>
<td>detection</td>
<td>88%</td>
<td></td>
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<tr>
<td>Kuwert(73)</td>
<td>1995</td>
<td>53</td>
<td>detection</td>
<td>50-82</td>
<td>differentiation high - low- benign. specificity 83-100%</td>
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<tr>
<td>Weber (93)</td>
<td>1997</td>
<td>19</td>
<td>detection</td>
<td>97%</td>
<td>IMT uptake ratios superior to FDG PET</td>
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<tr>
<td>Langen(94)</td>
<td>1997</td>
<td>14</td>
<td>detection</td>
<td>100%</td>
<td>similar to MET PET</td>
</tr>
<tr>
<td>Woesler (95)</td>
<td>1997</td>
<td>23</td>
<td>detection</td>
<td>83%</td>
<td>differentiation high- low grade, IMT similar to FDG PET</td>
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<tr>
<td>Grosu (96)</td>
<td>2000</td>
<td>30</td>
<td>detection</td>
<td>100%</td>
<td>significant impact on radiotherapy planning</td>
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<tr>
<td>Guth (97)</td>
<td>1995</td>
<td>17</td>
<td>evaluation</td>
<td>82%</td>
<td>recurrence detection</td>
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<tr>
<td>Molenkamp(98)</td>
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<td>11</td>
<td>evaluation</td>
<td>100%</td>
<td>detection of progression in low grade childhood tumors</td>
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<tr>
<td>Kuwert (99)</td>
<td>1998</td>
<td>27</td>
<td>evaluation</td>
<td>78%</td>
<td>recurrence detection, specificity 100%</td>
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<tr>
<td>Bader (100)</td>
<td>1999</td>
<td>30</td>
<td>evaluation</td>
<td>75-100%</td>
<td>detection of recurrence grade 2 - 4, superior to FDG PET</td>
</tr>
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</table>

of IMT uptake with Ki-67 was found in glioma patients (72). Somewhat surprising de Wolde et al. could not confirm these relations with proliferation markers for TYR uptake (n=20)(103).

Different MET accumulation in vivo was demonstrated between low-grade astrocytomas and oligodendrogliomas, uptake in astrocytoma being slightly above or even slightly below background uptake, whereas oligodendroglioma always demonstrated clearly increased uptake (104). In this study by Derlon et al., the authors suggested that this difference could be clinically useful. Good and possibly clinically useful differentiation (without overlap) between skull base meningiomas and benign neuromas was suggested by Nyberg et al. (total n=18) (105). The largest study was performed by Herholz et al. who found a 79% accuracy in distinguishing glioma from non-neoplastic lesions in 196 patients with a suspected brain tumor (106).

Using IMT for tumor grading, Kuwert et al. could differentiate high grade tumors from benign lesions with 82% sensitivity at 100% specificity, in the largest study reported (n=53). Separating high grade from low grade tumors resulted in 71% sensitivity and 87% specificity, whereas differentiation of low grade tumors from non-neoplastic lesions, that also demonstrated minor
Figure 4. Coronal, transverse and sagittal sections using $H_2^{15}$O (perfusion - left column), FDG (middle column) and TYR (right column) in a patient with a large low grade astrocytoma in the left temporo-parietal region. The tumor is not intensely perfused, and demonstrates low glucose metabolism. Amino acid uptake, however, clearly demonstrates irregularly increased uptake in a large area. Note amino acid uptake in the lacrimal gland.

uptake, was much more difficult, with sensitivity of 50% at 100% specificity (77). In that study uptake of IMT, albeit minor, is also described in some non-neoplastic lesions, such as infarction, and inflammation. More recently much higher uptake was described in another benign process, a desmoplastic ganglioneuroma (107). It is remarkable that nearly all papers comparing IMT SPECT to FDG PET or to MET PET suggested IMT SPECT equally useful for routine clinical purposes (Table 2, Figure 5)(93-95,100). One has to realize, however, that frequently PET resolutions are converted to SPECT resolution in such studies, and tumor-brain ratios are still higher for MET PET than for IMT SPECT (50,64)
Figure 5. IMT SPECT (upper row) and MET PET (lower row) images of the brain in a patient with a glioma, demonstrating very similar uptake and tumor delineation. The resolution of MET PET was converted to SPECT resolution.

Tumor delineation.
Many studies have demonstrated that the margins of tumors, as assessed by MET or IMT uptake, are frequently wider than the anatomical boundaries, as assessed by MRI or CT (92,96,108-114). This is explained by the lack of contrast enhancement in CT/MRI studies in areas within the tumor with an intact blood-brain barrier. This phenomenon may be even more pronounced in low grade tumors and in diffuse gliomatosis (113). Also in comparison with FDG-PET this better tumor delineation is reported (110,114) both for MET and IMT (93). In a recent study using MRI and IMT SPECT fusion images, IMT SPECT led to a significant change in planning of irradiation volumes (96).

Derived from these good delineation properties, an interesting new application is recently arising: MET or FDG scanning is used to localize the tumor extension, in combination with activation studies using radiolabeled water ($H_2^{15}O$) (115,116). Using this combination, the location of the tumor can be depicted in relation to functional brain areas, which might contribute to planning of surgical margins.
Table 3. Clinical studies using TYR PET.

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>year</th>
<th>n</th>
<th>tumor type</th>
<th>sensitivity</th>
<th>remarks/findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruim (78)</td>
<td>1995</td>
<td>22</td>
<td>primary brain</td>
<td>92%</td>
<td>specificity 67%, no correlation with grade</td>
</tr>
<tr>
<td>Heesters (123)</td>
<td>1998</td>
<td>10</td>
<td>primary brain</td>
<td>-</td>
<td>PSR* after radiotherapy within remaining tumor unchanged</td>
</tr>
<tr>
<td>Braams (130)</td>
<td>1996</td>
<td>11</td>
<td>oral cavity</td>
<td>83%</td>
<td>in nodal staging, better than MRI/CT. specificity 95%</td>
</tr>
<tr>
<td>Kole (131)</td>
<td>1997</td>
<td>13</td>
<td>breast cancer</td>
<td>100%</td>
<td>for primary tumor, visually less uptake than FDG in fibrocystic disease</td>
</tr>
<tr>
<td>Ginkel (132)</td>
<td>1999</td>
<td>17</td>
<td>sarcoma</td>
<td>82%</td>
<td>for difference partial-complete remission after chemoth, specificity 100%</td>
</tr>
<tr>
<td>Plaat (133)</td>
<td>1999</td>
<td>21</td>
<td>sarcoma</td>
<td>-</td>
<td>PSR correlates with Ki-67, not with grade.</td>
</tr>
<tr>
<td>Kole (79)</td>
<td>1999</td>
<td>25</td>
<td>sarcoma</td>
<td>-</td>
<td>FDG better for grading, TYR better correlation with proliferation.</td>
</tr>
<tr>
<td>Kole (134)</td>
<td>1998</td>
<td>10</td>
<td>non-seminoma</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Kole (135)</td>
<td>1997</td>
<td>22</td>
<td>various types</td>
<td>94%</td>
<td>chondrosarcoma not visualised</td>
</tr>
<tr>
<td>Que (136)</td>
<td>2000</td>
<td>10</td>
<td>cervix</td>
<td>80%</td>
<td>interfering bone marrow and intestinal uptake</td>
</tr>
</tbody>
</table>

*) PSR=protein synthesis rate

Biopsy localization.
Stereotactic biopsies of localizations based on either MET or FDG PET were demonstrated to be more successful in finding tumor tissue, than when biopsy trajectories were based on CT only (117). Especially strong uptake reduction of MET in necrotic parts or very high uptake in anaplastic parts, may influence the planning and the results of brain biopsies. Also using TYR, planning of biopsy trajectories was suggested to improve, especially in low-grade glioma (118).

Evaluation of therapy
Detection of recurrent or residual viable tumor can be troublesome in brain tumors treated by surgery or irradiation. As stated above, in vitro evidence is
somewhat conflicting, but clear demonstrations that MET PET is suitable to follow such treatment effects have been published (119-121). For example, Wurker et al. demonstrated a dose dependent reduction in uptake in low-grade glioma (n=10) up to 1 year after brachytherapy, while FDG uptake was unchanged (119). Sonoda et al. found no MET uptake in 6/7 cases of radionecrosis, that were very difficult to assess using MRI or CT (122). Also using IMT, several studies demonstrated good sensitivity and specificity for the detection of viable tumor tissue in previously treated patients (Table 2). IMT SPECT is suggested to complement MRI/CT in cases where detection of recurrent disease was difficult (97). Again remarkable, the protein synthesis rate determined using TYR PET was unchanged in 8/10 patients after radiotherapy (123).

Conclusion for brain tumors
Diagnostic accuracy (level 2, Table 1) of radiolabeled amino acids studies in brain tumors has been sufficiently demonstrated. In detection, both MET, IMT and TYR show adequate sensitivity and specificity. In grading, most studies demonstrate rather clear differences among various grades and histological tumor types, but frequently thresholds are defined retrospectively, which is methodologically not optimal. The true clinical impact therefore is unclear. Also the true clinical impact of better localization of biopsies is not fully clear. There is reasonable evidence that radiolabeled amino acids have supplemental value in evaluation of treatment and in recurrence detection.

What about ‘the diagnostic value’ - level 3?. There seems to be considerable evidence that radiolabeled amino acids provide better diagnostic information than FDG. However, nearly all studies have used amino acid imaging in addition to CT or MRI, and it does not seem very likely that these excellent anatomic modalities will be used less or differently, so PET or SPECT studies will be added to the diagnostic evaluation.

Finally, for nearly all these issues many ‘level 4 and 5 questions’ (Table 1) addressing ‘therapeutic value’ are still unanswered. For example, ‘Can these studies replace, diminish or change the current practice of biopsies, surgery and chemo- or radiotherapy?’ , ‘Do they result in better treatment and survival of patients?’ More research should provide answers.

Head and neck cancer
Management of head and neck cancer, usually both with surgery and radiation therapy, critically depends upon accurate assessment of the extent of local invasion and presence of nodal metastases. Detection of occult metastases in clinically negative patients (N0) is important in selection of patients for neck dissections and radiotherapy (124). An accurate method to detect lymph node
involvement might therefore contribute to nodal staging (125). Such a method might also detect recurrences, requiring additional therapy, that may be hard to detect using other techniques, because of post-therapy scarring or edema.

*Tumor detection, staging and grading.*
The Finnish group from Turku has extensively used MET PET to study head and neck cancer patients. They have demonstrated good uptake (using standardized uptake values (SUV) and transport rate analysis) of MET in these cancers. Their largest study (n=47) reports a sensitivity for detection of the primary tumor of 91%, in selected tumors > 1 cm (126). No explicit study of tumor staging has been published using MET. No relation with tumor grade could be assessed (126-128).

In a small study using TYR PET, Braams et al. found a 83% lesion-based sensitivity at a specificity of 95%, similar to FDG PET (129) (Table 3). Undetected metastases were either small (<5 mm) or in the vicinity of salivary glands with interfering physiological uptake. They found TYR PET to be superior to CT or MRI (129,130). An example is presented in Figure 6. Somewhat lower performance was reported by Flamen et al. using the SPECT tracer IMT. They found a 91% sensitivity for the primary tumor but only a 56% lesion-based sensitivity for metastases (137) (Table 4).

**Figure 6.** Coronal and sagittal projection of a TYR PET study in a patient with a large recurrent squamous cell carcinoma of the right maxillary sinus extending into the skull base. Irregularly increased TYR uptake in the tumor is present (thick arrows). Due to irradiation uptake in both parotid glands and the right submandibular glands has disappeared, uptake in the left submandibular gland is visible (thin arrows).
**Evaluation of treatment.**
All published studies come from Finland. The largest study comprises 15 patients with 24 tumor sites (128). In none of 9 sites, where uptake after radiotherapy remained high (SUV > 3.1), a complete response was found. In contrast, when post-treatment uptake was low (SUV < 3.1), most patients (70%) had a complete response. Pre-treatment level of MET uptake was not associated with histological response (67,140).

In a study published 3 years later no relation was found between initial MET uptake and overall survival. It was suggested that the absolute value of post treatment uptake had predictive value (128). However, in the study by Nuutinen there was no predictive value of SUV ratios before and during early treatment; both in relapsing and responding patients SUV decreased by 30% (141).

**Conclusion for head and neck cancer**
Although we now know MET is avidly taken up in head and neck cancer, nodal staging using MET has not been formally studied. There is only one small study using TYR that suggests good performance in nodal staging and one study using IMT SPECT suggesting less performance. MET uptake does not have prognostic meaning, and early monitoring of radiotherapy does not appear feasible. However, post-treatment imaging could separate complete responders from non-responders, which might have clinical meaning.

In terms of diagnostic performance (level 2) for nodal staging, accuracy of amino acid PET methods is presumably adequate, although evidence is limited and uncertainty remains regarding detection of small lesions. However, the diagnostic value (level 3) does not seem to be better than for FDG PET, where sensitivities between 70 and 90% in detection of metastatic lymph node involvement are reported (142,143). More research is currently carried out, but based on the limited available data, amino acid imaging does not appear clinically helpful.

**Lung cancer**
Unfortunately, only a minority of patients with lung cancer can be cured. The most important factors determining chances at survival, are tumor resectability and presence of mediastinal metastases. For this latter purpose currently CT and mediastinoscopy are the most important staging tools, but due to rather imperfect detection of mediastinal metastases, many patients undergo fruitless thoracotomies (estimated as high as 30-50%). The recent demonstrations that FDG PET is very helpful in characterization of solitary nodules and in mediastinal (and distant) staging may result in fewer invasive procedures (144,145). What value can radiolabeled amino acids have in this field?
Table 4. Studies using IMT in other than brain tumors.

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>year</th>
<th>#pat</th>
<th>tumor type</th>
<th>sensitivity</th>
<th>remarks/findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flamen (137)</td>
<td>1999</td>
<td>11</td>
<td>head-neck</td>
<td>91%</td>
<td>for primary tumors, ~60% for nodal spread</td>
</tr>
<tr>
<td>Jager (54)</td>
<td>1998</td>
<td>20</td>
<td>various types</td>
<td>-</td>
<td>feasible in breast, lung, sarcoma, and lymphoma.</td>
</tr>
<tr>
<td>Jager (69)</td>
<td>2000</td>
<td>22</td>
<td>carcinoid</td>
<td>43-60%</td>
<td>correlation with secretory activity</td>
</tr>
<tr>
<td>Boni (138)</td>
<td>1997</td>
<td>7</td>
<td>melanoma</td>
<td>37%</td>
<td>for lesion detection</td>
</tr>
<tr>
<td>Jager (61)</td>
<td>2000</td>
<td>32</td>
<td>sarcoma</td>
<td>100%</td>
<td>for difference benign-malignant, specificity 88%, correlation with proliferation.</td>
</tr>
<tr>
<td>Jager (139)</td>
<td>2000</td>
<td>17</td>
<td>lung cancer</td>
<td>94%</td>
<td>for primary tumors, for mediastinal lesions 60%</td>
</tr>
</tbody>
</table>

All studies have reported avid uptake of amino acids in primary lung cancer, both in small-cell and non-small-cell lung cancer. The intrinsic ability of tumors to concentrate MET, or TYR or IMT does not seem to be different. False negative results are generally caused by small tumor size in combination with technical factors such as resolution of PET/SPECT devices.

**Solitary pulmonary nodules.**
Many patients initially present with a solitary pulmonary lesion. A method that could reliably predict whether such a nodule is malignant or benign, could be of clinical benefit. Using MET PET in 24 patients, Kubota et al. found a sensitivity for the detection of malignancy of 93%, however at a 60% specificity. Calculated from these data the negative and positive predictive values are 86% and 76%, respectively (146). These figures are too low to reduce the need for invasive biopsies or surgery and therefore are unlikely to be clinical helpful, especially since surgery is the only chance of curation in lung cancer. However, a comparison with FDG PET (sensitivity and specificity around 90% (147,148)) is lacking and experience with amino acids is very limited. Difficulties in separation of malignant from benign disease using MET are also reported by Nettelbladt et al. using SUV and transport rate analysis (n=17)(84).
Figure 7. Coronal chest IMT SPECT section through a 6 cm squamous cell carcinoma in the right middle lobe, demonstrating high IMT uptake (Same patient as in figure 3).

Staging
Very few studies have employed radiolabeled amino acids to address this problem. The largest study (n=41) was performed by Yasukawa, who showed that in detection of mediastinal metastases MET was superior over CT in sensitivity (86% vs 53%) and specificity (91% vs 84%). However, these figures are based on a retrospective cut-off point of 4.1 for a tumor-to-muscle ratio, which demonstrates that considerable MET uptake (TMR 2.9) was present in non metastatic nodes (149). As clearly analyzed by Hubner, there is no evidence from this study that MET PET would be more clinically helpful than FDG PET (150).

Limited information is available from other studies, e.g. Nettelbladt who found the correct mediastinal lymph node status using MET and FDG in 4 patients with and in 10 patients without lymph node involvement (84).

A SPECT study using IMT (n=17) detected mediastinal metastases in 86% of involved patients but only 60% of all mediastinal lesions (Figure 7,8). Especially lesions < 1.5 cm were frequently not detected and aspecific uptake was found in irradiated normal lung tissue (Figure 3). Therefore, IMT SPECT does not appear clinically helpful (139).
Evaluation of therapy
Despite treatment with radiotherapy, chemotherapy, or combinations of these, survival is extremely low. Evaluation of the effect of treatment is currently based on reduction in tumor size, as assessed by chest X-ray or CT in addition to clinical parameters. Even in local control, many patients die of metastatic disease. The a priori relevance of imaging studies aimed at measuring therapy evaluation is therefore low. At the best, prediction of ineffectiveness early during treatment or presence of (a large percentage of) viable tumor tissue after treatment, might influence further treatment options, such as a change (or even stop) in chemotherapy or addition of chemotherapy after unsuccessful radiotherapy (151). However, accurate assessment of prognosis might be of value to individual patients.

As a prerequisite for successful treatment evaluation, Miyazawa demonstrated in lung cancer cells that uptake of MET is representative of tumor growth, based on good correlations between MET uptake versus DNA content, S-phase and S+G2/M phase fractions (n=24)(152). The main clinical description on the use of MET is from Kubota et al. (153). They found MET uptake to be drastically reduced in chemo- or radiotherapeutically treated patients (n=21) without local recurrence (although most of these patients died from metastatic disease on average 1 year later). However, in patients with a late recurrence (11-18 months) post treatment MET uptake was reduced to the
same degree. When MET uptake was not reduced after treatment, early recurrence was quite likely. Assessment of tumor volume changes using CT performed better in separation of patients with local control from those likely to relapse. MET PET therefore had no added value.

Only anecdotal evidence exists in analyzing early amino acid uptake reduction in relation to prognosis. MET uptake began to decrease within the first week of radiotherapy (154). Also reduction of TYR uptake and protein synthesis rate calculations appeared to take place within the first weeks of chemo- or radiotherapy (unpublished observations).

**Conclusion for lung cancer.**
The paucity of clinical data in lung cancer hardly permits a definitive conclusion. Diagnostic levels 1 and 2 seem to be adequate. However analyzing 'diagnostic value' (level 3), current data do not show a clinical benefit over FDG PET, neither in the determination of the nature of solitary pulmonary nodules, nor in mediastinal staging. The value of radiolabeled amino acids in the evaluation of chemo- or radiotherapy, in itself already of questionable clinical value, has not been proven.

**Breast cancer**

Only very limited clinical results are available. MET uptake correlated well with the proliferation rate (S-phase fraction) in primary and metastatic breast cancer lesions (n=11), suggesting amino acids to be suitable for treatment evaluation (155). Kole et al. studied the detection properties of TYR PET in 11 patients with breast cancer and 2 patients with only benign breast tumors (131). They found better visual uptake of FDG in malignant lesions, although uptake in fibrocystic diseases was less prominent using TYR. In contrast, Jansson found MET uptake to provide better tumor contrast, in comparison with FDG (156). In addition, they found very early reductions in MET uptake (within 1-2- weeks) after the onset of chemotherapy (n=11). Similar findings were reported in breast cancer metastases (n=8)(157). Uptake of the SPECT tracer IMT has been reported in 4 patients (54). These limited data only permit a ‘level 1 - 2 conclusion’ that amino acid studies are feasible in breast cancer. Clinical relevance remains to be defined.

**Lymphoma**

Traditionally, gallium-67 scintigraphy is applied in evaluation of post chemotherapy masses. FDG PET is now more and more used for this same purpose, and studies in primary staging are currently in progress. Using amino acids very limited data are available. Two studies have demonstrated that MET
accumulated strongly in most lymphomas, both of low and high malignancy grades. In one of these, MET was more sensitive than FDG (n=14)(158), in the other (n=23) both tracers were similar (159). Uptake of MET does not appear to be related to grade. This contrasts with FDG uptake that clearly increases in higher grading (n=14) (157). Kinetic analysis of MET data in 32 patients, however, allowed separation of high grade from other grade patients (159). However, final outcome of patients did not seem to be related to MET uptake. Further research is necessary, and appears most challenging in the evaluation of post-treatment tissue. Significant competition from FDG PET and 67-Gallium scintigraphy is to be expected.

**Figure 9.** Coronal IMT SPECT sections through the upper legs of a patient with a high grade malignant fibrous histiocytoma, before (left) and after (right) regional hyperthermic cytostatic perfusion of the leg. The irregular intense IMT uptake has completely disappeared after perfusion, in agreement with complete tumor necrosis, found after surgery.

### Soft-tissue sarcoma

Intensive uptake of both IMT and TYR has been described in soft-tissue sarcoma patients (Table 2,4) (61,79,132). Both IMT and TYR uptake correlated with various histological parameters of proliferation, such as Ki-67, mitotic index and AgNOR (61,79,133)(Figure 9). Using IMT SPECT benign and malignant tumors could be differentiated with high accuracy, and minimal overlap (61). TYR uptake appeared useful in evaluation of regional cytostatic perfusion, although it could not replace histology (132). In comparison with FDG, however, uptake appeared to be less influenced by inflammatory tissue. Staging of sarcoma patients using radiolabeled amino acids has not been described. Especially improved lymph node staging may be of clinical benefit.
**CHAPTER 2**

**Melanoma**

MET PET detected all lesions > 1.5 cm in 10 patients, but missed smaller lesions (161). Tyrosine, being a precursor in melanin synthesis, is theoretically an interesting tracer in melanoma detection. Studies using IMT have been performed in melanoma, as early as the 1970's (162). Although several small case descriptions exist on ocular melanoma, a recent study in detection of known melanoma lesions, provided disappointing results for IMT total body scintigraphy (138). Only large lesions (>1.5 cm) were detected using SPECT.

**Neuroendocrine tumors**

Since tyrosine is a precursor in catecholamine synthesis, uptake of IMT and TYR might be expected in pheochromocytomas, neuroblastomas and carcinoid tumors. Jager et al. reported uptake of IMT in roughly 50% of carcinoid lesions, which correlated both with serotonin and catecholamine metabolism in these tumors (69). Similarly MacFarlane et al. found uptake of p-[125I]-iodo-DL-phenylalanine in carcinoid tumors (68). Since carcinoids have a high amino acid demand, further studies could be successful, and might contribute to improved staging and treatment evaluation.

**Miscellaneous tumors**

TYR uptake was detected in only 20% of metastatic nonseminoma patients (134). MET uptake was found in 78% (18/23) of bladder cancers but was not very helpful in assessing response to chemotherapy (163,164), although on theoretical grounds the low urinary excretion of MET and TYR could provide adequate images of bladder tumors. Similar findings were done for TYR (unpublished data). For primary tumor detection or evaluation, clinical use is unlikely, as the bladder is easily accessible by other means (such as cystoscopy). Possibly in nodal staging, MET might play a role, but has not been studied yet. MET uptake is described in 7/7 ovarian cancers and 14/14 uterine carcinomas is described (165,166). From our own experience, TYR has not proven valuable in nodal staging of cervix or vulva cancer(136). Interfering and rather unpredictable bowel uptake frequently interfered with visualization of small metastases. There are no data regarding radiolabeled amino acids in colorectal cancer.
2.6 CONCLUSIONS

The theoretical and preclinical background of amino acid imaging is quite sound, and supports clinical applications. There is no convincing evidence that radiolabeled amino acids that are only transported into the cell are inferior for clinical applications in comparison with amino acids that enter protein synthesis, arguments for the opposite also exist. Amino acid imaging is less influenced by inflammation, which may be advantageous in comparison with FDG PET imaging, however, tumor specificity is not perfect.

In brain tumor imaging, the use of radiolabeled amino acids is quite established. The use of IMT SPECT appears to be equally valuable as PET methods. Diagnostic accuracy of amino acid imaging is adequate, and the diagnostic value probably advantageous. However, the true therapeutic value and final value in patient outcome still needs to be established.

Limited data in head and neck cancer and in lung cancer, suggests reasonable diagnostic accuracy, but inferior diagnostic value in comparison with FDG PET. In most other tumors, data do not permit definitive conclusions yet, but the general feasibility of amino acid imaging has sufficiently been demonstrated. However, in nearly all tumor types more research is required, in larger patient series and in well defined clinical settings. In these continuing efforts also newer radiolabeled amino acids such as [\(^{18}\text{F}\)]- fluorethyl-tyrosine will be of interest.

2.7 REFERENCES


