

Early phase Technology Assessment of nanotechnology in oncology

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ABSTRACT

To perform early Technology Assessment (TA) of nanotechnology in oncology. The possibilities of nanotechnology for detection (imaging), diagnosis and treatment of cancer are subject of different research programs where major investments are concerned. As a range of bio- nanotechnologies is expected to enter the oncology field it is relevant to consider the various aspects involved in especially early TA. This article provides two cases of early assessment of (predecessors of) nanotechnologies: Microarray Analysis and Photodynamic Therapy implementation, which methodology can be extrapolated to other nanotechnologies in oncology.

Constructive Technology Assessment (CTA) is used for the introduction of technologies that are still in a dynamic phase of development or in an early stage of diffusion. The selection of studied aspects in CTA is based on: clinical aspects (safety, efficacy, and effectiveness), economic (cost-effectiveness), patient related (QoL, ethical/juridical and psychosocial), organizational aspects (diffusion and adoption) and scenario drafting. The features of the technology and the phase of implementation are decisive for choices and timing of the specific aspects to be studied.

A framework was drafted to decide on the relevant aspects. In the first case, early implementation of Microarray Analysis; clinical effectiveness, logistics, patient centeredness and scenario drafting were given priority. Related to the diffusion-phase of Photodynamic Therapy however other aspects were evaluated, such as early cost-effectiveness analysis for possible reimbursement. Often CTA will result in a mixed method design. Especially scenario drafting is a powerful instrument to predict possible developments that can be anticipated upon in the assessment.

CTA is appropriate for the study of early implementation of new technologies in oncology. In early TA small series often necessitate a mix of quantitative and qualitative methods. The features of nanotechnology involved are decisive for the selection of CTA aspects, most likely: safety -especially possible interactions with other technologies-, ethics, cost-effectiveness and patient centeredness.

Continuously, new technologies emerge in the early detection, diagnosis and treatment of cancer. Related to the field of genomics and proteomics, nanotechnology is increasingly receiving attention as a promising biotechnology, also in oncology. For the involved professionals, but especially decision makers, insurance companies, and government agencies it is a challenge to keep up with these developments. Technology Assessment (TA) can be used to evaluate and improve its implementation and support (policy) decisions.

Nanotechnology is dealing with the engineering and creation of elements from materials that are less than 100 nanometers (one-billionth of a meter) in size, especially single atoms or molecules. Relevant processes of living organisms occur basically at nanometer scale, elementary biological units like DNA, proteins or cell membranes are of this dimension. It is anticipated that nanotechnology can have

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Note: 70-gene prognosis signature, performed by Agendia, Amsterdam; MammaPrint™ Agendia's 'MammaPrint diagnostic service' is cleared by the Food and Drug Administration as a medical device and is ISO-17025 accredited, utilizing a custom designed array chip "MammaPrint®".

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an enormous impact on human health¹. The possibilities of nanotechnology for detection (imaging), diagnosis and treatment of cancer are currently subject of different research programs². Examples of nanotechnology are: *nanowires*, sensors that react on molecules related to altered genes; *nanoshells* that absorb infrared light and selectively kill tumor tissue; *nanoparticles* that are bound to cancer cells in such a way that they are made visible (molecular imaging) or enable local drug delivery (targeted therapy) and *nanopatterns*³.

At an early stage in technology development, much is still unclear. Based on the first publications, the views on promising developments of scientists and industry, a scope of application domains becomes evident. In the phase of product development and early feasibility testing and - assessment, both the technology and the exact delineation of implementation possibilities gradually become clear. However, the institution involved, the policy maker or insurance company inevitably face choices in order to realize meaningful progress⁴. Future users are important stakeholders, especially related to the understanding of nanotechnology; when insufficient, the resulting limited acceptance might harm the diffusion speed of the innovation.

When do we decide whether a new (genomic- or nano-) technology is ready for implementation in clinical practice? In the absence of prospective data on the actual benefits, retrospective data analysis/validation, expert opinions and bioinformatics play an important role in early phase decisions. Applying traditional methodological requirements sometimes lead to very complicated and expensive (randomized) designs for prospective studies⁵. Thus, it might very well and possibly increasingly be that implementation of worthwhile but innovative or complex technology is postponed, in view of the incomplete available data and debate on the appropriate assessment methodology.

In literature, there are just a few articles on Health Technology Assessment (HTA) concerning nanotechnology. The aspects researched in these papers are mainly focused on safety and ethics. The question arises whether these particular aspects are chosen on grounded methodology, or is it appropriate to study others, like financial or logistic feasibility, in this early stage?

Especially in the early phases of technology development, there can be close interaction and mutual influence of both the technology, the environment and the actors involved and it can take a while before the technology and its application domain are stable. HTA commonly presumes a "ceteris paribus" situation, whereas it has become evident that environment and technology are often dynamic and mutually influencing each other. Besides 'studying' these changes, 'influencing' changes is sometimes necessary to improve ef-

fectiveness. Moreover it is known that the impact of HTA, which in practice is often constrained to economic evaluations, is limited; some reasons are the often unjustified presumption concerning the stability of the technology and the time lag that evolves between drafting the first study design and deciding about the results often 5 to 7 years later. The existence of interaction between various domains of technology development can make the implementation process more complex. This asks for a broader HTA approach that takes technology dynamics into account and leaves room for influencing the technology or its application during development and diffusion.

An appropriate method might be Constructive Technology Assessment (CTA), especially in the early dynamic phase of the introduction. Therefore, not only the new technology should be analyzed, but also changes in organization and societal environment. The purpose of CTA is to increase the efficiency and effectiveness of the technology, leading to an optimal quality of care and involves an integral assessment of clinical, economic, patient-related and organizational parameters⁶.

This article provides two cases of early stage implementation of (predecessors of) nanotechnologies into clinical practice in oncology, which can be extrapolated to similar nanotechnologies in this field. The first case is the introduction of microarray analysis, which is a predecessor to nanopatterns; macro devices with nanocomponents. A DNA microarray (also known as gene or genome chip, DNA chip, or gene array) is a collection of microscopic DNA spots, commonly representing single genes, arrayed on a solid surface by covalent attachment to a chemical matrix. Microarray technology is known in clinical practice with examples as the Oncotype DX⁷ and the 70-gene prognosis signature⁸. In this case, the introduction of the 70-gene prognosis signature will be presented. This technology proved to outperform traditional criteria in the selection of patients which need adjuvant systemic treatment in breast cancer. It proved feasible to implement this complex technology, in 16 community hospitals in the Netherlands⁹. The second case is related to nanoparticles: the implementation of photodynamic therapy (PDT) in clinical practice. PDT is an application for the detection and treatment of nonmelanomatous skin lesions and head and neck tumors. The Netherlands Cancer Institute is pioneering with this technology; it is however difficult to stimulate diffusion both because of the limited indication field and lacking insurance coverage. The technology is relative simple to use, but expensive and its use is limited to a small group of early adapter colleagues.

This article provides an overview of experiences in the methodology of early assessment of the introduction of (predecessors of) nanotechnology in oncology, which can lead to an outline of design- and

methodology related aspects of CTA in early nanotechnologies.

Methods

Decisions on the design of the CTA method have to take the features of the technology, the diffusion stage and the relevant aspects into account; scenarios can be used to structure this decision process.

The complexity of a broad CTA using mixed methods in a proper design, demands a lot of effort, organization, costs and knowledge on different areas such as psychology, economics and medical science. To achieve a manageable design, it is important to select the most appropriate aspects to be researched; in addition, finding a balance between broadness and depth will inevitably play a role in publishing CTA results. This asks for a thorough and broad discussion of those aspects in the design phase of the CTA. To properly study the dynamics, impact and consequences of a new technology, CTA has to start before the early majority phase when the new technology will be introduced more widely into clinical practice⁶.

The design and methods are related to, and determined by, the different implementation and diffusion phases, as described by Rogers¹⁰. The phases are shaped like a bell curve related to the numbers of adopters; the first (innovator) and last (laggards) phase refer to the smallest numbers. The early adoption phase follows the innovator phases and describes the implementation in the first hospitals. The early majority phase deals with the implementation in other hospitals that are relying on opinion leaders and want to use established logistics. The late majority is conservative and waits until there is no further debate on the validity, reliability or clinical value of the technology and the logistics are further improved.

Decisions on which aspect to choose are depending on the focus of the study and the diffusion phase: Clinical effectiveness (safety, efficacy, effectiveness): this is mostly researched in the earliest stage of development, the innovation phase. Economic aspects (cost-effectiveness): usually determined after finishing a trial with large inclusion numbers, however it is recommended to perform in an earlier stage, the early adopters' phase, to anticipate with possible financial problems. Patient related aspects (ethics, acceptability, patient centeredness, psychosocial impact): preferably measured alongside the clinical trial latest in the early adopter phase. Organizational aspects (diffusion, adoption, implementation, accessibility, skills routine): preferably measured in essential phases of diffusion as every diffusion population from innovators to laggards can have different adoption characteristics. Especially, anticipating the knowledge transfer of the complex biotechnology is an important issue, since any diffusion of the technology will not take place if it is not accepted by its users.

The selection of CTA aspects are based on Douma *et al.*, 2007⁶.

Clinical	Safety, efficacy, effectiveness
Economic	Cost-effectiveness
Patient-related	Ethical/juridical, acceptability, psychosocial reactions, patient centeredness, juridical
Organizational	Diffusion, adoption, implementation, timeliness, equity, skills/routines/logistics, education/training, juridical
Scenario/Roadmap	Diffusion scenario (using Rogers phases)

Scenarios, also called 'road maps', can be used to predict and monitor the implementation process through the various diffusion phases and can support and identify the need for evaluation or even interfere through formal decision making⁶. The method used in the first case is based on the Royal Dutch Shell approach, using a most likely course of development with 'There Is No Alternative' (TINA) elements and alternative course projections represented by 'what if'-deviations. Technological roadmaps align and build bridges between the scenarios, planning for technological forecasting, with the strategic vision of the institution. The roadmapping involves collaborative networking among experts from diverse disciplines¹¹.

Results

Case study 1: Microarray Analysis

In 2002, researchers at the Netherlands Cancer Institute (NKI, Amsterdam, the Netherlands) identified a 70-gene prognosis signature using microarray analysis¹ for lymph node-negative breast cancer patients¹². This signature has been validated in three retrospective patient series^{8,13,14}. It outperforms currently used clinical factors in predicting disease outcome and overall survival. Using the 70-gene prognosis signature instead of the clinical and pathological prognostic factors, the selection of patients that will benefit most from adjuvant systemic treatment could be more accurate. The fact that it would take at least 8-10 years to bring the 70-gene prognosis signature into clinical practice, when introducing it through the usual path of prospective trials, led to the conclusion that a controlled introduction would be appropriate to evaluate this technology⁶. Therefore, a Constructive Technology Assessment was conducted as a side study of the clinical RASTER-study (MicroarRAY PrognOSTics in Breast CancER), a multicenter prospective observational study, sponsored by the Dutch Board of Health Care Insurance (DBHCI). The logistics neces-

sary for profiling was complex, but was successfully implemented in all 16 participating hospitals. Changes in the pathology process and multidisciplinary decision making particularly influenced the duration of the implementation, with a mean value of 2.2 months. A defensive attitude of the physicians may have contributed to an increase number of prescription of adjuvant systemic therapy (because of the Dutch conservative guidelines) which was not anticipated. However, physicians valued the addition of the 70-gene prognosis signature information as beneficial for patient management. The impact on patients seems to depend on the communication to the patients and especially the discordant risk-groups (patients first received the result of low risk according to the clinical guidelines, followed by the result of a high risk according to the 70-gene signature). Because of this occurrence, it was recommended that patients should be informed about all diagnostic results in one contact session to reduce negative affects. Scenario drafting was helpful to map and anticipate on possible deviating developments, national as well as internationally. Although the 70-gene prognosis signature is officially FDA approved and accepted in the USA, relying on only retrospective validation series for catalogue decisions, caused serious debate in the Netherlands. A professional discussion on validity has emerged; although considered unlikely by professionals at the early stage of introduction, this 'what if-scenario' proved surprisingly relevant for the Dutch situation.

Related to a request of a patient an update proved necessary in the guidelines on patient-rights concerning banked tissue, and this project is being pursued at present.

Case study 2: Photodynamic therapy

Photodynamic therapy (PDT) is used in the detection and treatment of cancer. It involves three key components: a photosensitizer, light and tissue oxygen. 5-Aminolaevulinic acid (ALA) is an endogenous cellular component and is metabolized within the haem biosynthetic pathway to produce protoporphyrin IX (PpIX), a potent endogenous photosensitizer. Following exogenous administration of 5-ALA, PpIX is generated intracellular, which can then be activated by visible light for PDT treatment¹⁵.

PDT is most applied by nonmelanomatous skin lesions (using ALA) and head and neck tumors (using Foscan®). Foscan, the photosensitizer meta-tetrahydroxyphenylchlorin (mTHPC; Foscan®, Biolitec Pharma, Edinburgh, Scotland), is a photosensitizing agent (a light-sensitive drug), which contains temoporfin and is used lately in head and neck cancers. In October 2001, Foscan was approved in the European Union. At the moment, there are negotiations about registration by the FDA of Foscan in the US. Literature shows that the survival remains the same as with usual care, but major ad-

vantages in quality of life can be achieved. Usual care for head and neck tumors is radiotherapy or surgery, often associated with serious cosmetic or functional morbidity^{16, 17}. The Netherlands Cancer Institute has been using the PDT technology since 1996; however, the relatively small incidence makes it difficult to obtain data on large series and hampers further diffusion. The technology is relatively simple to use, but expensive and unknown by colleagues. And, like the first case study, partly due to the lack of RCT based evidence, a discussion is ongoing about the reliability of the treatment. The question is, however, whether it is ethical to conduct a RCT, and for that reason it was decided to conduct a prospective case study which in turn might not convince critical colleagues. Subsequently, there arises a dilemma, which is hard to tackle. To solve this problem, a cost-effectiveness analysis (CEA) using modeling techniques was conducted, which eventually made health insurance companies reconsider the case for possible reimbursement. In the CEA the aspects of costs, utilities (based on quality of life scores) and retrospective data on survival were synthesized in two Markov models.

In Table 1 we summarized the results of the two cases.

Discussion

Early assessment of the introduction of nanotechnologies

The wave of nanotechnology innovations asks for a view on TA taking both the features of the technology and the dynamics of development and diffusion into account. We defined which aspects can be studied in a CTA analysis in the field of nanotechnology and presented examples in two case studies. In the first case study of Microarray Analysis the aspects of clinical effectiveness, efficiency, patient centeredness and the instrument of scenario drafting were appropriate to research. In the second case study of Photodynamic Therapy, the aspects of clinical effectiveness, team functioning and cost-effectiveness were so far most important, whereas CEA using modeling techniques proved an important methodology.

The two cases show that implementation of two kinds of (predecessors of) nanotechnology can have different patterns of adoption and diffusion, and thus have different priorities of research aspects. In Table 1 we summarized the various aspects that can be studied in a CTA and related these to the two cases and two recent developed nanotechnologies.

The two major areas in which nanomedicine is presently being developed in cancer involve early detection of the tumor (1) and cancer treatment using targeted therapies (2):

1) Rapid Detection of Single Nucleotide Polymorphism (SNP) Using Nano Magnetic Device is a rising technology in the field of oncology. SNPs in genomic DNA are known to be related to a number of hereditary

Table 1 - Selection of early stage CTA aspects

		Technologies			
		Microarray	PDT	SNP	Abraxane®
Clinical	Safety		v		v
	Efficacy	v	v	v	v
	Effectiveness	?	?	?	
Economic	Cost-effectiveness		v		
Patient-related	Ethics			v	
	Acceptability			v	
	Psychosocial reactions	v			
	Patient centeredness	v	v		
	Patient related juridical aspects	v		v	
Organizational	Adoption	v		v	?
	Implementation	v			
	Accessibility/equity		v	v	
	Skills/routines/logistics	v	v		v
	Juridical	v		v	
	Education/training				
Scenario/Roadmap	Diffusion scenario	v		v	

CTA, Constructive Technology Assessment; v, evaluated in literature; ?, relevancy not clear or method debated; PDT, photodynamic therapy; SNP, Single Nucleotide Polymorphism.

conditions and cancers. With the help of DNA microarrays, a particular assay, labeled with gold nanoparticles (Au-np), can make the detection of SNPs more efficient and less time-consuming; it is however not clear what costs will be involved and what the exact application field will be¹⁸⁻²⁰.

2) An example of a nano-based drug for e.g., breast or non-small-cell lung cancer is 'Abraxane®', an FDA approved, paclitaxel protein-bound particles for injectable suspension cancer treatment with nanoscale devices, which can serve as targeted drug-delivery vehicles capable of carrying chemotherapeutic agents or therapeutic genes into malignant cells. The use of Abraxane® as a vehicle, demonstrated in a phase III trial, eliminates the solvent-related toxicities and obviates the need for steroid and antihistamine premedication²¹. The two new technologies are also processed in Table 1, in order to provide an overview.

In the early development or (early) innovator phase usually relatively few numbers of patients are involved and the technology, its exact features and use, is not yet stable. In a contingent approach, clinical safety, efficacy, implementation aspects and aspects related to patient-acceptation might be the most relevant ones in nanotechnology. Whether the patient-related ethical aspects should receive the attention as is given at present is easier explained from lack of knowledge and generalization than methodological reasoning. The clinical efficacy in appropriate fields of application within oncology is an obvious aspect of consideration. Furthermore, the costs involved in the application of nanotechnology in oncology as well as the temporal costs of introducing this new technology in clinical practice impacts the feasibility of its use. Patient-related concerns including acceptability, psychoso-

cial reactions to, and patient centeredness of this new and perhaps feared technology need to be considered. Finally, organizational aspects involved with the process of implementation of nanotechnology within clinical practice could seriously impact the quality of care. For example, a new technology might change the needed skills and routines, and it requires different levels of training or team composition to ensure its adequate application.

Data on these aspects can be derived from clinical trials, combined with results from qualitative methods such as inter-

views and questionnaires about the knowledge, opinions, and experiences of the stakeholders that actually shape the clinical practice of oncology. The results can be used for scenario drafting. In case the practical development seems to differ strongly from the projected scenario, expert panels or formal decision processes can be applied to suggest changes to improve the quality of implementation²². In the early adopters, early majority phases, costs, patient related aspects and organizational aspects can be analyzed using greater numbers of patients. As the use and characteristics of the early majority-, late majority- and laggard adopters can vary, it is advisable to continue the evaluation during the different phases, in order to assure and improve the quality of care during the lifecycle of the technology.

As an example of introduction of new technologies in the health care system, the DBHCI in the Netherlands has experimented with a program of controlled introduction of promising innovations in an early stage of development from 2004 onwards. The use of the 70-gene prognosis signature was one of the three technologies to be studied. Currently, the DBHCI and the Ministry of Health are discussing the most appropriate way of stimulating innovations in order to stimulate early clinical implementation, for instance through a "Coverage with Evidence Development"-like program (CED).

When applied from the early adopter phase onwards, it is likely that CED is an appropriate method to both study the complex features of bio-nanotechnology and provide coverage without having to wait on the finalization of lengthy trials following a methodological approach that was developed in a different technological era.

Conclusion

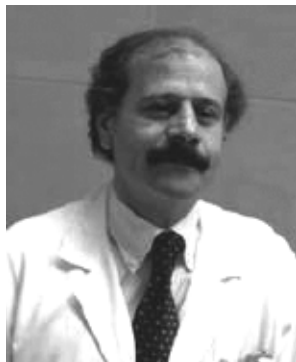
It seems appropriate to apply CTA on promising technologies in an early stage of development or dynamic circumstances. As it can involve various methods and takes technology dynamics into account, an explicit decision on the aspects to be studied is necessary, in relation to the diffusion phase, in order to prevent unnecessary complex study procedures. When the dynamics and uncertainties are dealt with early in the assessment, policy makers are facilitated to decide in an earlier stage, for instance, on the allocation of resources.

For the nanotechnology introduction in clinical practice, Table 1 provides relevant aspects to study related to earlier experiences and the presently known features of nanotechnology in oncology. So far, safety and ethical aspects seem to have priority in the literature, but safety seems not justified for every nano-application. We think that a more comprehensive route should be followed to support decision making in this complex field.

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PAOLO LEPERA

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