PRERADIATION DENTAL DECISIONS IN PATIENTS WITH HEAD AND NECK CANCER

TANDHEELKUNDIGE BESLISSINGEN VOORAFGAAND AAN RADIOTHERAPIE BIJ PATIËNTEN MET EEN HOOFD-HALSTUMOR

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(met een samenvatting het Nederlands)

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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The studies described in this thesis were performed at the *Department of Oral and Maxillofacial Surgery* and the *Department of Special Care Dentistry, University Medical Center Utrecht*, in collaboration with the *College of Dentistry, Ohio State University, Columbus, Ohio, U.S.*
Chapter 4 was prepared in collaboration with Professor Ray W. Cooksey, PhD, *School of Marketing and Management, University of New England, Armidale, Australia.*
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"If we begin with certainties, we shall end in doubts; but if we begin with doubts, and are patient with them, we shall end with certainties"

Sir Francis Bacon, 1605

Ter nagedachtenis aan mijn ouders

List of abbreviations

BP	Back Propagation
CC	Clinical Condition
CEJ	Cemento-Enamel Junction
CJA	Clinical Judgment Analysis
CRF	Clinical and Radiographic Findings
DRF	Dental Risk Factor
EPT	Electric Pulp Test
EV	Expected Value
Gy	Gray
ICD	International Classification of Diseases
JANNET	Judgment Analysis via Neural NETwork
LR	Likelihood Ratio
MDDS	Model for Dental Decision Support
MRRF	Malignancy Related Risk Factor
N-ST	Non-Strategic Teeth
ORN	Osteoradionecrosis
OV	Outcome Value
PATFACT	Patient's Dental IQ
PE	Probability Estimation
PNN	Probabilistic Neural Network
RD	Radiation Dose
ROC-curve	Receiver Operating Characteristic curve
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
ST	Strategic Teeth

Numeric convention

In this thesis, we will follow the English system of using the *dot* {.} for decimals and the *comma* {,} to indicate thousands.

PRERADIATION DENTAL DECISIONS IN PATIENTS WITH HEAD AND NECK CANCER

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CHAPTER 1

INTRODUCTION, OBJECTIVES, AND OUTLINE

Introduction

Overview

Patients with head and neck cancer have to cope not only with a life-threatening disease but also with the prospect of adverse effects of cancer therapies, frequently affecting the mouth and jaws.(1,2) This is especially true if high-dose radiation therapy to the oral and maxillofacial structures is part of the overall treatment regimen.(3) To reduce oral sequelae, extensive dental preventive and treatment measures before, during, and after cancer therapy are mandatory. (4,1,5)

In view of the risk that accompanies high-dose irradiation, special attention to preradiation dental planning appears critical. Each case must be managed individually on the basis of the patient's needs, the status of the tumor, and the risk known to exist for dental heath in irradiated tissues; a single-formula approach for all patients is contra-indicated.(6)

Evidence-based medicine is an approach to clinical decision-making in which the clinician uses the best evidence available to decide upon the intervention that suits an individual patient best.(7) This can be a challenging and complex task. The key to control is the implementation of 'good clinical decision-making'. For that reason, decision support systems to aid clinicians in reaching optimal decisions have become increasingly important. As described by Muir Gray,(7) '*good clinical decision making*' plus '*good (decision support) systems*' result in '*good clinical outcomes*'. In accordance with this view, the main subject of this thesis is to develop and test a decision support system, in order to enhance dental decision-making in patients with head and neck cancer.

Head and neck cancer (8,9)

Epidemiological data indicate that there are an estimated 40,000 - 60,000 newly reported cases of head and neck cancer in the Unites States every year.(10,11) The annual incidence is approximately 17 per 100,000.(8) This represents approximately 5% of all newly diagnosed cancers occurring in the United States per year. Worldwide, an estimated 400,000 - 500,000 new cases of head and neck cancer occur.(12,13) This ranks head and neck cancer as the sixth most common cancer.

Squamous-cell carcinoma (SCC) is the most common malignant neoplasm of the mucous membranes of the upper aero-digestive tract and accounts for more than 90% of newly diagnosed head and neck malignancies. In the Netherlands, cited by Slootweg and Richardson,(9) in 1994, 2034 new cases were registered out of approximately 63,500 new malignancies in a population of 15.4 million inhabitants.(14)

Primary tumors are specified by site of occurrence. About 38% percent of head and neck carcinomas occur in the larynx, 32% in the oral cavity, 20% in the pharynx, 4% in the major salivary glands, and 6% in the remaining head and neck sites.(14,15) However, it should be noted that significant geographic variations in the occurrence of head and neck cancer have been documented. For example, the highest incidence rates of oral cavity and pharyngeal cancer are reported for South Asia, whereas the highest incidence rates for laryngeal cancer are found in Southern Europe.(16) The incidence of SCC is two to three times higher in men than in women. Laryngeal cancer has an even higher incidence in men. The male-female ratio is 5:1.(9) However, the incidence in women continues to rise, probably because of the increasing number of female smokers.

The overall age-adjusted head and neck cancer death rates have remained unchanged over the past 30 years.(10) The 5-year survival rates average about 40-50% (10,14) and vary from about 40% for nasopharyngeal carcinomas, through 50-60% for oral and pharyngeal carcinomas, up to 67-70% for laryngeal and salivary gland carcinomas. The annual age-adjusted death rate in the United States due to SCC of the head and neck is estimated at 13,000 cases per year.(8) Based on the overall mortality rates reported by Visser et al.,(14) in the Netherlands, this number is estimated at 1340 patients per year. It was estimated that worldwide in the year 2000, approximately 286,000 patients died as result of oral and oropharynx cancers.(12)

Tobacco use is the major risk factor for development of SCC of the oral cavity, oropharynx, and larynx. As a second important etiological factor, alcohol appears to potentiate the effect of tobacco. Excessive use of both tobacco and alcohol increases the risk of oral cancer by a factor of 15, compared with individuals who use neither. The effect of tobacco and alcohol is time- and dose-dependent. Other suggested etiological factors include genetic predisposition, dietary factors, betel nut use, viral infections, poor oral hygiene, and mechanical irritation from teeth or dentures. Occupational exposure to asbestos, wood dust, or certain vapors or metals increases the risk for development of sino-nasal carcinomas.(17,18)

The choice of head and neck cancer treatment depends on the anatomic site and extent of the tumor, and on histological factors. Final treatment decisions taken by the multidisciplinary cancer team are influenced by a number patient factors, including age, medical condition, compliance, and possible continuation of smoking and drinking, and the relative morbidity of the various treatment options. The treatment regimen consists primarily of surgery and radiation, either alone or in combination. Generally, tumors of limited size can be treated with equal effectiveness by either radiation therapy or surgery. Combination therapy is the preferred modality for advanced tumors. The approach should be directed toward the elimination of the cancer while preserving function and quality of life. The surgical approach therefore requires not only ablative but also reconstructive procedures. The possibility or presence of neck metastasis requires surgical management with a neck dissection. Adjuvant radiation therapy is mostly used as post-surgical treatment. This treatment decision is usually based on histological parameters. Chemotherapy has been of little benefit to patients with head and neck cancer and cannot yet be considered to be part of the standard treatment regimen. However, chemotherapy may be given as palliative treatment to patients with bulky, unresectable tumors, locally recurrent disease, or distant metastases.(19) cited by (9)

Oral sequelae (1,2)

Radiotherapy to the head and neck region, which includes oral and maxillofacial structures and salivary glands, may result in serious side effects. The short-term effects are mucositis, loss of taste and smell, secondary or 'opportunistic' infections, and reduced salivary function. The long-term effects include persistence of reduced salivary function, radiation caries, progression of pre-existing periodontal disease, limited mouth opening (trismus), soft-tissue breakdown and failure to heal, and radiation bone injury, which in its severest form develops as osteoradionecrosis. As a secondary effect, patients with head and neck cancer experience significant tooth loss, prior to and following radiotherapy. In pediatric patients, radiotherapy may also cause developmental dental and maxillofacial abnormalities.

Mucositis may appear in the second week after the start of radiotherapy. Initially, the affected mucous membranes appear reddened and edematous as a result of hyperemia. The mucosa may then become ulcerated and covered with a fibrinous exudate.(6,20-23) The lips, cheeks, soft palate, and floor of the mouth are at greater risk of mucositis. Discomfort and a burning sensation are commonly present. Mucositis worsens if smoking is continued.(24) Pain varies considerably in severity and may be intensified by certain foods. In addition, the patient may develop problems in swallowing and speaking. Severe symptoms usually dissipate within 6 weeks following completion of radiotherapy, but reactions may be prolonged and late mucosal reactions may even develop.(25)

Alteration and loss of taste may be noticed as early as 2 weeks after initiation of radiotherapy (6,26) The rate and extent of taste loss are related to the radiation dose delivered to the area involving taste receptors. After 3 weeks of therapy, it takes 500 to 8000 times normal concentrations of taste stimulant to evoke normal taste responses.(2) Taste function usually returns to normal 2 to 4 months following completion of therapy.

Oral mucosal alterations resulting from irradiation create a favorable environment for the growth of microorganisms.(27) Secondary or 'opportunistic' infections are therefore common. While Candidiasis (*Candida albicans*) is most common, any bacterial, mycotic, or viral organism may cause infections. Candida infection usually presents as painless, pearly white, raised flecks or patches that adhere firmly to the underlying mucous membrane.

Oral dryness or 'xerostomia' is one of the most common complaints.(20,28) Saliva is often reduced in volume and is more viscous. The overall diminished salivary flow and the lack of lubricating mucin account for this oral dryness. Further, the remaining salivary secretions become more acidic, thus promoting decay of the remaining teeth. Radiation xerostomia is rapid in onset and is usually persistent. Some of the oral sequelae of head and neck radiation already mentioned, such as mucosal alterations and soft tissue infections,(29) taste loss, and radiation caries, have been linked to lack of normal salivation.(6)

Rapid demineralization and breakdown of tooth structure often occur following radiotherapy(6,20) and may start as early as 12 weeks after treatment. The teeth need not be directly in the field of radiation. Dental demineralization may also occur when the major salivary glands are included in the field of radiation. An inadequate supply of saliva deprives the tooth structure of calcium and phosphate ions, resulting in demineralization.(30) Even patients who may not have complaints of oral dryness may have changes in saliva composition. Not only is the saliva more viscous, with a reduced pH-buffering capacity, its antibacterial properties are also diminished.(29) This results in a highly cariogenic oral microflora, which, coupled with poor oral hygiene and dietary changes, leads to heavy dental plaque formation. The microbial, chemical, immunological, and dietary changes(31-33) add up to an enormous increase in incidence of dental caries.(34,35) The usual pattern is one of circumferentially progressive caries, and widespread caries is often seen (Fig 1.1 and 1.2). Exposed root surfaces are especially susceptible to caries.

Figure 1.1

Figure 1.2

The periodontium also is sensitive to the effects of radiation at high doses, leading to widening of the periodontal space. The periodontal ligament's specific network of fibers becomes disoriented and thickened.(36-39) Cementum demonstrates changes similar to those seen in bone. Reports of increased periodontal disease activity are sparse, but progressive destruction of the periodontium following radiation treatment is a realistic outcome and(20,40-42) is a major cause of postradiation tooth loss.(42)

Trismus characterized by spasms and/or fibrosis of the muscles of mastication and by injury to the temporomandibular joint may develop when these tissues are in the field of radiation.(43-46) Consequently, mouth opening can be severely limited (trismus) and oral function seriously impaired. Trismus may become evident during radiotherapy but is usually manifested 3 to 6 months after treatment.

Oral cavity soft-tissue breakdown, failure to heal, and bone necrosis may develop because tissues in the field of radiation become hypovascular, hypoxic, and hypocellular.(47-49) Bone necrosis or 'osteoradionecrosis' (ORN) may develop spontaneously or may be induced by trauma. Trauma often results from tooth extraction, invasive periodontal procedures, or the use of poorly fitting prosthodontic appliances.(42,50-57) ORN occurs in approximately 2% to 10% of those exposed to high radiation doses;(58-60) the majority of patients may present with milder forms of radiation tissue injury.(52,54,58,61-64) Patients are most vulnerable to ORN in the first two years after irradiation,(52,55,58,65-68) although this complication can occur any time thereafter.(64,69) There is general agreement that the lower jaw is much more susceptible to ORN than the upper jaw.(60) Clinically, the necrotic bone is denuded, (Fig 1.3, 1.4, and 1.5) greenish gray, suppurative, foul smelling, and painful at rest, at night, and especially during chewing.(49,51,53,54,56,59-61,66,70,71) Possible consequences are pathologic fracture, intraoral/extraoral fistulation, and local/systemic infection.(55,60,72-76)

Figure 1.3

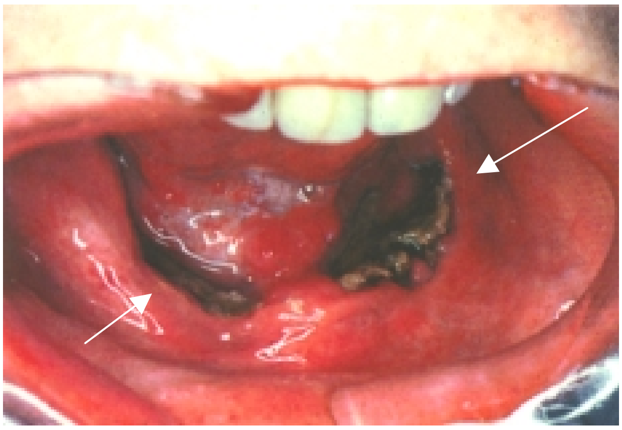


Figure 1.4

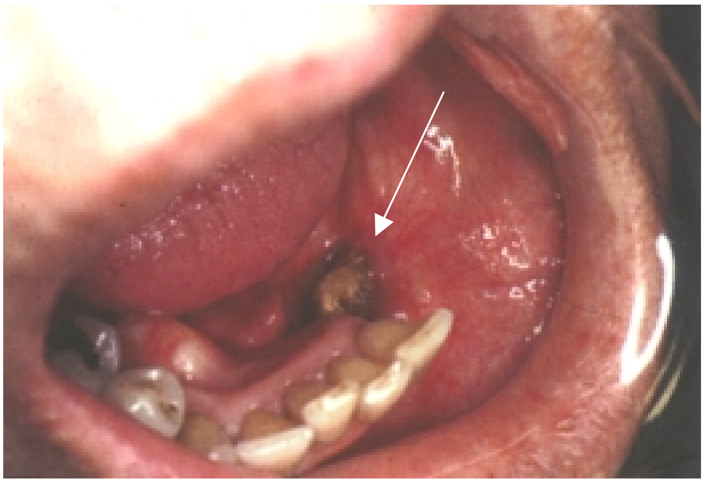


Figure 1.5

Children undergoing radiotherapy may experience significant changes or abnormalities in the growth and development of dental and maxillofacial structures. These alterations include blunted roots, incomplete calcification, delayed or arrested tooth development, asymmetrical facial growth, and abnormal occlusal relationships.(77-79)

Pretherapy oral screening

To reduce oral sequelae, extensive dental preventive and treatment measures before, during, and after cancer therapy are mandatory.(1,4,5) Implicit in the preventive approach is pretherapy oral screening to identify and eliminate dental risk factors.(5) The current standards for dental care before radiotherapy include extraction of teeth with significant bone loss, extensive caries, and/or extensive periapical lesions. In addition, partially impacted or incompletely erupted teeth and residual root tips not fully covered by bone and/or showing radiolucency to x-rays should be removed.(3,5,6,80,81) The essential elements of the pretherapy oral screening are outlined in Chapter 2.

Important factors in the dental management of these patients include among others, the following considerations:(6)

(1) Anticipated radiation field and dose;
(2) Pre-therapy dental status, dental hygiene, and retention of teeth that will be exposed to high-dose irradiation;
(3) Patient motivation ('dental IQ') and ability to comply with preventive measures.

Persons with head and neck cancer have a higher incidence of dental and oral pathology than the general population. Particularly elderly persons and persons of lower socioeconomic status form a substantial proportion of patients with head and neck cancer.(15,82) The prevalence and incidence of dental disease in these groups are high, and compliance with dental care recommendations is usually poor (44,83-88) For example, Lockhart and Clark(89) conclude on the basis of clinical examinations of 75 dentulous head and neck cancer patients that almost all (95%) of them needed some form of dental treatment. However, in spite of strong urging from members of the cancer team, only a small proportion of the patients (19%) were compliant in seeking dental care for their treatment needs. This pattern of non-compliance for dental treatment in head and neck cancer patients has been reported by several other investigators.(90-94)

Although several studies strongly support the efficacy of the pretherapy oral screening,(80,95,96) evidence-based clinical guidelines(97-99) to aid clinicians in deciding which options for dental intervention best suit these patients are not yet widely available. In view of the risks that result from high-dose irradiation, special attention to preradiation dental planning appears critical. Each case must be managed individually; a single-formula approach for all patients is contra-indicated.(6) Dental management can thus be a challenging and complex task. The key to control may be the implementation of a dental decision-support system, derived from an evidence-based approach.

Evidence-based approach

Evidence-based medicine is an approach to clinical judgment and decision-making in which the clinician uses the best evidence available to decide upon the intervention that suits an individual patient best.(7) This approach involves evaluating rigorously the effectiveness of health-care interventions, disseminating the results of these evaluations, and using these findings to determine clinical practice.(100) Good clinicians use both personal clinical expertise and the best available external evidence, and neither alone is enough. External clinical evidence can inform, but can never replace individual expertise. Evidence-based medicine is therefore not an obligatory 'cookbook' approach.(101)

One of the basics of evidence-based practice is the implementation of 'good clinical decision-making'. This could explain why decision support systems that aid clinicians in reaching optimal decisions have become increasingly important. As stated by Muir Gray,(7)

good clinical decision making + good (decision support) systems
=
good clinical outcomes

Decision strategies

Optimal decision-making calls for a strategy that is appropriate to the situation. Thompson,(102) cited by Keuning,(103) explains that two basic situational factors influence the choice of decision strategy:

(1) Insights into the structure of the problem (cause-effect relations);
(2) Preferences regarding possible outcomes.

A matrix summary distinguishes four different strategies (Fig 1.6).

		Clear preferences regarding possible outcomes	
		Yes	No
Certainty of beliefs about cause-effect	Yes	Computational	Compromise
	No	Judgmental	Gambling

Figure 1.6

(1) ***Computational strategy***: good insight into the decision problem and certainty with regard to causation and outcome preferences imply adoption of a computational strategy for decision-making. For example, the technique of 'folding back and averaging out' a decision tree, further explained in Chapter 2, provides such a solution. However, in many instances, the levels of certainty concerning underlying decision factors and outcomes are reduced. In these cases, higher levels of certainty or 'belief' cannot easily be derived by experimentation, for example by a randomized controlled clinical trial.

A Baysian approach,(104-107) briefly introduced in Appendix 1, provides a mathematical rule explaining the methodology of changing existing beliefs in the light of new clinical data or evidence. In other words, it allows clinicians to combine new data with their existing knowledge and expertise. Baysian methods have become the primary tool for decision support systems that acknowledge uncertainty.(106,108,109) These systems will be briefly introduced in Chapter 6.

(2) ***Judgmental strategy***: when outcome preferences are clear but cause-effect relationships are uncertain, a judgmental strategy for decision-making is required. With such problems, the decision makers, given lack of clear insight into the decision problem, fall back entirely on their judgmental abilities. Judgment analysis,(110) more fully explained in Chapters 3 and 4, provides methods for capturing, comparing, and aggregating decision and judgment policies of individuals.

(3) ***Compromise strategy***: if those involved in the decision problem (e.g. patient and clinician) have a clear understanding of the problem but have different concerns, a compromise strategy is required. For example, the patient's main concern may be the maintaining of oral function by preservation of teeth, whereas the main concern of the dental clinician may be the elimination of risk factors by means of extracting remaining teeth, to prevent adverse outcomes. In this controversial situation the compromise strategy will be required, involving consideration and negotiation, during which both parties will have to shift their positions to a certain extent, leading to an acceptable solution and 'informed consent'.

(4) ***Gambling strategy***: when there is no insight into the decision problem and no consent with regard to the preferences or goals, a solution can only be reached by gambling. In medicine and dentistry, this approach does not belong to standards of 'good clinical practice' and can lead to serious professional misconduct.

Objectives

In view of the risk that accompanies high-dose (> 55 Gy) head and neck irradiation, and in accordance with the evidence-based approach that underlies the health-care paradigm of this new millennium,(7,111) the main subject of this thesis is to develop and test a decision support system, in order to enhance dental decision-making in patients with head and neck cancer. More specifically, studies were conducted to:

(1) Identify the decision dilemma and perform a clinical decision analysis (base-case analysis);
(2) Analyze the judgment policies of clinicians familiar with and experienced in preradiation dental screening;
(3) Propose a method for judgment analysis, to identify the characteristics of individual judgment policies of dental clinicians with respect to the prophylactic extraction of teeth;
(4) Assess which factors included in the base-case decision analysis are most strongly associated with tooth loss in patients with head and neck cancer;
(5) Develop and test 'SCREDENT', a system for dental decision support in patients with head and neck cancer.

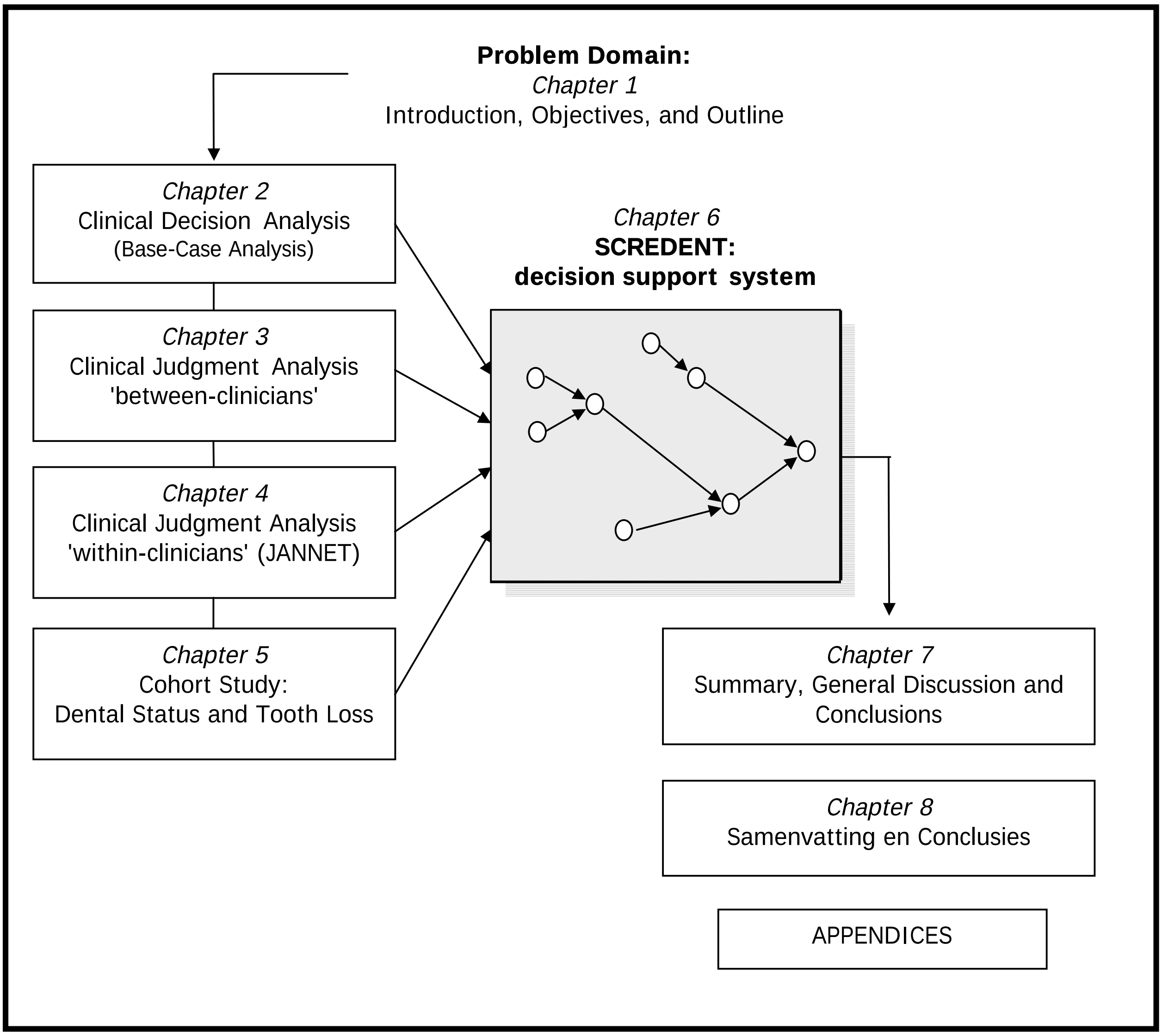
Outline

The outline of this thesis is displayed in Fig 1.7.

Chapter 1 presents a general introduction to the problem domain and a statement of the objectives.
Chapter 2 offers a clinical decision analysis, comprising four basic steps:

(1) Identification and analysis of the decision dilemma, and construction of a decision tree;
(2) Analysis of the decision tree, using the method of 'folding back and averaging out';
(3) Presentation of the optimal decision alternatives;
(4) Probabilistic sensitivity analysis, using second-order Monte Carlo simulations.

Chapter 3 involves an international survey using a judgment analysis questionnaire to capture the decision policies of clinicians familiar with and experienced in preradiation dental screening. As all policies were aggregated together, this is a 'between-clinicians' analysis.
Chapter 4 proposes JANNET, a new tool for Judgment Analysis, using a probabilistic neural network (PNN). JANNET can be used when the assumptions underlying multiple regression analysis (the main method for judgment analysis) are not met. JANNET is used to analyze the decision policies of individual clinicians. Therefore, this is a 'within-clinician' analysis.
In ***Chapter 5***, a cohort study to search for clinical evidence is presented. This study was designed to investigate the association of tooth loss with dental status, dental risk factors (DRFs), and radiotherapy-related factors in a sample of patients with head and neck cancer. It involves a retrospective and follow-up study of 209 head and neck cancer patients in the Netherlands who received a dental evaluation prior to radiotherapy. Patients who met the inclusion criteria were subsequently evaluated after a follow-up period of 1-5 years (median 3 years) in order to establish the end points.
In ***Chapter 6***, the results from Chapters 2-5 are used to construct and test SCREDENT, a system for dental decision support in patients with head and neck cancer.
To validate the decision support system, it is used to analyze the dental treatment planning in an additional sample of 30 patients who were treated in the University Medical Center Utrecht.
In ***Chapter 7***, a summary, general discussion, and conclusions are provided.
A summary and conclusions in Dutch are given in ***Chapter 8***.
In ***Appendix 1***, the Bayesian Approach is briefly introduced, and an explicatory example is given. In ***Appendix 2***, the SCREDENT form and guidelines are presented and ***Appendix 3*** provides the SCREDENT "getting started" document.


Problem Domain:
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Chapter 2
Clinical Decision Analysis
(Base-Case Analysis)
Chapter 3
Clinical Judgment Analysis
'between-clinicians'
Chapter 4
Clinical Judgment Analysis
'within-clinicians' (JANNET)
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Cohort Study:
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decision support system
Chapter 7
Summary, General Discussion and Conclusions
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Samenvatting en Conclusies
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Figure 1.7

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CHAPTER 2

Pretherapy dental decisions in patients with head and neck cancer:
a proposed model for dental decision support

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Abstract

Objective

The proposed model was designed to function as a tool for the development and testing of evidence-based guidelines for the pretherapy oral screening and dental management of patients with head and neck cancer.

Study Design

Methods of clinical decision analysis were used to analyze the decision dilemma and construct a decision algorithm and decision tree. The robustness of the model was tested by means of a probabilistic sensitivity analysis with second-order Monte Carlo simulations (n = 10.000).

Results

Clinical criteria for evaluating dental pathologic conditions and malignancy- and patient-related conditions were transformed in probability estimates. The tradeoffs between the benefits and drawbacks of dental intervention were integrated into the model to identify the optimal option for dental intervention. The calculation process of 'folding back and averaging out' the decision tree enabled the identification of the optimal options for dental intervention in four different pretherapy risk conditions.

Conclusions

A priori testing of the proposed model with 95% confidence intervals suggests that it has great potential for solving clinical dilemmas associated with pretherapy dental decision-making. In addition, it seems a useful tool for the development of evidence-based clinical guidelines. A posteriori clinical testing should further validate the model before assimilation into clinical practice takes place.

Introduction

Patients with advanced head and neck cancer have to cope not only with a life-threatening disease but also with the prospect of adverse effects of cancer therapies.(1) This is experienced as extremely traumatic.(2-4) The wide spectrum of adverse effects in particular influences the entire mouth and jaws,(5-9) resulting in severe impairment of oral function.(3,10-12) This seriously affects both the tolerance of treatment and the quality of life.(13)

Numerous reports indicate that in addition to the cancer therapy itself, preexisting dental disease, tooth extraction, and dental treatment are major risk factors for oral complications.(7,9,14-19) To prevent oral complications and to improve patient outcomes, extensive preventive and treatment measures before, during, and after cancer therapy are necessary.(7,20-22) This is especially true if radiation therapy is part of the overall head and neck cancer treatment regimen.

Implicit in the preventive approach is pretherapy oral screening to identify and to eliminate dental risk factors (DRFs; see Table 2.2, page 25). Elimination of DRFs is possible through dental treatment or tooth extraction. To be safe, a minimum interval of 14 days' healing time between tooth extraction and the onset of radiation reactions is recommended (radiation reaction established at 10 to 12 days after initiation of external beam radiation).(21) Criteria for the extraction of teeth before radiation therapy include the following:(7,21,23)

- moderate to advanced periodontal disease,
- extensive periapical lesions of roots,
- extensive tooth decay,
- partially impacted or incompletely erupted teeth,
- residual root tips not fully covered by bone and/or showing translucency to x-rays.

Table 2.1 Essential elements of pretherapy oral screening[a]

History	Medical history, dental history, dental complaints
Consultation	Family dentist, oncologist, surgeon, consultant radiotherapy
Cancer- and cancer therapy-related factors	Clinical staging and location, cure or palliation; type of therapy; mode, dose, and field of radiotherapy, immediacy of treatment
Patient related factors	Age; patient's preferences; dental awareness; level of oral hygiene
Clinical examination	
Extraoral:	Examination of head and neck: soft tissue examination; swellings, mouth opening
Intraoral:	Examination of oral mucosa and alveolar process; periodontal examination; evaluation of dentition, dentures
Radiographic examination	Panoramic radiograph, intraoral radiographs when indicated: detection of foci (periapical infections, periodontal disease, unerupted or partially erupted teeth, residual root tips, cysts)

[a] Modified after Jansma et al,(7) and Stevenson-Moore and Epstein.(21)

Although several studies strongly support the efficacy of pretherapy oral screening, evidence-based clinical guidelines(24-26) to aid clinicians in deciding which option for dental intervention suits these patient best are not yet widely available. Current standards for dental care prior to radiation therapy and chemotherapy were developed at a Consensus Development Conference on Oral Complications of Cancer Therapies(23) and were published as a NCI monograph.(20) In our view, these standards are primarily based on clinical experience, show great diversity,(7) and are formulated in broad terms. Because the clinical situation is often complex and the available information on the primary disease ambiguous, we believe that the process of pretherapy dental decision making needs to be more adequately structured. It also includes the need to determine more precisely which dental conditions are indicative risk factors and of significant importance in the process of pre-cancer therapy dental decision-making. This is essential because a substantial proportion of patients with head and neck cancer consists of the elderly and those of lower socio-economic status.(27,28) The prevalence and incidence of dental disease in these groups are high,(22,29-34) which makes the pretherapy management of DRFs mandatory.

In this article we propose and a-priori test a Model for pretherapy Dental Decision Support (MDDS). The proposed model is based on the accepted standards for pretherapy dental intervention.(20) A protocol based on the work of Jansma et al.(7) and a review and comment by Stevenson-Moore and Epstein(21,23) have served as sources of more current information. The MDDS is designed to function as a tool for the development and testing of evidence-based clinical guidelines for the pretherapy oral screening and dental management of patients with head and neck cancer. Evidence-based decision support is a rapidly expanding approach in which clinicians use the best evidence available, in consultation with the patient, to decide which option suits the patient best.(35)

Methods

The proposed MDDS was constructed using techniques of clinical decision support. Overviews of these methods and examples are given by Paulker and Kassirer,(36) McCreery and Truelove,(37,38) and Petitti.(39) (An explanation of how to perform a decision analysis goes beyond the scope of this article; For better understanding of the practical issues we refer to a series of articles on this topic.(40-44))

The decision-analytic approach includes a number of basic steps:(39,41-45)

(1) Identify and analyze the decision dilemma and construct a baseline decision algorithm (a set of decision-making steps) and decision tree (a graphical display of the logical sequence of the decision problem (see Fig 2.2, page 29), explained more fully below);
(2) Calculate the Expected Value (EV) of each decision alternative;
(3) Choose the optimal decision alternative;
(4) Perform sensitivity analyses.

The robustness of the model was tested by means of a probabilistic sensitivity analysis using second-order Monte Carlo simulations.(46) (We refer to an article by Doubilet et al.(47) for an excellent overview and illustration of this method.)

A personal computer and software for clinical decision analysis, SMLTREE version 2.9+ (copyright Hollenberg, JP, Roslyn, NY, 1985-1993), were used to construct the tree and to perform the analyses. The tree was printed using SMLTREE's graphic interface.

Results

The decision dilemma

The assumption that pretherapy decision making in patients with head and neck cancer is challenging, often involving clinical dilemmas, is based on three specific considerations.

The first of these considerations is that the current standards for pretherapy dental intervention (7,20,21,23) primarily involve only gross dental pathology of teeth that must be extracted. They do not cover the area of "moderate" dental disease, for which alternative dental treatment options exit. For example, what type of intervention is indicated for teeth with pocket depths of 4-6 mm: no treatment, periodontal treatment, or tooth extraction? Is such a condition a significant DRF if these teeth will be exposed to the radiation used to treat the cancer? Is continuing dental management following radiation therapy of “moderate” dental disease a realistic possibility? Current literature gives no unequivocal answers to these questions. For example, a series of clinical cases presented by Epstein et al.(48) demonstrates that in carefully selected cases periodontal management is successful even after high-dose radiation therapy. However, Lockhard and Clark(22) conclude on the basis of clinical examinations of one hundred thirty-one head and neck cancer patients that 81% (59) of the dentulous patients who needed some form of dental intervention did not seek the indicated treatment. In these cases it is clear that unacceptable risks for cancer therapy complications will remain. Perhaps a more radical approach involving tooth extraction is more appropriate in these cases of low attitudes toward dental health.

For the purpose of the proposed MDDS presented here, we introduce the *dental risk factor*. DRFs are examined and identified at the level of each individual tooth and can be eliminated by dental intervention: either tooth extraction or dental treatment (including oral surgery, e.g. root resection). Clinical prediction rules(49) based on clinical and radiographic findings of dental disease were used to rank a dental condition as "high" or "moderate" risk. Table 2.2 gives the results of this ranking procedure. The definition of a DRF is: "dental disease unrelated to cancer or cancer therapy that directly and/or indirectly increases the risk for oral complications of cancer therapy." The term *indirect* implies that pre-existing dental disease increases the likelihood of post-cancer therapy tooth extractions or extensive dental treatment, which are major causes of trauma-induced complications (e.g. the onset of osteoradionecrosis following tooth extraction at an irradiated site).(50,51)

Not only do the criteria for tooth extraction cited above address only gross dental pathology, they are also formulated in rather broad, undefined terms. For example, teeth with “extensive periapicale lesions” should be extracted.(21) However, a descriptive term such as *extensive* is imprecise and subjective. Furthermore, the assessment of the endodontic condition of a tooth is not made exclusively on a single criterion such as periapicale condition; rather it is multi-criterial.(52,53)

The second consideration underlying the assumption that pretherapy decision-making in patients with head and neck cancer is challenging is based on recommendations by Stevenson-Moore and Epstein,(21,23) Beumer et al.,(9) and Jolly.(54) The planning of tooth extraction and dental treatment prior to radiation therapy should also consider factors related to cancer, cancer therapy, and medical conditions. This recommendation is not evident in the current guidelines for pretherapy dental intervention. We therefore introduce the *malignancy-related risk factor* (MRRF): defined as "nondental risk factor, related to cancer, cancer therapy, and the medical condition, that increases the risk of oral complications." MRRFs are examined and identified at organ (head and neck) and patient level. MRRFs cannot be eliminated by dental intervention. The MRRF scores appear in Table 2.3 and Fig 2.1.

The third consideration underlying the assumption that pretherapy dental decision-making frequently involves dilemmas is that optimal patient care also depends on thoughtful analysis of the tradeoffs between the benefits and drawbacks of clinical actions.(8,55-57) Can the ends justify the means? How effective is the pretherapy removal of questionable teeth in reducing the incidence of oral complications? Does this affect oral functioning? What are the adverse effects of pretherapy tooth extraction? What is the “optimal” oral outcome of the pretherapy dental interventions? To answer these questions, the various oral outcomes of the pretherapy dental interventions should be identified and assessed. The measuring of the outcome of intervention is a basic component of expected value decision making.(40-44,46,58) We used a category-scaling method,(59) differentiating between strategic and non-strategic teeth, to assign values to the outcomes of dental intervention. The procedure is as follows: the best outcome is given a value of 1, the worst outcome a value of 0. Direct scaling is used to assign values to all intermediate outcomes. They are then ranked in order of preference between the best and worst outcome. Outcome Values (Ovs) below O.3 are labeled "negative," thus undesirable. Table 2.4 summarizes the hierarchy of the OV’s.

On the basis of the three considerations discussed above, the dental decision dilemma is identified as follows: *Which pretherapy action --tooth extraction or dental treatment to eliminate DRFs-- leads to the optimal oral outcome, with respect to the MRRFs that are present?*

The decision problem is structured in the next steps of the decision analysis.

Table 2.2 Dental Conditions to assign Dental Risk Factor (DRF) Score

Clinical and Radiographic Findings (CRF)[a]	Weighting	
Periodontal disease		
Probing depth / Proximal bone loss[b]: 3 to 6 mm	Medium	
Probing depth / Proximal bone loss: > 6mm		High
Gingival recession: 3 to 6 mm	Medium	
Gingival recession: > 6 mm		High
Bleeding upon probing	Medium	
Spontaneous gingival bleeding		High
Furcation involvement / Bone loss in furcation area		High
Mobility < 1-2 mm side to side	Medium	
Mobility > 2 mm side to side and/or 1 mm vertical		High
Pulpal disease and periapical lesions		
Abnormal response to tests[c], no previous endodontic treatment, no rarefying osteitis[d]	Medium	
Abnormal response to tests, no previous endodontic treatment, rarefying osteitis		High
Swellings and/or sinus tracts		High
Rarefying osteitis, < 3mm, with adequate root canal filling[e], without (percussion) pain	Low/Medium	
Rarefying osteitis, < 3mm, with inadequate root canal filling[e], with (percussion) pain		High
Rarefying osteitis, > 3 mm		High
Condensing osteitis [f]/hypercementosis[g] with normal reactions to tests	Low	
Condensing osteitis with abnormal reactions to tests	Medium	
Internal/external root resorption		High
Extensive caries		
Primary caries < 2/3 of the clinical crown	Medium	
Primary caries > 2/3 of the clinical crown/pulpal involvement		High
Defective restoration[h] with secondary caries[i], no pulpal involvement	Medium	
Root caries < 1/2 of root circumference, no pulpal involvement	Medium	
Root caries > 1/2 of root circumference		High
Non Functional teeth		
Partially impacted (incompletely erupted) teeth or permucosal residual roots		High
Residual root tips not fully covered by alveolar bone and /or showing periodontal ligament or radiolucency		High
Fully impacted teeth,without follicle enlargement and fully covered by bone	Low	
Fully impacted teeth, with follicle enlargement and/or not fully covered by bone,		High
Oral Hygiene, dental awareness, co-operation		
Low level of oral hygiene, low dental awareness, lack of cooperation		High

[a] Identified at tooth level, which means tooth-related.

[b] Radiographic standard for interpretation of bone proximal bone loss is that the alveolar crestal bone must be greater than 3 mm from the CEJ.[69]

[c] Pulp sensitivity: cold, heat, electric (EPT) and percussion tests.

[d] Rarefying osteitis: radiolucent periapical bone destruction communicating with the periodontal ligament space via a discontinuity in the lamina dura.[70]

[e] Criteria for assessment of root canal obturation: The prepared and filled canal should contain the original canal and should be filled completely (0.5-2 mm from radiographic apex). No space between canal filling and canal wall should be seen. No canal space should be visible beyond the end point of the root canal filling. The whole canal system/ all roots should be obturated (Consensus Report European Society of Endodontology) [53]

[f] Hypersclerotic trabeculi in the bone adjacent to the periapical region and communicating with the periodontal ligament space.[70]

[g] Distortion of the apical third of the tooth root characterized by increased width while the periodontal ligament space and lamina dura remain unaltered.[70]

[h] Restorations are defective if any of the following conditions are present: marginal discrepancies >0.5 mm, part of the restoration missing, bulk fracture, or marginal staining of composites suggesting leakage.[71]

[i] True radiographic secondary (i.e., recurrent) caries and/or residual caries.[71]

Table 2.2 continued

Interpretation of Weightings to assign the Dental Risk Factor (DRF) Score:

- If *one or more* CRFs have a *High* Weighting, then DRF is High;
- If three or more CRFs have a *Medium* weighting , then DRF score is High;
- If one or two CRFs have a *Medium* weighting and no CRF has a *High* weighting, then DRF score is Medium;
- If no CRF has a *High* or *Medium* weighting, then DRF score is low.

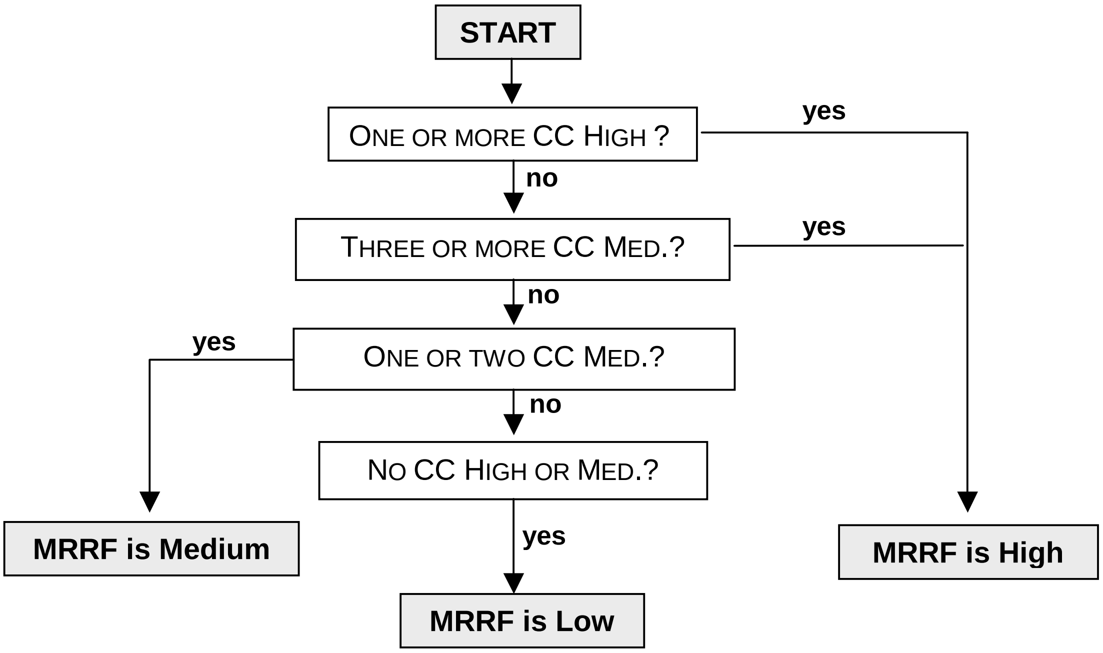

Figure 2.1. Flowchart for interpretation of clinical condition (CC) weightings (see Table 2.3) to assign MRRF score.

Table 2.3 Clinical Conditions to assign Malignancy Related Risk Factor (MRRF) Score

Clinical Conditions (CC)		**Weighting**
Radiation Therapy		
40 < RD < 55	Field includes >50 % of major salivary glands	Medium
40 < RD < 55	Field includes teeth in upper/lower jaw	Medium
RD > 55	Field includes teeth in lower jaw	High
RD > 55	Field includes teeth in upper jaw	High
Interstitial radiation therapy, teeth adjacent to radiating implant		High
Chemotherapy		High
Teeth in close proximity to tumor		High
Immediacy of radiotherapy: < 14 days		High

RD: radiation dose

Interpretation of Weightings to assign the Malignancy Related Risk Factor (MRRF) Score:

- If *one or more* Clinical Conditions (CCs) have a *High* weighting, then MRRF score is "High";
- If three or more CCs have a *Medium* weighting , then MRRF score is "High";
- If one or two CCs have a *Medium* weighting, and no CC has a *High* weighting, then MRRF score is "Medium";
- If no CC has a *High* or *Medium* weighting, then MRRF score is "Low".

Table 2.4 Hierarchical values of Oral Outcomes: Outcome Values (OV)

Clinical description	Outcome Value OV[b]
POSITIVE OUTCOME	
Functional tooth / strategic, healthy	1.0
Functional tooth/ strategic, following treatment of medium DRF condition/ MRRF med[a]	0.9
Functional tooth/ strategic, following treatment of medium DRF condition/ MRRF high[a]	0.8
Functional tooth/ strategic, following treatment of high DRF condition/ MRRF high/med	0.7
Non-functional tooth/non- strategic, following treatment of medium DRF condition/ MRRF med[a]	0.6
Non-functional tooth/non- strategic, following treatment of high/med DRF condition/ MRRF high[a]	0.5
Healthy, edentate segment of processus alveolaris	0.3
NEGATIVE OUTCOME, ORAL COMPLICATION	
Osteoradionecrosis or other serious oral complication	0.0

[a] The oral outcomes of dental intervention are classified using a hierarchical scale: Strategic Teeth (ST) have OV Values from 1.0 – 0.7. Non-Strategic Teeth (N-ST) have Outcome Values of 0.6 or 0.5 .

[b] The MRRFs have influence on OV: if MRRF is high, a tooth has a greater probability for post-therapy dental /oral complications (e.g. radiation caries) and therefore the OV is somewhat lower. The same is true for the DRF scores. A tooth following treatment of a high DRF condition has a greater probability for dental/oral complications than a tooth following treatment of a medium DRF condition. This difference is reflected in the OV.

Baseline decision algorithm

A baseline decision algorithm is a set of step-by-step instructions for solving a problem. In this model for MDDS they are as follows:

(1) Perform pretherapy oral screening and gather essential information (see Table 2.1).
(2) Assign DRF scores (see Table 2.2).
(3) Assign MRRF scores (see Table 2.3).
(4) Evaluate the extent to which patient's level of oral hygiene and cooperation can be favorably influenced, if necessary, and take action to do so (immediately, in future, or both).
(5) Identify the alternatives for dental intervention (either tooth extraction or dental treatment);
(6) Do a Probability Estimation (PE) --estimate the probability of each chance event-- and assign values to the various outcomes of each decision alternative. Positive and negative outcomes are differentiated. The positive outcomes are categorized as "outcome/strategic" if the tooth in question contributes significantly to oral functioning, and "outcome/non-strategic" if the tooth can be considered as non-strategic (the Outcome Values are summarized in Table 2.4);
(7) Calculate the Expected Values (EV) using the process of "folding back and averaging out," which is briefly explained below;

(8) Choose the alternative with the highest EV as the preferred course of action ("best option") to eliminate DRF; repeat this procedure until all decisions to eliminate all DRFs are taken;

(9) Carefully consider and judge patients' wishes, expectations, and attitudes towards dental treatment and dental health,(54) inasmuch as these are an essential part of the clinical decision-making. Determine whether all decisions to eliminate the DRFs are applicable to the patient: if so, then make a treatment plan; if not, then reconsider patient preferences and/or modify decisions for dental intervention until all decisions are applicable, and then make a plan to carry them out;

(10) Evaluate clinical outcomes over time and take additional measures if required.(7)

Decision tree

A decision tree is a schematic representation of the decision problem in a logical and temporal sequence. By convention, a decision tree is built from left to right, with decision nodes represented by squares and chance nodes by circles. The outcomes are specified in boxes at the "tips" of the branches, on the right. The branching of the decision tree for the model presented in this article is given in Fig 2.2. Only "high" and "moderate" risk factors are included. "Low" risk conditions were left out because they are not critical in this process of decision-making. Including only relevant aspects leads to an increased responsiveness of the model.(60,61)

The model's decision tree is made up of the following elements:

- eight decision nodes --points in the decision tree at which several clinical judgments (high or medium risk) or choices (the decision alternatives- tooth extraction or dental treatment) are made.
- eight chance nodes, at which chance (probability) determines which outcome state will occur (a positive outcome is and a negative is not desired). We have used Probability Estimations to rank these chances (probabilities) by order of magnitude;

Ovs --health states that occur as result of each dental intervention. As explained above and summarized in Table 2.4, hierarchical rankings (OVs) are assigned to the outcomes.

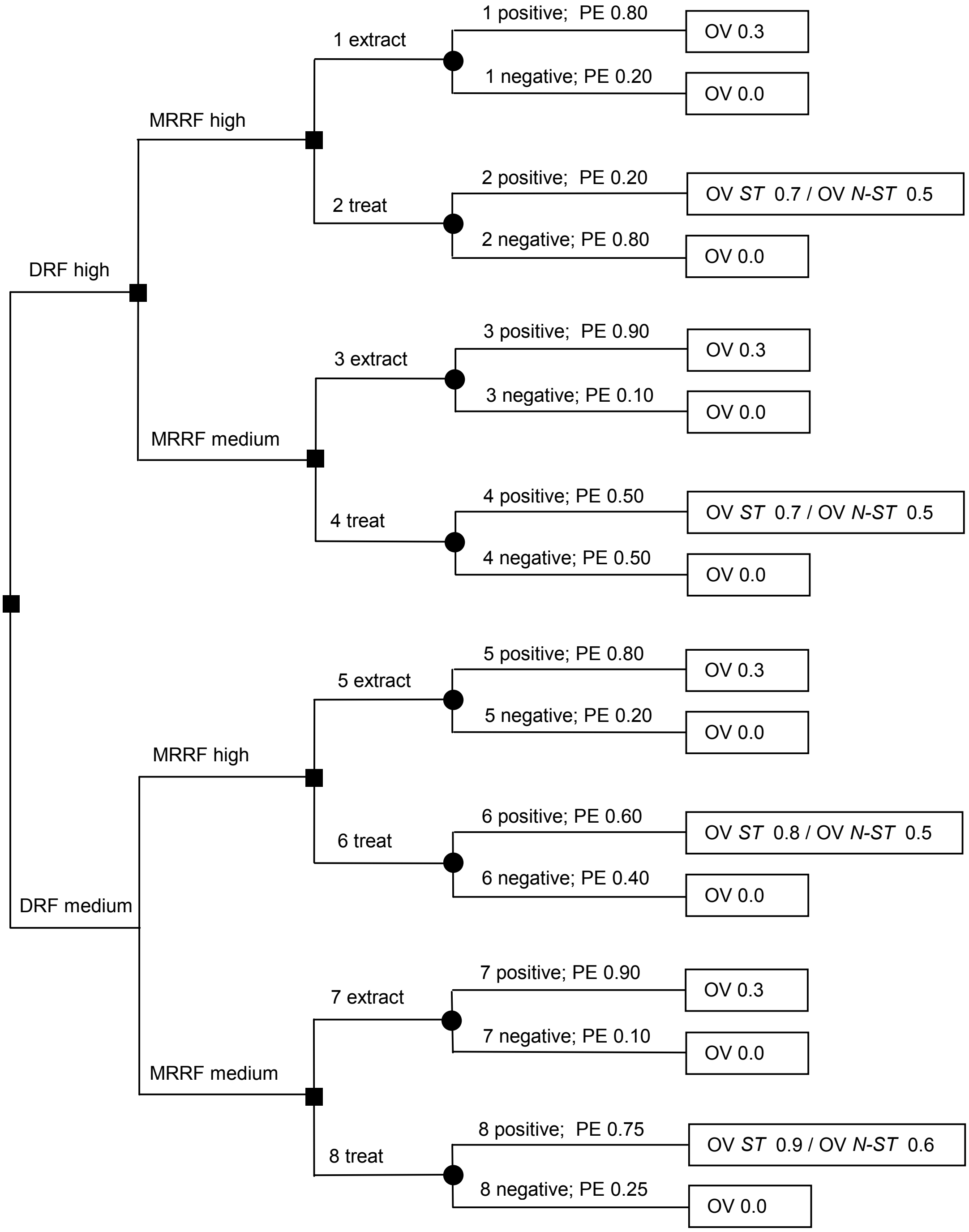

Figure 2.2 Graphical representation of decision tree: black square = decision node; black circle = chance node; *ST*, strategic tooth; *N-ST*, nonstrategic tooth. Values in boxes represent values of outcome of dental intervention. Table 2.4 summarizes hierarchy of Outcome Values (OVs)

Expected values and optimal decision alternatives

A calculation process called "folding back and averaging out" analyzes the decision tree. The process starts at the tips of the branches (Outcome Values). The Outcome Value (OV) is multiplied by the Probability Estimation (PE) of that outcome. This calculation is repeated for all outcomes emanating from the decision node being evaluated. The values are added together, rendering the Expected Value of the decision alternative. For example, the Expected Values of the decision alternatives branching out from the first decision node (DRF high/ MRRF high) are (as seen in Table 2.5):

Strategic tooth:

- EV (extract)= (0.3 x 0.80) + (0 x 0.20) = 0.24 (= optimal decision alternative)
- EV (treat) = (0.7 x 0.20) + (0 x 0.80) = 0.14

Non-strategic tooth:

- EV (extract)= (0.3 x 0.80) + (0 x 0.20) = 0.24 (= optimal decision alternative)
- EV (treat) = (0.5 x 0.20) + (0 x 0.80) = 0.10

The decision alternatives with the highest EV are the "optimal" decision alternatives. The EVs of all decision alternatives are given in the column labeled "*EV*", and the "best options" in the column "*Choose*" in Table 2.5.

Table 2.5 The decision tree displayed as a spreadsheet

Risk Condition		Decision Alternative	Outcome	PE[a]	Outcome Value (OV)[b]		Expected Value (EV)[e]		Choose:
DRF score	MRRF score				ST	N-ST	ST	N-ST	
High	High	Extract	Pos.	0.80	0.3	0.3	0.24	0.24	If ST[c]: extract If N-ST[d]: extract
			Neg.	0.20	0	0			
		Treat	Pos.	0.20	0.7	0.5	0.14	0.10	
			Neg.	0.80	0	0			
	Medium	Extract	Pos.	0.90	0.3	0.3	0.27	0.27	If ST: treat If N-ST: extract ≈ treat
			Neg.	0.10	.0	0			
		Treat	Pos.	0.50	0.7	0.5	0.35	0.25	
			Neg.	0.50	0	0			
Medium	High	Extract	Pos.	0.80	0.3	0.3	0.24	0.24	If ST: treat If N-ST: treat
			Neg.	0.20	0	0			
		Treat	Pos.	0.60	0.8	0.5	0.48	0.30	
			Neg.	0.40	0	0			
	Medium	Extract	Pos.	0.90	0.3	0.3	0.27	0.27	If ST: treat If N-ST: treat
			Neg.	0.10	0	0			
		Treat	Pos.	0.75	0.9	0.6	0.67	0.45	
			Neg.	0.25	0	0			

ST: if the tooth in question is a strategic tooth; *N-ST*, if the tooth in question is a nonstrategic tooth; *Pos*. positive; *Neg*. negative

[a] Reflects probability of such an event after tooth extraction or dental treatment. Positive and negative outcomes are differentiated --e.g., probability of a positive outcome of tooth extraction, if DRF and MRRF are high, is 0.80. This means that tooth extraction has an 80% chance of a positive, desired outcome (no osteoradionecrosis) and a complementary 20% chance of (1 – 0.80 = 0.20) of a negative outcome (osteoradionecrosis). For example, the chance of 0.2 is based on data from literature.[50]

[b] A hierarchic value is assigned to each outcome; this is explained in text and summarized in Table 2.4.

[e] Result of the calculation process of the “folding back and averaging out” the decision tree.

Probabilistic sensitivity analysis

The baseline estimates of probabilities (PEs) and of OVs were quantified through the use of direct ranking methods. This implies a degree of uncertainty and susceptibility to biases. Because the analysis of the model is done with these "estimates" it is called a *base-case analysis*.(58) In the Discussion, its limitations and strengths are outlined.

A sensitivity analysis (58) is carried out to see whether uncertainties in the estimates affect the robustness of the MDDS. If the optimal choices for dental intervention of the MDDS are sensitive to variation of the baseline estimates (PEs and OVs), then the potential use of the MDDS as a tool to develop clinical guidelines is limited. Further data collection is necessary in order to make accurate estimations. On the other hand, if the optimal choices are not influenced by variation of the baseline estimates, the model is considered to be robust and useful.

For the purpose of varying the baseline estimates, we assume that each PE and OV possesses a probability distribution and that these distributions are logistic-normal distributions, determined by their means and upper (97.5 %) and lower (2.5%) limits(47) (see Table 2.6). After multiple simulations (*n* =10.000) in which each PE and OV is randomly assigned a value taken from its distribution, the following is calculated: mean EV, standard deviation of the EVs, frequency with which each decision alternative is optimal, and 95% confidence intervals. The results of the probabilistic sensitivity analyses, using the second-order Monte Carlo simulations explained above, appear in Table 2.7.

Table 2.6 Data used in Probabilistic Sensitivity Analyses

Risk Condition		Decision Alternative	Outcome[a]	PE Value[b]			Outcome Value OV [a]					
							Strategic Tooth			Non-Strategic Tooth.		
DRF score	MRRF score			*2.5 %*	**50 %**	*97.5 %*	*2.5 %*	**50 %**	*97.5 %*	*2.5 %*	**50 %**	*97.5 %*
High	High	Extract	Pos.	*0.65*	**0.80**	*0.90*	*0.19*	**0.29**	*0.42*	*0.19*	**0.29**	*0.42*
		Treat	Pos.	*0.10*	**0.19**	*0.34*	*0.60*	**0.70**	*0.79*	*0.40*	**0.50**	*0.60*
	Medium	Extract	Pos.	*0.74*	**0.91**	*0.97*	*0.19*	**0.29**	*0.42*	*0.19*	**0.29**	*0.42*
		Treat	Pos.	*0.39*	**0.50**	*0.60*	*0.60*	**0.70**	*0.79*	*0.39*	**0.50**	*0.60*
Medium	High	Extract	Pos.	*0.65*	**0.80**	*0.90*	*0.19*	**0.29**	*0.42*	*0.19*	**0.29**	*0.42*
		Treat	Pos.	*0.49*	**0.60**	*0.69*	*0.70*	**0.80**	*0.87*	*0.39*	**0.50**	*0.60*
	Medium	Extract	Pos.	*0.80*	**0.90**	*0.96*	*0.19*	**0.29**	*0.42*	*0.19*	**0.29**	*0.42*
		Treat	Pos.	*0.60*	**0.75**	*0.86*	*0.80*	**0.90**	*0.95*	*0.50*	**0.60**	*0.69*

ST, Tooth in question is a strategic tooth; *N-ST*, tooth in question is a nonstrategic tooth; *Pos*, positive; *Neg*, negative.

[a] Negative outcome conditions need not be described inasmuch as their probability distributions are complementary to the distributions of the positive outcomes (sum of the PE values of Pos and Neg is 1) and the OV of Neg. are zero by default.

[b] Distributions of PEs and OVs are assumed to be logistic-normal distributions, determined by their **means** and upper or lower *limits* of their 95% confidence ranges.47 After multiple simulations (*n* =10.000) in which each PE and OV is randomly assigned a value taken from its distribution (the shaded columns), the following is calculated: mean and standard deviation of EV, frequency with which each decision alternative is best, and the 95% confidence intervals of these frequencies. These data appear in Table 2.7.

Table 2.7 Results of probabilistic sensitivity analyses with second-order Monte Carlo simulations (n= 10.000) [a]

		DECISION ALTERNATIVE			
Decision node		ST Extract	ST Treat	N-ST Extract	N-ST Treat
DRF High / MRRF High	Mean EV [b]	0.24	0.14	0.24	0.10
	SD of EV	0.05	0.04	0.05	0.03
	Frequency “Best” [c]	94%	6 %	98%	2 %
	95% Confidence Interval [d]	93.5-94.5%	5.5-6.6%	97.7-98.3%	1.7-2.3%
DRF High / MRRF Med	Mean EV	0.27	0.35	0.27	0.25
	SD of EV	0.05	0.04	0.05	0.03
	Frequency “Best”	12 %	88%	61%	39%
	95% Confidence Interval	11.4-12.6%	87.4-88.6%	60.1-61.9%	38.1-39.9%
DRF Med /MRRF High	Mean EV	0.24	0.48	0.24	0.30
	SD of EV	0.05	0.06	0.05	0.04
	Frequency “Best”	1%	99%	17%	83%
	95% Confidence Interval	0.8-1.2%	98.8-99.2%	16.3-17.7%	82.3-83.7%
DRF Med / MRRF Med	Mean EV	0.27	0.67	0.27	0.44
	SD of EV	0.05	0.07	0.05	0.06
	Frequency “Best”	1 %	99 %	2%	98%
	95% Confidence Interval	0.8-1.2%	98.8-99.2%	1.7-2.3%	97.7-98.3%

SD, Standard Deviation.

[a] In each simulation a PE and OV are randomly assigned a value taken from their distribution (see Table 2.6). The following is calculated (these headings appear in column 2): mean EV, SD of EV, frequency with which each decision alternative is “best” (calculated using the "folding back and averaging out" as explained in text), and the 95% confidence intervals.[47] The results appear in rows to the right of entries in column 2. Simulations (*n*=10.000) were performed for both conditions: if tooth in question is strategic (ST) and non-strategic (N-ST). In total 2 x 10.000 = 20.000 calculations were made for each of the four risk conditions.

[b] Mean Expected Values (EV) correspond with the baseline EVs (Table 2.5)

[c] Frequencies of “Best “ Decision Alternatives are binomially distributed.

[d] Using standard techniques for normal approximation to the binomial distribution, the 95 % confidence interval is approximately as follows: $p \pm 1.96 \times \sqrt{\ }\,(p \times 1-p/n)$ where p= frequency of "Best" and n= number of simulations (n=100 by default).

Discussion

We used clinical decision analysis to design a MDDS in patients with head and neck cancer in order to solve decision dilemmas associated with pretherapy dental screening. Current management guidelines address only gross dental pathology, are formulated in rather broad terms, do not fully consider malignancy-related risk factors, and do not analyze the tradeoffs between the benefits and drawbacks of pretherapy dental interventions.

The MDDS presented here uses a decision tree to separate the decision dilemma into three components: DRFs, MRRFs, and OVs. The components differ with respect to their "dimension" or the "domain" to which each belongs. The DRFs are of primary interest and are tooth-related. They are described in terms of clinical criteria and can be eliminated by dental intervention. The MRRFs, however, are disease-related and cannot be influenced through pretherapy dental management. The Outcome Values (OVs) belong to the domain of oral functioning(57) and have a strong impact on the quality of life.(62) We have differentiated between strategic and nonstrategic teeth because of the implications for oral function.

The decision-analytic approach is qualitative because it uses precisely defined clinical criteria instead of broadly described dental pathologic conditions. The oral outcomes of the dental intervention are incorporated into the model. In addition, the approach is also quantitative: the clinical criteria and conditions are transformed into PEs and OVs. The calculation process called "folding back and averaging out" enables identification of the optimal option for dental intervention.

The model identifies four different pretherapy risk conditions, represented by the four decision nodes in Fig 2.2. Table 2.5 summarizes all decision results of the MDDS. The MDDS gives clear answers to the decision problem in three of the four risk conditions. Only when the DRF score is high, the MRRF score is medium, and the tooth in question is nonstrategic does the MDDS fail to indicate the "optimal" pretherapy action. ("If N-ST: extract ≈ treat," in the column labeled *Choose* in Table 2.5). Under this risk condition the "optimal" decision apparently depends more strongly on complementary decision factors such as clinical possibilities and costs, timing of the dental intervention, and follow-up period necessary to evaluate clinical success or failure. However, if under this risk condition (DRF high/MRRF medium) the tooth in question is strategic, dental treatment is the optimal option. Here the effectiveness of the MDDS in analyzing the tradeoffs between the benefits and drawbacks of the dental intervention is evident. In this case the benefit of maintaining of oral function by retaining a strategic tooth (through dental treatment) weighs more heavily than does the benefit of preventing of oral complications when extracting the tooth; it is thus worthwhile to take the risk. It should be emphasized that retaining strategic teeth in order to maintain or to improve oral function is extremely important for these patients because of the significant consequences for the quality of life.(1,8,57,63-65)

As explained earlier, instead of objective data, PEs and estimated OVs were used in this model for dental decision-making, and it is therefore called a *base-case analysis*. According to Weinstein and Fineberg,(58) this does not prevent the model from producing pragmatic conclusions. They point out that clinical decisions must after all be made. Without clinical decision analysis, a clinician also uses subjective judgments of uncertain events. These judgments are not always "structured" in great detail and are not easily incorporated into the intuitive process of mental decision-making.(58,66) Using clinical decision analysis permits a more logical approach. It divides the decision-making process into manageable components. Most important, the approach is quantitative,(46,58,67) and is intended to aid clinicians in deciding what they should do under a given set of circumstances. In addition, it allows sensitivity analyses to be carried out. All this will result in decisions that are more consistent with the underlying uncertainties and outcome values. Moreover, clinical decision-making will also reveal those areas in which further clinical research would be most valuable.(58) However, an important limitation of using a "base-case analysis" comes from the built-in judgment biases(68) and the instability over time of the estimations through changing circumstances

--e.g. changes in cancer therapy and patient compliance(3) and changes in prognosis of disease control.

For the purpose of a priori testing of the model, we preformed probabilistic sensitivity analyses. We used second order Monte Carlo simulations(47) with 95% confidence intervals. As explained earlier, we used estimations based on the literature and our clinical experience to assign values to probabilities and outcomes. It must be pointed out here that instead of absolute values we used hierarchical rankings. For example, a sound tooth has a higher OV than an endodontically treated tooth, and a tooth extraction (ie, an edentulous site) is better than a strong chance of osteoradionecrosis. Given a high MMRF, the probability of a negative outcome is greater when retaining a tooth with a high DRF than when such a tooth is extracted. The probabilistic sensitivity analysis was performed to allow exploration of the dependence of the optimal decisions on the change of the apparent rankings.

The results of the probabilistic sensitivity analysis indicate that, in general the conclusions of the model are robust. The frequencies and confidence intervals for the "optimal" interventions are summarized in Table 2.7. It should be emphasized that the robustness applies particularly to the structure or "internal logic" and "coherence"(66) of the model as well as to the ranking or "interrelation" of the baseline data. The robustness is somewhat lower in three risk conditions: (1) DRF high /MRRF medium for strategic teeth, and (2) DRF high /MRRF medium for nonstrategic teeth, and (3) DRF medium/MRRF high for nonstrategic teeth. In these cases there remains some uncertainty as to what the optimal decisions are. We have already discussed the importance of the modifying decision factors when DRF is high, MRRF medium, and teeth are non-strategic (i.e. situation 2). In the remaining two risk conditions--(1) DRF high/MRRF medium for strategic teeth, and (3) DRF medium/MRRF high for non-strategic teeth-- the probabilistic sensitivity analyses reveal that the MDDS will result in the opposite option for dental intervention in approximately 10% to 20% of all simulations. It appears that the subjective estimates used in these areas should be assessed more exactly. It is clear that clinical research in these areas is most useful.

Our overall conclusion is that the MDDS is a useful tool for the development and analysis of clinical guidelines. Building the model has helped us to gain more understanding of the decision dilemmas involved, and using the concept of EV decision-making has given us more insight into how risks and outcomes of dental intervention affect the process of clinical decision-making. We believe that the MDDS has great potential to assist clinicians in dealing with pretherapy dental decisions in patients with head and neck cancer. However, we would strongly emphasize that the principal role of the clinician in choosing the optimal strategy for dental intervention is of paramount importance.

Evaluation of the clinical effectiveness of the model as an aid for clinicians should be carried out with scientific rigor before assimilation into clinical practice can take place. Clinical testing of the model should result in objective data that will make an a posteriori validation possible. A representation of the MDDS in the format of a 2X2 contingency table (Table 2.8) permits the comparison and analysis of clinical data from retrospective or prospective clinical studies in this area. This format is especially useful if a Chi-Square statistical evaluation of the relationship between the DRFs and MRRFs is to be carried out.

Table 2.8 Results of the Dental Decision Making model displayed as a 2X2 contingency table

	DRF High		DRF Medium	
MRRF	Strategic	Non-Strategic	Strategic	Non-Strategic
High	Extract	Extract	Dental treatment	Dental treatment
Medium	Dental treatment	Extract ≈ Dental treatment [a]	Dental treatment	Dental treatment

[a] Best decision depends on modifying decision factors: consistency of plan, time required for evaluation of dental treatment, patient's preferences, costs, etc.

At present we are conducting an international, multi-center clinical study in order to further validate the MDDS. In addition, the validity of the clinical and dental criteria and of the Malignancy Related and Dental Risk Factors Scores is being tested using "clinical judgment analysis" of the opinions of clinicians.(66) For that purpose an international consensus project has been set up at a number of locations in the United States of America, Australia, and Europe.

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CHAPTER 3

Preradiation dental extraction decisions in patients with head and neck cancer

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Abstract

Objective

The first objective of this international survey was to study how dental- and radiotherapy-related risk factors influence clinicians' preradiation dental decision-making in patients with head and neck cancer, and to evaluate clinicians’ degree of certainty in making such decisions. A further objective was to examine the correlation of clinicians' policies with the policy based on a model for dental decision support (MDDS), presented in an earlier article.

Study design

A consensus questionnaire was mailed to 54 oral-maxillofacial surgeons and hospital-based dentists at a number of international locations. The responses were aggregated and anonymously analyzed through use of a multiple regression procedure.

Results

Forty-four clinicians returned the questionnaire (response rate of 81%). Nine clinicians (20%) were using printed clinical guidelines for preradiation dental screening. Eighty-eight percent of clinicians’ preradiation decisions and 49% of their certainty could be explained by the studied risk factors. Not all risk factors were significant at $p < 0.001$. Clinicians’ policies showed high correlation (0.85) with the policy based on the model for dental decision support.

Conclusions

The findings support our previous assumption that policies in this field seem to be primarily based on clinical experience and opinions rather than on evidence-based clinical guidelines. We conclude that the clinical usefulness and validity of the model for dental decision support should now be tested and that it could also serve as a training tool.

Introduction

Preradiation dental decision making in head and neck cancer patients for the purpose of identifying and eliminating risk factors for the oral complications of cancer therapies is often challenging.(1) In our view, current management guidelines(2-4) address only gross dental pathoses, are formulated in rather broad terms, and do not fully assess the trade-offs between the benefits and drawbacks of preradiation dental extractions.

To contribute to the development of guidelines for preradiation dental screening, we proposed a model for dental decision support (MDDS) in this field.(1) The MDDS was designed to help solve decision dilemmas and to develop evidence-based clinical guidelines for preradiation dental screening. Its robustness and coherence(5) were a-priori tested, using the method of probabilistic sensitivity analysis.(6) Our overall conclusion was that the proposed MDDS is useful as a tool for the development and analysis of clinical guidelines.

In order to further validate the MDDS we set up an international survey to analyze the policies of clinicians. The first objective of the survey was to study how variations in dental- and radiotherapy-related risk factors influence clinicians' preradiation dental decision-making. More specifically, is a decision for preradiation dental extraction affected by:

(1) the dental condition of teeth (moderate versus gross dental pathosis) and/or
(2) the functionality of a tooth (strategic versus nonstrategic) and/or
(3) the location of teeth (upper versus lower jaw) and/or
(4) the radiation dose on the teeth (40 - 55 Gray vs > 55 Gray) ?

Do these 4 risk conditions influence the degree of certainty the clinician has in the decision? The second objective of the survey was to examine the matching of the policies of the clinicians with the policy based on the proposed MDDS. A correlation analysis was used to accomplish this second objective.

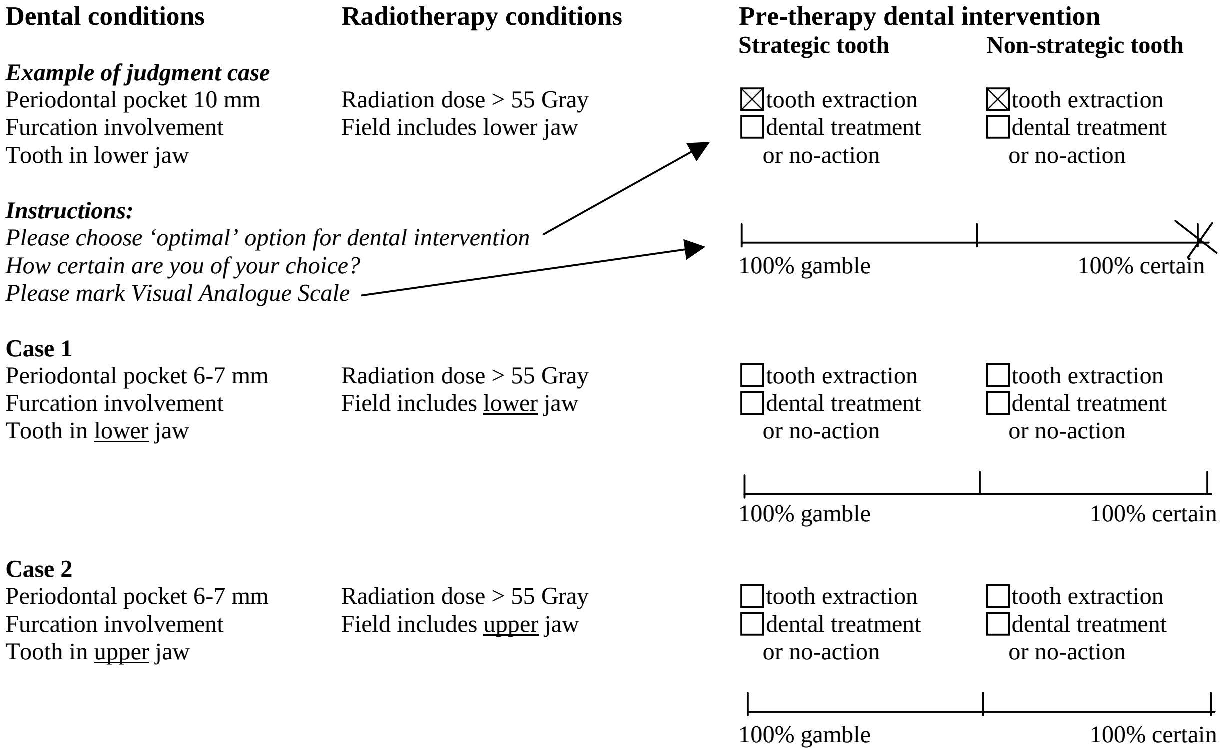
Material and methods

A judgment analysis questionnaire was mailed to 54 oral-maxillofacial surgeons and hospital-based dentists at a number of locations in North America, Australia, and Europe. Their names and addresses were obtained by contacting the secretaries of their professional organizations. The secretaries were asked to select those clinicians who were expected to be familiar with(7) and experienced in the domain of preradiation dental decision making.

The questionnaire was constructed, using specific design considerations described by Cooksey,(5) from 48 simulated paper cases in a fractional factorial design.(8,9) This type of design allows the comparison of a number of (risk) conditions or factors. It should be noted that not all relevant decision factors, such as patient's previous dental performance or timing considerations, could be included in the questionnaire. The importance of these factors has been discussed previously.(1) The questionnaire addresses those cases in which decision making was expected to be critical. Cases in which past dental performance and possibilities for dental care are minimal, for example, usually lead to partial or full mouth clearance, as previously explained.(1) These "obvious cases" were left out in order to improve the responsiveness of the questionnaire.(10;11) Six replicated cases were included to permit analysis of the reliability of the responses, using Cronbach's alpha.

The clinicians were informed of the objectives of the survey and assured of its confidentiality and anonymity. They were queried concerning their professional qualifications and clinical posts, and asked whether they were involved in the preradiation dental screening of patients with head and neck cancer. In addition, the clinicians were asked to estimate the average number of new patients with head and neck cancer per year in their hospital or institute and to return printed guidelines for preradiation dental screening if any were available. They were also invited to make written comments on the questionnaire.

The paper cases were presented to the clinicians in the format of verbal categories derived from the aforementioned MDDS, which had not yet been published. Fig 3.1 displays edited examples of the questionnaire format. Clinicians were asked to choose the optimal option for dental intervention. In addition, they were instructed to express the degree of certainty in the appropriateness of their decision on a visual analogue scale (from a 100% gamble to 100 % certainty). The paper cases were presented in a particular order to avoid response bias --e.g. clinicians' tendency to repeat the same score patterns.(12)



Dental conditions	**Radiotherapy conditions**	**Pre-therapy dental intervention** **Strategic tooth**	 **Non-strategic tooth**
Example of judgment case Periodontal pocket 10 mm Furcation involvement Tooth in lower jaw	Radiation dose > 55 Gray Field includes lower jaw	☒tooth extraction ☐dental treatment or no-action	☒tooth extraction ☐dental treatment or no-action
Instructions: *Please choose 'optimal' option for dental intervention* *How certain are you of your choice?* *Please mark Visual Analogue Scale*		100% gamble	100% certain
Case 1 Periodontal pocket 6-7 mm Furcation involvement Tooth in lower jaw	Radiation dose > 55 Gray Field includes lower jaw	☐tooth extraction ☐dental treatment or no-action	☐tooth extraction ☐dental treatment or no-action
		100% gamble	100% certain
Case 2 Periodontal pocket 6-7 mm Furcation involvement Tooth in upper jaw	Radiation dose > 55 Gray Field includes upper jaw	☐tooth extraction ☐dental treatment or no-action	☐tooth extraction ☐dental treatment or no-action
		100% gamble	100% certain

Figure 3.1 Questionnaire format (sample).

We first analyzed the questionnaire through use of descriptive statistics. No attempt was made to compare the results originating from each international location. Responding clinicians were treated as a single group. The first analysis resulted in the aggregated totals for extraction versus treatment and no-action of each paper case and the mean rates and SDs of clinicians' certainty in making the decisions. The categorical independent variables (IV's), summarized in the first column of Tables 3.1 and 3.2, were transformed into discrete dummy variables through use of a dummy-coding scheme.(13) A standard multiple regression procedure was then used to analyze the relationships between the dependent variables and the independent variables, a process that resulted in two regression models. The unstandardized regression coefficients were transformed to relative regression coefficients, which are an indication of the relative importance of the independent variables.(5,14) The underlying assumptions of both the multiple regression models were tested using normal probability plots and "residual-predicted" scatterplots.(5,14,15)

A personal computer and a software package for statistical analysis (SPPS 8.0 with Advanced Statistic option, SPSS Inc, Chicago, Ill) were used for the analyses.

Table 3.1 Parameters of standard multiple regression analysis: dependent variable = EXTR

Independent Variable	*Regression coefficient*	*Relative regression coefficient*	*Significance level P. less than ….*
Constant	-22.698	21 %	.001
DP	21.774	20 %	.001
DE	23.019	21 %	.001
DI	20.598	19 %	.001
RTX	9.211	10 %	.001
JAW	3.632	3 %	.100
STRAT	-6.361	6 %	.005

R = .935 (p <.001), R Squared = .874;
EXTR, extraction decision; *DP*, periodontal condition; *DE*, endodontic condition;
DI, impacted teeth; *RTX*, radiation dose; *JAW*, location of tooth;
STRAT, functionality of tooth.

Table 3.2 Parameters of standard multiple regression analysis: dependent variable = CERTAIN

Independent Variable	*Regression coefficient*	*Relative regression coefficient*	*Significance level P. less than ….*
Constant	80.953	88 %	.001
DP	1.038	2 %	.909
DE	-.614	0 %	.659
DI	-2.067	3 %	.226
RTX	4.022	4 %	.001
JAW	.282	0 %	.836
STRAT	-2.762	3 %	.041

R = .694 (p <.001), R Squared = .482;
CERTAIN, Clinicians' level of certainty.
(For other abbreviations, see footnote to Table 3.1)

Results

Forty-four clinicians returned the questionnaire and provided usable data for analysis. This is a response rate of 81%. All participants, oral-maxillofacial surgeons (n = 21; 48%) or hospital-based dentists (n = 23; 52%); all stated that they were familiar with and experienced in preradiation dental screening of patients with head and neck cancer. In all, the clinicians represent in total 30 general or specialized hospitals or cancer institutions. The total estimated number of new patients with head and neck cancer per year for all institutions was 6,500. The median number of new patients per hospital or institute was 100 patients (range, 15 - 900).

Nine clinicians (20%), representing 3 hospitals/institutions (one in North America and the other two in Europe) reported that they were using printed clinical guidelines for preradiation dental screening. Comments written on the questionnaires revealed that clinicians find judgment and decision making with respect to paper cases to be rather constraining. Some clinicians pointed out that lack of comprehensive clinical information affected their judgment performance, leading to less certainty in the decisions. However, this did not prevent a number of these participants from making very supportive comments on the project. Some clinicians emphasized that their decision-making in clinical practice was largely influenced by patients' previous dental performance and by socio-economic considerations. They regretted that these factors were not included in the questionnaire.

Descriptive statistics produced frequencies of dental extraction decisions over the paper cases and mean rates of clinicians’ certainty. A summary of these results appears in Tables 3.3 and 3.4. The reliability index based on Cronbach's alpha was .81. The multiple regression analyses produced 2 models that included all independent variables. Inspection of the normal probability plots and "residual/predicted" scatterplots revealed no major violations of the regression assumptions. Tables 3.1 and 3.2 display the unstandardized regression coefficients, and constants, the relative regression coefficients, and the R and R^2 for each regression model. The regression coefficient of the extraction decision (EXTR) and the clinicians' level of certainty (CERTAIN) were R = .94 and R = .69, respectively; both differed significantly from zero ($P < .001$). With the exception of the independent variable location of tooth (JAW), all independent variables contributed significantly to the explanation of EXTR. CERTAIN could be significantly explained only by the independent variable radiation dose (RTX), with $P < .001$. The contribution of the other independent variables was not significant at a .001 probability level. (see Table 3.2). In all, on the basis of the values of R^2, 88% of clinicians' preradiation decisions and 49% of their certainty could be explained by variations in dental-related and radiotherapy-related risk factors.

The extent to which the policies of the clinicians correlate with the MDDS-based policy is high. A correlation coefficient of 0.85 was found.

Table 3.3 Frequencies of preradiation dental extractions versus treatment/no-action and mean clinicians' certainty

			Pre-radiation Dental Intervention		
Dental Condition, tooth in radiation field	*Radiation dose*	*Radiation field includes …*	*Extraction/ no-treatment totals*[1]	*Mean certainty (%)*	*SD (%)*
Fully impacted tooth (e.g. third molar) without follicle enlargement and fully covered by bone	>55 Gy	Lower jaw	11/32	81	20
Fully impacted tooth (e.g. third molar) with follicle enlargement and not fully covered by bone	>55 Gy	Lower jaw	35/9	84	24
Fully impacted tooth (e.g. third molar) with follicle enlargement and not fully covered by bone	40 - 55 Gy	Lower jaw	31/13	82	24
Incompletely erupted tooth (e.g. third molar)	>55 Gy	Lower jaw	42/2	90	19

[1] Options for dental intervention include: *extraction*, (surgical) removal of tooth, *no-treatment*, tooth is left in situ.

[2] Mean of clinicians' certainty of the appropriateness of their decision, measured on a visual analogue scale: 0% certain = 100% gamble, 100% certain = 0% gamble.

Table 3.4 Frequencies of preradiation dental extractions versus treatment and means of clinicians' certainty

			Preradiation dental intervention					
			Strategic tooth			*Non-strategic tooth*		
Dental condition of tooth in radiation field	*Radiation dose*	*Radiation field includes ..*	*Extraction/ treatment totals*[1]	*Mean certainty*[2] *(%)*	*SD (%)*	*Extraction/ treatment totals*	*Mean certainty (%)*	*SD (%)*
No periodontal pocket, sulcus depth: 1-3 mm.[3]	>55 Gy	Lower jaw	0/ 44	93	15	0/ 44	95	9
Periodontal pocket 3-5 mm bleeding upon probing	> 55Gy	Lower jaw	6/ 38	85	17	8/ 36	89	14
Periodontal pocket 6-7 mm, furcation involvement	>55 Gy	Upper jaw	31/ 13	84	25	40/ 4	94	13
		Lower jaw	44/ 0	90	21	44/ 0	95	13
Periodontal pocket 6-7 mm, furcation involvement	40-55 Gy	Lower jaw	33/ 11	81	23	38/ 6	90	14
Periodontal pocket 3-5 mm, bleeding upon probing, poor overall dental health	None	Either jaw	1/ 43	83	21	7/ 37	81	22
Periodontal pocket 6-7 mm, furcation involvement, poor overall dental health	None	Either jaw	14/ 30	81	20	26/ 18	80	16
Periodontal pocket 6-7 mm, furcation involvement, tooth adjacent to radiating implants	Interstitial	Lower jaw	39/ 5	88	15	41/ 3	92	11
Rarefying osteitis [4] Ø < 3mm) no root canal filling, percussion pain	>55 Gy	Upper jaw	12/ 32	85	17	23/ 21	81	24
		Lower jaw	20/ 24	84	19	31/ 13	85	19
Rarefying osteitis (Ø > 3mm) inadequate root canal filling[5], percussion pain	>55 Gy	Upper jaw	30/ 14	86	19	41/ 3	91	16
		Lower jaw	40/ 4	86	23	42/ 2	95	10
Rarefying osteitis (Ø > 3mm) no root canal filling, abnormal response to pulp sensitivity tests	>55 Gy	Lower jaw	26/ 18	82	21	34/ 10	88	17
Condensing osteitis[5], no root canal filling, abnormal response to pulp sensitivity tests	>55 Gy	Lower jaw	19/ 25	82	18	28/ 16	86	16
Defective restoration[6] with secondary caries, no pulpal involvement	>55 Gy	Lower jaw	2/ 42	89	14	9/ 35	90	16

[1] Options for dental intervention include: *extraction* (surgical) removal of tooth; *treatment*: dental treatment (including e.g. surgical endodontics).

[2] Mean of clinicians' certainty in the appropriateness of their decision, measured on a visual analogue scale, 0% certain = 100% gamble; 100% certain = 0% gamble.

[3] No dental treatment other than prophylaxes is required in this particular case.

[4] Rarefying osteitis: radiolucent periapical bone destruction communicating with the periodontal ligament space via a discontinuity in the lamina dura.

[5] Condensing osteitis: hypersclerotic trabeculi in the bone adjacent to the periapical region and communicating with the periodontal ligament space and having a distinct border.

[6] Restorations are defective if any of the following conditions are present: marginal discrepancies > 0.5 mm, part of the restoration missing, bulk fracture, or marginal staining of composites suggesting leakage.

Discussion

This international survey, using a judgment analysis questionnaire, showed not only great similarities in the preradiation dental extraction policies of 44 clinicians but also a high correlation with the MDDS. In addition, the clinicians had a rather high overall degree of certainty (mean, 86.3 %, SD, 18.6%) in the appropriateness of their decisions, which was significantly correlated only with the radiation dose on teeth.

As cues for clinicians' extraction decisions, dental conditions (independent variables: periodontal condition, endodontic conditions, and impacted teeth) which altogether had a relative importance of 62% (Table 3.1), were far more important than RTX, which had a relative importance of 10%, and tooth functionality, which had a relative importance of 6%. The similarity in clinicians' policies is lower in the case of moderate dental pathosis (e.g. teeth with periodontal pockets of 3-5 mm and bleeding upon probing), condensing osteitis, or fully impacted third molars in the lower jaw (Tables 3.3, and 3.4, Fig 3.2). Tooth location (upper versus lower jaw) did not significantly contribute to the decision-making.

This survey thus shows that given optimal conditions such as favorable past dental performance and possibilities for dental care, clinicians' pretherapy dental decision making is mainly influenced by dental conditions. Yet clinicians' degree of certainty in the appropriateness of their decisions is significantly influenced only by the radiation dose on teeth and not by dental conditions or tooth functionality. All this could support our previous assumption(1) that clinical policies in this field seem to be based primarily on clinical experience and opinions and not on evidence-based clinical guidelines. This conclusion is strengthened by our discovery of the limited use of printed guidelines.

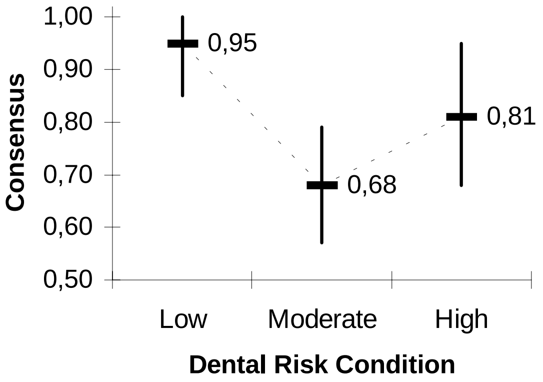


Figure 3.2. Mean levels of clinicians' consensus for all 3 dental risk conditions (vertical lines represent SDs). Consensus was calculated by dividing majority of clinicians of each paper case by total number of clinicians (n = 44). 1.00, 100% consensus; 0.50, no consensus (i.e. 50% of clinicians favored one type of intervention and 50% favored the other type).

Because the responding clinicians are involved in the multidisciplinary care of nearly 6,500 new head and neck cancer patients per year, we believe that the results of this survey are not only important for further validation of the MDDS, but are also noteworthy for clinical practice.

As a factor that influenced clinicians' extraction decisions, periodontal condition had a relative importance of 20%. All clinicians agreed on preradiation extraction of strategic and non-strategic teeth in the lower jaw with periodontal pocket depth of 6 mm and more and with root furcation involvement if they were within the planned radiation field of more than 55 Gy. This consensus corresponds with current management guidelines.(2-4) When non-strategic teeth with advanced periodontal disease were located in the upper jaw within a planned radiation field of more than 55 Gray, 40 clinicians (91%) judged that extraction was the optimal strategy; 31 clinicians (70 %) would extract strategic teeth under these conditions. In comparison with the lower jaw (with respect to which 100 % of the respondents favor the extraction of strategic and non-strategic teeth) the upper jaw is obviously associated with less concern among a minority of clinicians that teeth with severe periodontal disease in the upper jaw may cause serious oral complications such as osteoradionecrosis (ORN), either directly or following post-radiation extraction. From the periodontal epidemiologic and management points of view, teeth in the upper jaw with pockets larger than 6 mm and with furcation involvement are not of less concern than teeth in the lower jaw.(16-19) Periodontal care of such advanced conditions is time-consuming and requires optimal patient compliance.(20-24) Many epidemiological surveys have demonstrated that severe periodontitis exists in a very small proportion of the population and that patients in the lower socio-economic and educational groups are at significantly greater risk for severe periodontitis.(25) A substantial proportion of patients with head and neck cancer belong to these risk groups.(26;27) Inasmuch as non-compliance and low interest in oral health are frequently encountered in patients with head and neck cancer,(28-31) the MDDS complies with the view of most clinicians and advises pre-therapy extraction of teeth with advanced periodontitis, if they are within a planned radiation field over 55 Gy, regardless of whether they are in upper or lower jaw.

Before a radiation dose of over 55 Gy is received, should nonvital teeth exhibiting rarefying osteitis and percussion pain be extracted or endodontically treated, surgical endodontics included? (The question assumes that practical and economic considerations allow such a choice). Almost three fourths of the clinicians (73 %) were in favor of endodontic treatment of strategic teeth in the upper jaw if the periapical lesion was less than 3 mm in diameter. If a strategic tooth with such an endodontic condition was located in the lower jaw, the percentage dropped to 54%. If the lesion exceeded 3 mm in diameter, 41 % of the respondents were in favor of endodontic treatment of a strategic tooth in the lower jaw, whereas if the tooth had in addition an inadequate root canal filling, a vast majority --91%-- was in favor of extraction. Thus, the decisions were influenced by the diameter of the periapical lesion and by whether endodontic treatment was a primary treatment or involved retreatment. Clinicians' policies in this area coincide with current approaches for endodontic therapy(32;33) in which success rates between 70% and 95% have been reported.(33-35) Whether these success rates can also be achieved in cases in which an endodontically treated tooth will subsequently receive radiation could not be deduced with confidence from the literature. According to Kielbassa et al.,(36) several studies have shown that success for endodontic treatments carried out *after* radiation is not severely impaired by previous radiation therapy; prospective clinical surveys providing evidence-based information would be very helpful in determining whether this is also true for endodontic (re)treatments, endodontic surgery included, carried out *before* radiation therapy.

Tooth functionality had a relative importance of only 6% in clinicians' extraction decisions. Maintaining of oral function by retaining strategic teeth was apparently less important than minimizing the risk of oral complications by extracting strategic teeth. The MDDS is based on the principle that optimal patient care also depends on thoughtful analysis of the tradeoffs between the benefits and the drawbacks of clinical actions.(37-40) The model shows that, in selected cases and under certain risk conditions, it is worthwhile with regard to better patient outcomes to accept some degree of risk of an adverse outcome.(1) However, abundant evidence from judgment analysis studies suggests that the aversion to "risky choices" does not depend only on the mathematic weighting of probabilities and outcome values, on which method the MDDS is mainly based; decision-makers also use "clinical wisdom" and a number of simplifying operations called *heuristics*, which can lead to biases in judgments and decisions.(41) Nonetheless, we believe that opinion-based and experience-based decision-making is an essential part of the clinical thought process and that the clinician's role in reaching the optimal decision is of paramount importance.(1) In our survey, this is confirmed by the high correlation found between the policies of the responding clinicians and the MDDS. This finding might impair the supplementary usefulness of evidence-based decision-making in clinical practice. Some opponents of an evidence-based approach state that certain clinical decisions are made for practical and economic reasons, not because of evidence-based ideals. According to Muir Gray,(42) however, an evidence-based approach initiates strategies to increase the good-to-harm ratio of therapies and promotes innovations in clinical practice, resulting in an increase of the effectiveness of health care.

Some caution must be taken in generalizing the outcomes of this survey. Again, some judgment analysis studies using paper cases have demonstrated limitations on how well judgment analysis can model real-life clinical settings. According to Wigton,(43) the simulated cases contain only a fraction of the variables presented in a real-life clinical setting. Furthermore, factorial designs as used in this survey present the variables in the simulated cases as categoric, whereas in the clinical setting they are mostly continuous; as a consequence, judgments could be biased. However, according to Kirwan et al.(44;45) and Rovner et al.,(46) judgments made using paper cases have been shown to agree closely with judgments made on real patients. It is therefore reasonable to assume that paper policies can accurately model actual clinical practice policies. (It should be remembered that this survey addressed "ideal" cases without considering real-life economic and practical constraints.)

Results of our international survey indicate that the responding clinicians and the MDDS are both less certain under moderate dental risk conditions where in addition other decisional considerations are significant. We expect that further development of the MDDS could give more insight into this particular area of judgment and decision-making, in which the clinical effectiveness of the accepted guidelines could perhaps be improved. In addition, the MDDS could be further developed as a training tool for inexperienced residents. We have modified the MDDS and are currently conducting a multicenter cohort study in order to test whether the concept is valid and workable in a clinical setting and could be useful as a training tool.

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CHAPTER 4

JANNET,
a neural network approach to judgment analysis

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Abstract

In most clinical judgment analyses, the statistical process of multiple regression analysis is used to model judgment processes. However, this technique based on linear models is susceptible to a variety of difficulties and makes stringent and sometimes unrealistic assumptions about the structure of the data. The authors present JANNET (Judgment Analysis via Neural NETwork), which may be used when the assumptions underlying multiple regression analysis are not met. To illustrate this alternative approach, it was applied in order to gain insight into how a number of dental clinicians weight certain dental and radiotherapy conditions as important indications for prophylactic extraction of teeth in patients with head and neck cancer. The JANNET approach made it possible to recognize probabilistic "patterns" in "nonlinear" judgment policies and subsequently to group clinicians with related policies together. The authors conclude that this neural network approach to judgment analysis is promising and should be further tested and applied.

Introduction

Judgment and decision-making are both cardinal elements of the clinical process. Clinical judgment is based on the weighting and combining of information so as to arrive at conclusions that can serve as a basis for clinical decision-making. The latter process involves selecting courses of clinical action in order to achieve optimum outcomes. Whereas the paradigm of clinical decision analysis and its underlying "expected utility theory" have become something of a growth industry(1) and have reached a "normative status," (2) clinical judgment analysis (CJA) has received far less attention in biomedical research. A review by Wigton(3) summarized 24 reports on specific applications of clinical judgment analysis to biomedical problems. These reports appeared in 14 different biomedical journal titles from 1964 through 1988. In the past decade, however, there has been little evidence of the application of clinical judgment analysis in the biomedical domain becoming more widespread.

We first summarize some merits of the research on clinical judgment. After briefly reviewing the advantages of bringing judgment analysis into a constructive relationship with clinical decision analysis, we recall the assumptions underlying multiple regression techniques, which are typically used for this kind of research. We then propose a new approach, JANNET (Judgment Analysis via Neural NETwork), which may be used when the assumptions underlying multiple regression analysis are not met.

There are reasons to believe that analysis of clinician judgments is important in order to enhance clinical decision-making. First, decision-makers often use "clinical wisdom" and a number of simplifying operations called "heuristics," which can lead to biases in judgments, predictions, and decisions.(4) Abundant evidence from judgment analysis research has revealed a gap between the judgments people make intuitively and the probabilities yielded by explicit calculation or empirical observations. As early as 1954, Meehl(5) stated that many clinical predictions could best be made by statistical rather than by intuitive means. Slovic et al. (1976)(6) concluded on the basis of diverse research findings that people systematically violate the principles of rational decision-making when judging probabilities, making predictions, or otherwise attempting to cope with probabilistic tasks. Clinical judgment analysis provides useful procedures for more clearly understanding these judgment processes.(7)

The usefulness of clinical judgment analysis is also demonstrated when the methodology is applied to describe, aggregate, and compare clinicians' individual judgment policies. Policy clustering is the process of aggregating together clinicians having similar predictive policies.(7) It has proved a powerful method for revealing areas of divergence and consensus between individual judgment policies, especially when complex and interrelated clinical factors are investigated.(3) Not only are the results valuable in explaining these variations, they also provide cognitive feedback to clinicians for learning and teaching purposes. In 1980(8) and again in 1996,(9) Hammond emphasized the advantages of bringing clinical judgment analysis into a constructive relationship with the paradigm of clinical decision analysis. The present availability of literature on the application of clinical judgment analysis encourages this integration.

(For example, Cooksey has recently presented a comprehensive tutorial and the concomitant theoretical backgrounds).(7)

In most judgment analysis studies, the statistical process of multiple regression analysis is used as a technique to model the judgment processes of individual judges. This statistical technique, which is based on the linear model, provides a powerful tool for studying clinical judgment making.(3) However, as explained by, among others, Cooksey(7) and Fox,(10) multiple regression analysis is susceptible to a variety of difficulties and makes stringent and sometimes unrealistic assumptions about the structure of the data.

The four key assumptions associated with multiple regression analysis are(7) (see Tabachnick and Fidell(11) and Fox(10) for further discussion of regression assumptions and diagnostics):

(1) "*normality*": the residuals, that is, the differences between obtained and predicted judgment scores, are normally distributed around the predicted judgment scores;
(2) "*linearity*": judgments and predicted judgment scores are linearly related;
(3) "*homoscedasticity*": the variance of the residuals around predicted judgments scores is the same for all predicted judgments;
(4) "*independence*": the residuals associated with different judgments are uncorrelated.

Although there is some disagreement in the statistical literature over how serious the violations of the regression assumptions can be before parameter estimates are distorted or biased,(12) it is claimed that multiple regression equations should routinely be checked.(13)

Violation of multiple regression assumptions can be detected by means of statistical tests and by visual examination of typical patterns in plots, for example in a plot of standardized residuals versus standardized predicted values. Most statistical packages provide these plots in their regression programs. Several approaches are available to deal with regression violations, such as including more representative variables, increasing the number of cases and identifying outlying cases, mathematical transformation of variables, and bootstrapping and cross-validation.(7,11,13) Logistic regression analysis, which is more flexible and makes no assumptions about the distributions of predictor variables, has been used for analyzing dichotomous judgments.

To the toolkit for the clinical judgment analyst, we propose the addition of JANNET, an alternative analytical technique employing neural network computing that can be used when the assumptions underlying multiple regression analysis are not met, especially under judgment conditions involving nonlinear cue relations or when clinicians' interpretation of the cue profiles exhibits strong nonlinear characteristics. The probabilistic neural network (PNN),(14) an outgrowth of the "Bayesian classifier," is used, which we believe has not previously been applied to clinical judgment analyses. This probability-based approach is nonparametric, that is, not dependent upon underlying distributions and assumptions. The PNN is particularly useful in classifying patterns or predicting outcomes, including judgments, from sparse or limited datasets.(14-16) Further, information weights are "grown" and revised in a nonlinear fashion through exposure of the model to successive judgment cases, a simple form of dynamic judgment modeling alluded to by Cooksey.(7)

The aim of the present study is to explore the application of the PNN, which may provide useful information for future CJA research. To illustrate this alternative approach, we applied it to gain insight into how dental clinicians weight certain "risk factors" as important indications for prophylactic extraction of teeth in patients with head and neck cancer, prior to radiotherapy.(17,18)

The choice of the PNN as an analytical tool was based on the excellent mathematical credentials and performance of this type of artificial neural network.(15,19) Unlike neural network models using a feed-forward back-propagation (BP) learning algorithm,(20) the PNN learns from single-pass exposure to the training data, which makes it easier to train and many times faster than BP networks. It is also less subject to computational errors such as overfitting of data, as explained by Specht(15) and Specht and Shapiro.(21)

Although so far there have been relatively few applications of PNN modeling in biomedical situations, all have performed well.(22) However, data sampling and coding remain critical issues when using a PNN application.(23) A full explanation of the PNN paradigm and its associated computer algorithms lies beyond the scope of this paper. Readers looking for detailed information on PNNs are referred to comprehensive introductory texts.(14-16,24)

Material and methods

The JANNET approach presented here incorporates three basic steps:

1. Aims, design, and execution of the judgment task
2. Modelling of conditional probabilities
3. Grouping of individual judgment policies

Step 1: Aims, design, and execution of the judgment task

The aim of the study was to establish the characteristics of individual judgment policies of dental clinicians with respect to the prophylactic extraction of teeth in patients with head and neck cancer, prior to radiotherapy.(17) A second aim was to form clusters of judges whose policies are most similar (judgment policy aggregation and typing).

A judgment analysis questionnaire, part of a guidelines development study,(18) was mailed to 54 oral-maxillofacial surgeons and hospital-based dentists at a number of locations in North America, Australia, and Europe. Their names and addresses were obtained by contacting the secretaries of their professional organizations. The secretaries were asked to select those clinicians who were expected to be familiar with and experienced in the domain of dental screening of head and neck cancer patients. The clinicians were informed of the objectives of the survey and assured of its confidentiality and anonymity. They were queried concerning their professional qualifications and clinical posts and asked whether they were involved in the pre-radiation dental screening of patients with head and neck cancer.

The questionnaire was constructed using the specific design considerations described by Cooksey(25) from 48 simulated paper cases in order to analyze the conditional importance of a number of clinical conditions, presented as "clinical cues." In addition to "*tooth function*," two more attributes, "*dental conditions*" and "*radiotherapy conditions*," were included in the paper cases as clinical cues for judgment making. A fourth attribute concerning the location of a tooth (upper versus lower jaw) was not incorporated in the present analysis because an earlier analysis had showed that this particular cue did not contribute significantly to explaining clinician's judgment making.(18) A verbal format, incorporating the three aforementioned attributes, was used to present the paper cases to the clinicians. Clinicians were asked to choose the optimal option for dental intervention: "tooth extraction," "dental treatment," or "no action." An example of the questionnaire format and an explanation of how the verbal categories are related to the three clinical cues is given elsewhere(17) (see Chapter 3). We used a ratio of six cases (cue profiles to be judged) to each level of the three cues that were used to construct the judgment task. This 6 to 1 ratio exceeds the recommended minimum ratio 5 to 1 generally required in any study employing multiple regression techniques.(25) The paper cases were presented in a semi-randomized order to avoid response bias, e.g. clinicians' tendency to repeat the same score patterns.(26)

Step 2: Modelling of conditional probabilities

All completed questionnaires were analyzed at an individual level ("within judge" analysis). No attempt was made to compare the results originating from each international location**.** All three aforementioned cues and three response options were coded into independent and dependent variables, using a dummy coding scheme.(27) We first analyzed each data matrix using descriptive statistics and multiple regression procedures.(11) Regression diagnostics were performed through visual inspection of standardized residual/predicted judgment scatterplots and histograms depicting standardized residuals. A personal computer and a software package for statistical analysis (SPSS 9.0 with Advanced Statistic option, SPSS Inc, Chicago, IL) were used for these procedures.

Model vectors

The next phase of the analysis was the neural-network modeling. Preprocessing of variables is a vital step in neural-network computing.(22) We assume that the judgment task subjected to analysis can be modeled with so-called "model vectors." The model vectors represent the paper cases with input (independent) and output (dependent) variables. General formulation of the model vector {mv} may be written as:

$$\{\mathrm{mv}\}^N = \mathrm{input}\{\mathrm{cue\_1, cue\_2; cue\_3; \ldots cue\_M.}\}^N\ \mathrm{output}\{\mathrm{response\_1; \ldots .response\_L}\}^N$$

where M represents the number of cues, L the number of response options, and N the number of model vectors. A judgment task characterized with N model vectors $\{\mathrm{mv}\}^N$ (these model vectors are also called "judgment profiles") may be written in matrix form as shown in Fig 4.1.

model vector	=	**input cue_1**	**input cue_2**	**...**	**input cue_M**	**output response_1**	**output response_2**
mv$_1$	=	m_value$_{11}$	m_value$_{12}$	...	m_value$_{1M}$	m_value$_{1,M+1}$	m_value$_{1,M+2}$
mv$_2$	=	m_value$_{21}$	m_value$_{22}$	...	m_value$_{2M}$	m_value$_{2,M+1}$	m_value$_{2,M+2}$
.	.	.	.		.	.	.
.	.	.	.		.	.	.
mv^N	=	m_value$_{N1}$	m_value$_{N2}$	...	m_value$_{NM}$	m_value$_{N,M+1}$	m_value$_{N,M+2}$

pv$_1$	=	m_value$_{N+1,1}$	m_value$_{N+1,2}$	...	m_value$_{N+1,M}$	p_value$_{1,M+1}$	p_value$_{1,M+2}$
pv$_2$	=	m_value$_{N+2,1}$	m_value$_{N+2,2}$	...	m_value$_{N+2,M}$	p_value$_{2,M+1}$	p_value$_{2,M+2}$
pv$_3$	=	m_value$_{N+3,1}$	m_value$_{N+3,2}$	...	m_value$_{N+3,M}$	p_value$_{3,M+1}$	p_value$_{3,M+2}$

Figure 4.1. An example of a judgment task, which is completely described with N model vectors; each model vector (**MV**) has M input variables and two output variables (M+1, M+2). The **MV**s with known input and output values are used for the prediction of missing *p_values* (values of output variables-- see dark gray cells) for three new prediction vectors (**PV**). These **PV**s have known values of input variables only. The PNN predicts these unknown *p_values* of output variables of the **PV**s on the basis of all **MV**s. (Adapted with permission from the author, from Krajnc, 1997 (31,32))

The PNN modelling was performed using the "aiNet" software (aiNet for Windows, version 1.25, aiNet, Celje, Slovenia).[1] Its operation and performance were first successfully tested by analyzing two benchmark problems from the Proben database.(28) The first benchmark problem came from Proben's "*heartc*" dataset (source, Robert Detrano, MD PhD, Cleveland Clinic Foundation CA, 1989).(29) The second problem came from Proben's "*breast cancer*" dataset (source, William H.Wolberg, MD, University of Winconsin Hospital, Madison, WI, 1990).(30)

Conditional probabilities

We used the PNN(14) to model clinicians' responses as conditional probabilities (Baysian posterior probabilities). To compute these conditional probabilities, first the model vectors were fed into the network using aiNet's graphical user interface, which is designed like a spreadsheet application (Fig 4.2).

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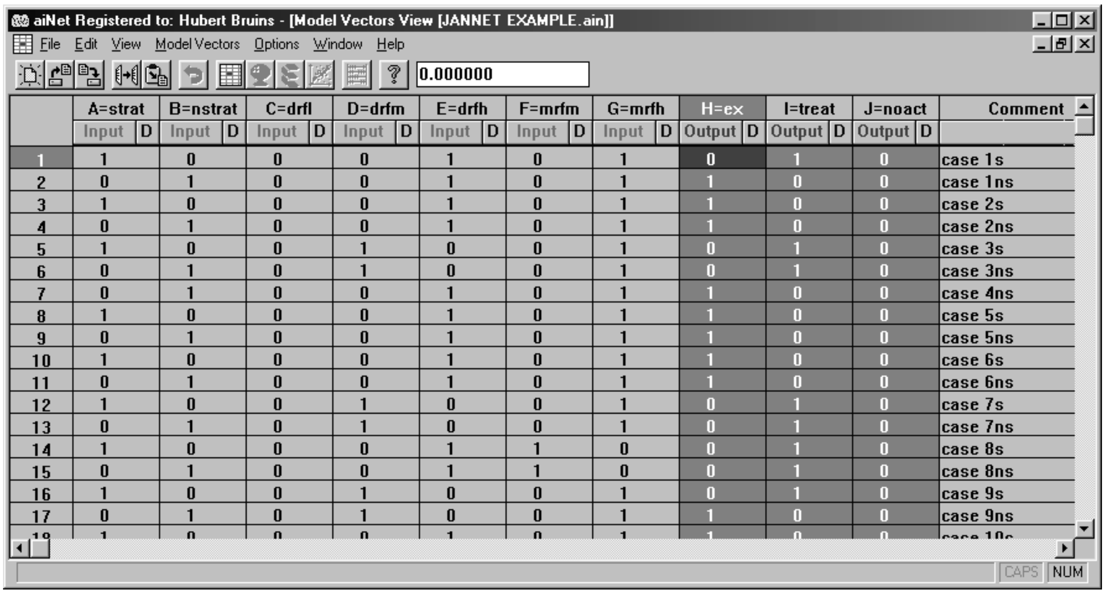
[1] A full working version of aiNet is available for FTP-download from the Internet at: http://www.ainet-sp.si/NNdownload.htm or at http://www.mexsys.net



	A=strat		B=nstrat		C=drfl		D=drfm		E=drfh		F=mrfm		G=mrfh		H=ex		I=treat		J=noact		Comment
	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Output	D	Output	D	Output	D	
1	1		0		0		0		1		0		1		0		1		0		case 1s
2	0		1		0		0		1		0		1		1		0		0		case 1ns
3	1		0		0		0		1		0		1		1		0		0		case 2s
4	0		1		0		0		1		0		1		1		0		0		case 2ns
5	1		0		0		1		0		0		1		0		1		0		case 3s
6	0		1		0		1		0		0		1		0		1		0		case 3ns
7	0		1		0		0		1		0		1		1		0		0		case 4ns
8	1		0		0		0		1		0		1		1		0		0		case 5s
9	0		1		0		0		1		0		1		1		0		0		case 5ns
10	1		0		0		0		1		0		1		1		0		0		case 6s
11	0		1		0		0		1		0		1		1		0		0		case 6ns
12	1		0		0		1		0		0		1		0		1		0		case 7s
13	0		1		0		1		0		0		1		0		1		0		case 7ns
14	1		0		0		0		1		1		0		0		1		0		case 8s
15	0		1		0		0		1		1		0		0		1		0		case 8ns
16	1		0		0		1		0		0		1		0		1		0		case 9s
17	0		1		0		1		0		0		1		1		0		0		case 9ns

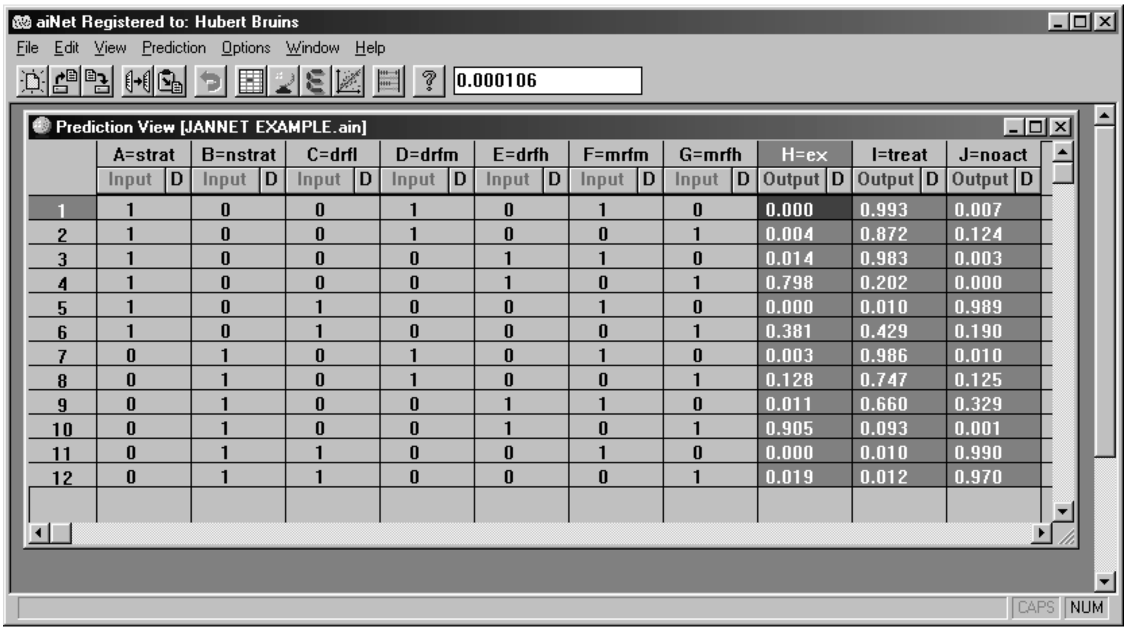
Figure 4.2. aiNet's Model Vectors View

Using aiNet's "Verification Tool,"(31,32) the value of each output variable for each model vector is predicted on the basis of all other model vectors in the model vector spreadsheet that functions as a database. Each model vector under consideration is therefore temporarily removed from database. By means of aiNet's nonparametric mathematical algorithm, this "leave-one-out" procedure(24) generates a global error estimate, which in turn depends on an underlying probability density function (PDF).(14,32) Next, the PDF is applied for the prediction of unknown outcome values, which are the conditional probabilities. To accomplish this prediction procedure, a set of twelve prediction vectors was processed using aiNet's "Prediction Tool."(31,32) These twelve prediction vectors represent the two levels of the six input variables. This process results in the wanted conditional probabilities of all three response options (see columns labelled H , I, and J in Fig 4.3).

For example, given that a strategic tooth (cue 1, level 2) with a dental condition considered as "medium risk" (cue 2, level 2) is within the planned radiation field of over 55 Gray (cue 3, level 2) the conditional probabilities of the response options of a particular clinician are:

$\overline{P}$ $[R_1 \mid C1,2; C2,2; C3,2] = 0,128$ (see cell H:8 in Fig 4.3)
$\overline{P}$ $[R_2 \mid C1,2; C2,2; C3,2] = 0,747$ (see cell I:8 in Fig 4.3)
$\overline{P}$ $[R_3 \mid C1,2; C2,2; C3,2] = 0,125$ (see cell J:8 in Fig 4.3)

where $\overline{P}$ represents the conditional probability, R_n the response option, and $C_{N,N}$ a clinical cue. The | symbol means "conditional upon." Note that, while the three response options are mutually exclusive, the sum of the three conditional probabilities equals 1. As the main interest of the present survey was the effect that cue 1 ("*tooth function*") had on clinicians' judgments,(18) the conditional probabilities for this particular cue were devised for all three response options, as explained in BOX 1 (see page 65).



	A=strat	B=nstrat	C=drfl	D=drfm	E=drfh	F=mrfm	G=mrfh	H=ex	I=treat	J=noact
	Input	Input	Input	Input	Input	Input	Input	Output	Output	Output
1	1	0	0	1	0	1	0	0.000	0.993	0.007
2	1	0	0	1	0	0	1	0.004	0.872	0.124
3	1	0	0	0	1	1	0	0.014	0.983	0.003
4	1	0	0	0	1	0	1	0.798	0.202	0.000
5	1	0	1	0	0	1	0	0.000	0.010	0.989
6	1	0	1	0	0	0	1	0.381	0.429	0.190
7	0	1	0	1	0	1	0	0.003	0.986	0.010
8	0	1	0	1	0	0	1	0.128	0.747	0.125
9	0	1	0	0	1	1	0	0.011	0.660	0.329
10	0	1	0	0	1	0	1	0.905	0.093	0.001
11	0	1	1	0	0	1	0	0.000	0.010	0.990
12	0	1	1	0	0	0	1	0.019	0.012	0.970

Figure 4.3 aiNet's Prediction View

Next, the likelihood ratios of these conditional probabilities were computed. At this point, the Likelihood Ratio (LR) is defined as the ratio of the probability of a predicted response given that a tooth is "strategic" (cue1,1) to the probability of that response given that the tooth is "nonstrategic" (cue1,2), which is summarized in the following equation:

$$\text{Likelihood ratio (LR)} = \frac{\overline{P}\,[R_{\#} \mid C\,1{,}1]}{\overline{P}\,[R_{\#} \mid C\,1{,}2]}$$

where $\overline{P}$ represents the conditional probability of a response, $R_{\#}$ the response option, and C the clinical cue. BOX 1 (page 65) shows an example set of three likelihood ratios derived from the predicted responses depicted in Fig 4.3. The LR represents the cue weight for the attribute "*tooth function*". These cue weights are the standard expected outcomes for judgment analysis.

Step 3: Grouping of individual judgment policies

After the characteristics of each individual's judgment process are established in step 2, the resulting profiles of judgmental characteristics across judges are analyzed in the search for groups sharing common characteristics. We used the "K-means cluster analysis" algorithm(33) to accomplish this. The measure for clustering was the "Euclidian distance." The goal of this procedure was to form clusters of judges whose LRs were most similar. We chose to cluster on basis of the LRs because they are very useful for characterizing clinical information.(34) We tested a range of three to five clusters in an iterative approach. In addition, One-way ANOVA and F-test statistics were performed in order to test the contribution of the Likelihood Ratios (independent variables) to the separation of the clusters (dependent variable: distances between final cluster centers).

It should be noted that, when the goal of the analysis is directed only to the analysis of each individual judgment process, step 3 is not required.

Results

Forty-four clinicians returned the questionnaire (response rate of 81%) and provided usable data for analysis. The multiple regression analyses produced a total of 44 individual regression models. As anticipated, inspection of the normal probability plots revealed major violations of the regression assumptions, indicating strong nonlinear relationships within the judgment data. Consequently, no further attempts were made to use these linear models for purposes of this clinical judgment analysis study.

Modeling and prediction procedures of aiNet software were relatively simple and rapid. The performance testing of aiNet revealed that the overall predictive accuracy matched the results of other performance evaluations using the same benchmark problems.(29,30,35,36). All 44 data matrices deriving from the questionnaires were processed by the aiNet software without any difficulties. The procedures rendered 44 sets of predicted judgments, expressed as conditional probabilities.

The K-means cluster analysis based on the LRs of response 1, 2 and 3 of each individual judge resulted in four clusters. A summary profile of the clusters is given in Table 4.1 and Fig 4.4. The F-tests revealed significance level p = 0.003 (df 3.40; F =5.342) for the variable "*LR of response-1*" ; significance level p = 0.0001 (df 3.40; F =269.395) for variable "*LR of response 2,*" and significance level p = 0.885 (df 3.40; F = 0.216) for variable "*LR of response-3*." Thus, the "LR *of response 3*" ("no-action") failed to contribute significantly to the clustering of the judges, indicating that significant differences between the policies of the clustered judges exist only in cases in which a tooth should be extracted or treated.

Table 4.1 Summary profile of the 4 clusters

	Cluster 1	*Cluster 2*	*Cluster 3*	*Cluster 4*
Number of clinicians	9	32	1	2
Final cluster centers, based on Likelihood Ratios of responses (strategic vs. nonstrategic teeth)				
Response 1	.602	1.019	.447	.670
Response 2	3.378	1.494	13.649	6.280
Response 3	.595	.517	.580	.650
Distances between final cluster centers				
Cluster 1		1.931	10.272	2.904
Cluster 2	1.931		12.169	4.801
Cluster 3	10.272	12.169		7.372
Cluster 4	2.904	4.801	7.372	

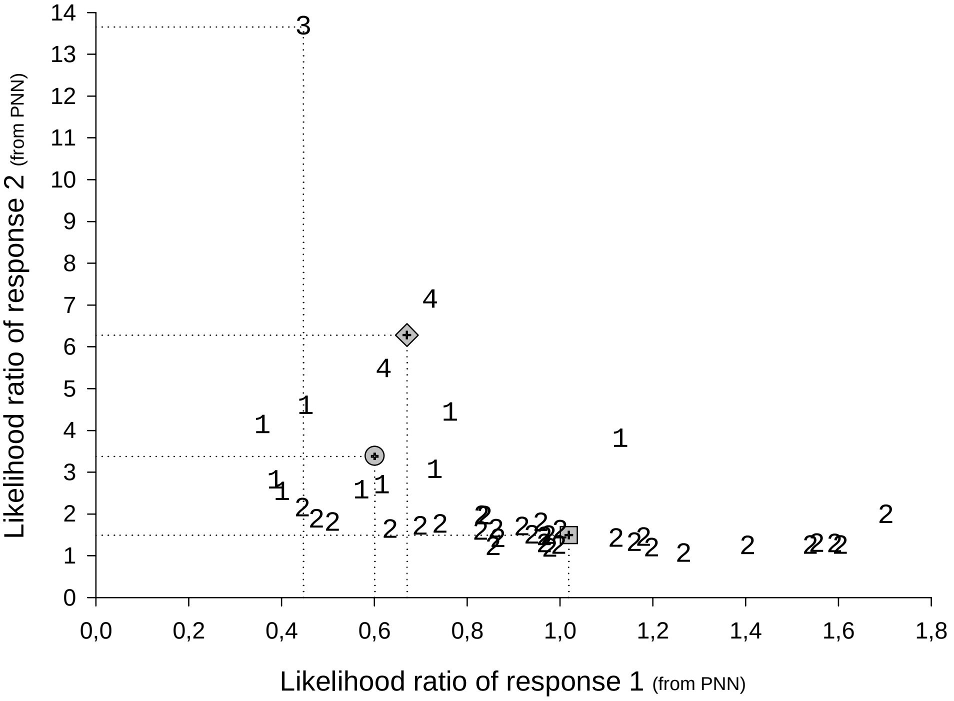


Fig 4.4. Graphical depiction of all cluster members. Each number represents a clinician and the cluster number to which he/she belongs.

⊕ = center of *Cluster 1*; ⊞ = center of *Cluster 2*; ◈ = center of *Cluster 4*

Discussion

A questionnaire comprising paper cases and a probabilistic neural network (PNN) application were used to examine the relevance of tooth functionality in the process of clinical judgment and decision-making in a dental domain. By means of this nonparametric ("free of assumptions") approach, we were able to identify four groups of dental clinicians on the basis of likelihood ratios (LRs) of responses concerning strategic teeth versus nonstrategic teeth.

Assuming that judgments made on paper cases agree closely with judgments made on real patients,(37-39) the results of this survey indicate that the clinicians from the four clusters differed with respect to how tooth functioning was weighted. However, this applies only to response 1 (*tooth extraction*) and response 2 (*dental treatment*), but not to response 3 (*no-action*). For example, the probability that clinicians belonging to cluster 2 would carry out a dental treatment on a strategic tooth prior to radiation therapy is on average approximately 1.5 times higher then the probability of dental treatment on a nonstrategic tooth (weighted over all combinations of dental and radiotherapy conditions). The value of the center of cluster 2 (depicted with a gray square symbol in Fig 4.4) for response 2 is 1.494; i.e. mean value of "*LR of response-2*," which can be read where the dotted drop line from the gray square symbol meets the y-axis in Fig 4.4 (see also the values of cluster centers in Table 4.1) On the other hand, if the condition of a tooth requires extraction (response 1), clinicians in cluster 2 vary considerably with respect to the weighting of tooth function. This can be clearly seen in Fig 4.4 by the spread along the x-axis ("*LR of Response-1*") of cluster 2 clinicians (see the spread of the "2" numbers in Fig 4.4). However, the clinician in cluster 3 (see number "3" in Fig 4.4) weights tooth function rather heavily ("*LR of Response-2*" = 13,649). This may be interpreted as follows: in the case of strategic teeth, this particular clinician is prepared to take the risk of a complication (should the dental treatment fail, or if the tooth develops new dental pathosis following radiation --see Chapter 5) in pursuit of a better patient outcome (maintaining strategic teeth contributes to oral functioning).(40) As discussed previously, such an insight into this particular area of nonlinear judgment and decision-making could be helpful for development of evidence-based guidelines and for training of clinicians.(18)

An important difference between this study and previous work on clinical judgment analyses is the use of a probabilistic neural network (PNN) that allows the use of nonlinear models. Most judgment analysis studies use linear models as the statistical technique for analyzing clinician's judgments. By means of multivariate analysis of judgment data, these models represent judgment as the weighted sum of each clinical cue. The linear model of judgment, known as the "Lens Model," was proposed by Egon Brunswik in the 1950s, and was further developed and enhanced by Kenneth Hammond and others into the present paradigm for studying intuitive judgments. However, as mentioned earlier, the paradigm related to linear models is restricted in the validity of its underlying regression techniques. It is therefore not surprising that interest in deriving a form of judgment analysis that could cope with nonlinear judgments began to emerge. So far, as discussed by Cooksey (pp. 280-292)(7) these nonlinear approaches are a challenging issue for judgment analysis.

The PNN application used for this study showed considerable power in capturing conditional probabilities deriving from judgments made on paper cases. The JANNET approach enabled us to recognize probabilistic "patterns" in "nonlinear" judgment policies and subsequently to group clinicians with related policies together. It revealed how the weighting of cues, expressed as likelihood ratios, dynamically evolves when clinical information (judgment data) varies. We therefore believe that this neural network approach to Judgment Analysis is promising and should be further tested and applied. However, as the JANNET approach is conceptually different from most other Judgment Analysis studies using the "Lens Model," where cue weights are computed using multiple regression procedures and individual measures of consistency are also reported, it could impede the comparison of the results of two approaches.

Box 1: Composing of conditional probabilities

The definition of conditional probability is the probability that an event (e.g. outcome "X") is true, given that another event (e.g. condition "Y") is true, formally defined by:

$$P[X \mid Y] = \frac{P[X \; and \; Y]}{P[Y]}$$

Let the conditions and outcomes be given in a probability matrix (in spreadsheet syntaxes: A1:J12), where columns A:G represent the conditions. "1" means condition is present (true), "0" means condition is absent (false), and H:J represent the probabilities of 3 mutually exclusive outcomes, i.e. the predicted responses. As explained in the main text, the conditional probabilities of the outcomes were computed by the neural network on basis of the data from the questionnaire. Rows 1:12 (see also Fig 4.3) represent the cases for which these conditional probabilities were calculated (this was done for each participating clinician, n=44, resulting in 44 sets of predicted outcomes).

	A	**B**	**C**	**D**	**E**	**F**	**G**	outcome **H**	outcome **I**	outcome **J**
1	1	0	0	1	0	1	0	0.000	0.993	0.007
2	1	0	0	1	0	0	1	0.004	0.872	0.124
3	1	0	0	0	1	1	0	0.014	0.983	0.003
4	1	0	0	0	1	0	1	0.798	0.202	0.000
5	1	0	1	0	0	1	0	0.000	0.010	0.989
6	1	0	1	0	0	0	1	0.381	0.429	0.190
7	0	1	0	1	0	1	0	0.003	0.986	0.010
8	0	1	0	1	0	0	1	0.128	0.747	0.125
9	0	1	0	0	1	1	0	0.011	0.660	0.329
10	0	1	0	0	1	0	1	0.905	0.093	0.001
11	0	1	1	0	0	1	0	0.000	0.010	0.990
12	0	1	1	0	0	0	1	0.019	0.012	0.970

Using the formal definition of conditional probability, it can be shown that the conditional probability of outcome H, given that condition A= true and B=false is:[2]

$$P\;[H \mid A] = \frac{P^m[H \; and \; A]}{P^m[A]} = \frac{(H1:H6)}{(H1:J6)} = \frac{1.197}{6} = 0.199$$

where P^m is the matrix probability (note that: $1 \leqslant P^m \leqslant 12$).
The same method is applied to compute the conditional probability of outcome H, given A=false and B=true:

$$P\;[H \mid B] = \frac{P^m[H \; and \; B]}{P^m[B]} = \frac{(H7:H12)}{(H7:J12)} = \frac{1.066}{6} = 0.177$$

The Likelihood Ratio (see text) is: $\frac{0.199}{0.177} = 1.124$

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[2] We used spreadsheet syntaxes, whereas this calculation could also be easily performed with the use of matrix algebra.

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CHAPTER 5

Association of tooth loss with dental status and dental risk factors in a sample of patients with head and neck cancer

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Submitted

Abstract

Objective

This study was designed to investigate the association of tooth loss with patient's dental status (number of teeth present at baseline), dental risk factors (DRFs), and radiotherapy-related factors, respectively, in a sample of head and neck cancer patients. A further objective was to study the incidence of radiation caries and osteoradionecrosis.

Study Design

A retrospective and follow-up analysis was performed on 209 head and neck cancer patients in the Netherlands who had received a dental evaluation prior to radiotherapy for head and neck cancer. Patients were subsequently evaluated 1-5 years postradiation (median 3 years).

Results

Tooth loss was greater in the study population compared to data on tooth loss in the general population, and is significantly associated with dental status, DRF's, and radiotherapy-related factors. Radiation caries at the time of the follow-up evaluation was significantly associated with the number of DRFs at baseline. The incidence of osteoradionecrosis was relatively low (5 cases; 2.3%).

Conclusions

The survey supports the clinician's judgment to be uncompromising in preradiation treatment planning, especially in patients initially presenting with poor oral health. A survey study that would further define the relationship between a head and neck cancer patient's perception regarding the need for dental rehabilitation and his or her ability to comply with the advised dental treatment and oral hygiene measures is recommended.

Introduction

It has long been known that head and neck cancer patients tend to have higher levels of dental pathosis compared to the general population.(1) In particular, elderly persons and those of lower socioeconomic status form a substantial proportion of patients with head and neck cancer.(2,3) The prevalence and incidence of dental disease in these groups are high and compliance with dental care is usually poor.(4-9)

Numerous reports indicate that head and neck cancer therapies induce a wide spectrum of undesirable side effects, particularly affecting the mouth and jaws.(10) This is especially true if radiotherapy to the oral and maxillofacial structures is part of the overall treatment regimen.(11) It has been shown that these side effects seriously affect both the tolerance of treatment and the quality of life.(12,13)

To reduce oral complications, extensive dental preventive and treatment measures before, during, and after cancer therapy are mandatory.(10,13,14) Implicit in the preventive approach is preradiation oral screening to identify and eliminate dental risk factors (DRFs). Preradiation dental decision-making has been described in previous publications.(15,16) The dental risk factors (DRFs) were found to be the most important factors in this process.(15) DRFs include caries, periodontal disease, periapical dental pathosis, impacted teeth, residual root tips, cysts, and other radiographic abnormalities. Table 5.1 summarizes the DRFs.

Elimination of DRFs is possible through dental treatment or tooth extraction. Criteria for the extraction of teeth before radiotherapy include the following:(14)

- moderate to advanced periodontal disease,
- extensive periapical lesions of the teeth,
- extensive dental caries,
- partially impacted or incompletely erupted teeth,
- residual root tips not fully covered by bone and/or showing radiolucency to x-rays.

Pre-existing dental pathoses logically seem to be a risk factor for tooth loss. Patients with high levels of dental pathosis prior to radiotherapy need extensive dental intervention, frequently resulting in partial or even total loss of dentition.(17) In addition, patients with remaining teeth would also seem to be at risk for development of novel dental pathoses, such as radiation caries. Although this association has long been apparent,(1) its strength and functional form has not yet been clearly recognized in an evidence-based approach.(18,19)

The objective of the present clinical survey was to investigate the association of pre and postradiation tooth loss with patient's dental status (number of teeth present at baseline), dental risk factors (DRFs), and radiotherapy-related factors, respectively, in a sample of patients with head and neck cancer. A further objective was to study the incidence of radiation caries and osteoradionecrosis. For these purposes, a retrospective and follow-up evaluation was performed on 209 head and neck cancer patients in the Netherlands, who had received a dental evaluation prior to radiotherapy for head and neck cancer.

Table 5.1 Dental Conditions to assign Dental Risk Factor (DRF) Score

Clinical and Radiographic Findings (CRF)[a]	Weighting	
Periodontal disease		
Probing depth / Proximal bone loss:[b] 3 to 6 mm	Medium	
Probing depth / Proximal bone loss: > 6mm		High
Gingival recession: 3 to 6 mm	Medium	
Gingival recession: > 6 mm		High
Bleeding upon probing	Medium	
Spontaneous gingival bleeding		High
Furcation involvement / Bone loss in furcation area		High
Mobility 1-2 mm side to side	Medium	
Mobility > 2 mm side to side and/or 1 mm vertical		High
PULPAL DISEASE AND PERIAPICAL LESIONS		
Abnormal response to tests,[c] no previous endodontic treatment, no rarefying osteitis[d]	Medium	
Abnormal response to tests, no previous endodontic treatment, rarefying osteitis		High
Swellings and/or sinus tracts		High
Rarefying osteitis, Ø < 3mm, with adequate root canal filling,[e] without (percussion) pain	Low/Medium	
Rarefying osteitis, Ø < 3mm, with inadequate root canal filling,[e] with (percussion) pain		High
Rarefying osteitis , Ø > 3 mm		High
Condensing osteitis[f]/ hypercementosis[g] with normal reactions to tests	Low	
Condensing osteitis with abnormal reactions to tests	Medium	
Internal/external root resorption		High
EXTENSIVE CARIES		
Primary caries < 2/3 of the clinical crown	Medium	
Primary caries > 2/3 of the clinical crown/pulpal involvement		High
Defective restoration[h] with secondary caries,[i] no pulpal involvement	Medium	
Root caries < 1/2 of root circumference, no pulpal involvement	Medium	
Root caries > 1/2 of root circumference		High
NON FUNCTIONAL TEETH		
Partially impacted (incompletely erupted) teeth or permucosal residual roots		High
Residual root tips not fully covered by alveolar bone and /or showing periodontal ligament or radiolucency		High
Fully impacted teeth, without follicle enlargement and fully covered by bone	Low	
Fully impacted teeth, with follicle enlargement and/or not fully covered by bone,		High
ORAL HYGIENE, DENTAL AWARENESS, CO-OPERATION		
Low level of oral hygiene, low dental awareness, lack of cooperation		High

[a] Identified at tooth level, which means tooth-related.

[b] Radiographic standard for interpretation of proximal bone loss is that the alveolar crestal bone must be greater than 3 mm from the CEJ. (20)

[c] Pulp sensitivity: cold, heat, electric (EPT) and percussion tests.

[d] Rarefying osteitis: radiolucent periapical bone destruction communicating with the periodontal ligament space via a discontinuity in the lamina dura.(21)

[e] Criteria for assessment of root canal obturation: The prepared and filled canal should contain the original canal and should be filled completely (0.5-2 mm from radiographic apex). No space between canal filling and canal wall should be seen. No canal space should be visible beyond the end point of the root canal filling. The whole canal system/ all roots should be obturated (Consensus Report European Society of Endodontology)(22)

[f] Hypersclerotic bone trabeculi adjacent to the periapical region and communicating with the periodontal ligament space. (21)

[g] Distortion of the apical third of the tooth root characterized by increased width while the periodontal ligament space and lamina dura remain unaltered. (21)

[h] Restorations are defective if any of the following conditions are present: marginal discrepancies >0.5 mm, part of the restoration missing, bulk fracture, or marginal staining of composites suggesting leakage.(23)

[i] True radiographic secondary (i.e., recurrent) caries and/or residual caries.(23)

Methods

Subjects

The subjects of this clinical survey, conducted in 1999, were patients who had undergone head and neck cancer therapy at the Department of Otorhinolaryngology and allied departments of the University Medical Center Utrecht, the Netherlands, between 1993 and 1998. Patients selected for inclusion in the clinical survey were required to satisfy the following conditions, they:

(1) were in the regular oncology follow-up schedule;
(2) had undergone primary cancer treatment, including radiotherapy, for squamous cell carcinoma in head and neck, one to five years previously;
(3) were treated with the intention of curing the disease (patients receiving only palliative treatment or patients with active disease were not included for medico-ethical reasons);
(4) had undergone preradiation dental screening;
(5) were able to be examined postradiation.

Informed consent was acquired from the patients who were found to meet the criteria for entry in the study protocol.

Measures

The data on patient characteristics (i.e. age, gender) and comprehensive information on the head and neck cancer were retrieved from the hospital's *ONCDAT* database (courtesy of Prof. Dr. G.J. Hordijk). Data on radiotherapy, such as doses and fields, were obtained from the appropriate records, simulation radiographs, and computerized treatment planning. Using a specially designed clinical assessment form (the SCREDENT form, see Appendix 2), data on dental health status and tooth loss were obtained from the clinical records and from intraoral and extraoral radiographs by one examiner, a hospital dentist (HHB). A number of clinical records were re-analyzed in order to be able to assure satisfactory levels of intra-examiner reliability.

The clinical follow-up evaluation was carried out only on dentate patients and consisted of the same procedure as the preradiation oral screening. Patients' dental status was measured in terms of the number of teeth present (tooth retention). In addition, other essential findings of the clinical examination were recorded. DRFs that were measured according to the methods described earlier(16) are in outlined in Table 5.1. In this survey, radiation caries is defined as extensive, primary circumferential caries involving more then one third of the crown and/or root circumference in patients who underwent high-dose radiotherapy in the head and neck region. Information on the incidence of osteoradionecrosis was retrieved from hospital records and the *ONCDAT* database.

Analysis

Initially, all data were transferred to a data matrix. The statistical analyses were done in SPSS 9.0 with the Advanced Statistic option (SPSS Inc. Chicago, Il) and S-PLUS 2000 for Windows (MathSoft Inc., Cambridge, MA), using a personal computer.

We first used descriptive statistics for the purpose of data screening and description of the sample of patients. We anticipated that tooth loss would not follow the normal distribution. A stem-and-leaf plot (Fig 5.1) indicated that tooth loss followed a Poisson distribution. Therefore, associations of tooth loss with age, gender, dental status, DRFs, and radiotherapy-related factors, respectively, were analyzed by means of a Poisson regression analysis.(26) In addition, the Poisson regression analysis was done to test possible predictors for radiation caries at the time of the follow-up evaluation. In this survey, radiation caries is defined as extensive, primary root caries involving more then one third of root circumference. Statistically significance levels are designated as two-sided probability values, with $p < 0.05$.

```
Frequency    Stem &  Leaf

    52.00        0 .  0000000001111222233333444
    21.00        0 .  566667899
    15.00        1 .  011234
     6.00        1 .  579
     3.00        2 .  &
     1.00 Extremes    (>=24)

Stem width: 10; Each leaf: 2 case(s);
"&" denotes fractional leaves (only 1 case per leaf).
```

Figure 5.1 Stem and leaf plot of tooth loss in 98 patients, indicating a Poisson distribution.

Results

In total, 398 patients were initially selected for this clinical survey. Two hundred and nine patients (78.5 % male and 21.5 % female) fulfilled all inclusion criteria. The mean age was 60 years (median 60; range 33-84). The age distribution of males and females did not differ significantly ($p > 0.05$). The median of follow-up time was 36 months (range 12-60).

The prevalence of head and neck cancer by site of occurrence for males and females is presented in Table 5.2.

Table 5.2 Frequency of head and neck cancer by site

Sites of Squamous Cell Carcinoma (SCC)	ICD -9-CM[#] code	Number of patients		Frequency …%	
		M	F	M	F
Oral cavity					
lips	140	4	0	1.9	0.0
tongue	141	13	6	6.2	2.9
floor of the mouth	144	10	6	4.8	2.9
unspecified	145	11	3	5.2	1.4
Oropharynx	146	9	9	4.3	4.3
Nasopharynx	147	4	0	1.8	0.0
Hypopharynx	148	12	1	5.7	0.1
Nasal cavities	160	5	2	2.4	1.4
Larynx	161	94	15	44.8	7.1
Unspecified head and neck	199	3	2	1.4	1.4
Total		165	44	78.5	21.5
		209		100	

[#] International Classification of Diseases, Ninth Revision, Clinical Modification, as published by the U.S. Public Health Service and Health Care Financing Administration. M= male, F=female.

It was found that 111 patients (53%) were edentulous, and 98 patients (47%) had a (reduced) natural dentition at the time of the preradiation oral screening (baseline). The total number of teeth present in 98 patients at baseline was 1,475 (mean number of teeth per patient: 15, range 31), of which 559 (37%) were situated in the upper jaw and 916 (63 %) in the lower jaw. The total number of DRFs with high-risk level in the 98 dentate patients at baseline was 339 (mean number of high DRFs per patient: 3, range 15)

The incidence of total tooth loss in the 98 dentate patients was 602 (mean tooth loss per patient: 6, range 24). Prior to radiotherapy, 441 teeth (31 % of the total number of teeth at baseline) were lost, and 161 teeth (11%) were lost thereafter. Table 5.3 presents a cross-tabulation of tooth loss by time and arch. As a result of the preradiation tooth extractions, 33 patients became edentulous. Thus, a full mouth clearance prior to radiotherapy was performed in 34% of the dentulous patients. In addition, 7 patients (7%) became edentulous in the follow-up period after radiotherapy.

Table 5.3 Cross-tabulation of total tooth loss by time and arch (in 98 patients)

	Preradiation Tooth Loss			**Postradiation Tooth Loss**			**Total Tooth Loss**		
	in 98 patients	per patient		in 65 patients	per patient		in 98 patients	per patient	
	number	*mean*	*range*	*number*	*mean*	*range*	*number*	*mean*	*range*
Upper Arch	112	1.14	10	50	0.52	12	162	1.65	12
Lower Arch	329	3.36	13	111	1.02	14	440	4.38	14
Total	**441 (73%)**	**4.50**	**24**	**161 (27%)**	**1.64**	**24**	**602**	**6.03**	**24**

Review of the simulation radiographs and computer-based treatment planning revealed that 185 teeth (12%) present at baseline in 35 patients would be in the planned field of radiation (dose > 55 Gy). Using the same radiation planning information, we estimated that the major salivary glands (parotid and/or submandibular glands) of 165 patients (79 %) were bilaterally, partially (at least for 50%), or totally in these radiation fields of 55 Gy or more. After preradiation dental extractions, 125 teeth (8% of the teeth present at baseline) in only 24 patients (24%) were actually in the field of radiation and received a dose of > 55 Gy.

At the time of the follow-up evaluation, 25 of the 56 dentate patients (45%) had one or more teeth affected by radiation caries that required extensive dental treatment or tooth extraction. This treatment need would of course further increase total tooth loss.

The Poisson regression analysis showed that association of tooth loss with dental status, the number of high DRFs, and the number of teeth in the high-dose field of radiation, are statistically significant, $p < 0.001$. The estimated association between expected tooth loss and dental status is shown in Fig 5.2. There was no statistically significant association between age and gender respectively, and total tooth loss. In addition, the Poisson regression analysis revealed that patients' number of teeth with radiation caries at the time of the follow-up evaluation was statistically significantly associated with the number of high DRFs at baseline with; $p < 0.001$).

The incidence of osteoradionecrosis (ORN) was 2.3%, i.e. 5 cases in the lower jaws of 1 edentulous and 4 dentate patients. These documented cases of osteoradionecrosis were successfully treated according to accepted protocols.(27)

Discussion

This clinical survey involved a retrospective and follow-up evaluation of 209 patients treated for cancer of the head and neck. The main objective was to investigate the association of tooth loss with dental status, dental risk factors (DRFs), and radiotherapy-related factors, respectively.

Analysis of patient-related and cancer-related characteristics revealed that the sample in the main compared with epidemiological data on age and gender of head and neck cancer patients.(12) At baseline, 53% of the patients were edentulous. This proportion is rather large compared to other countries. For example, in the United States, Marcus et al.(28) and Hunt et al.(29) found a proportion of about 24-29% in similar age groups, i.e. older white males and females. However, patients included in this study did not differ significantly from the population in the Netherlands within the same age groups.(30)

Total tooth loss in all patients was 602 (mean per patient: 6, range 24), which can be considered quite high. For example, in comparable age groups in the United States, the mean tooth loss among older white adults in an 18-month period was 0.4.(29) From the present study, it may be concluded that tooth loss in the head and neck cancer patients in this sample is considerably higher than the amount of tooth loss described in epidemiological studies concerning the general population. (4,6,28-30,32-44)

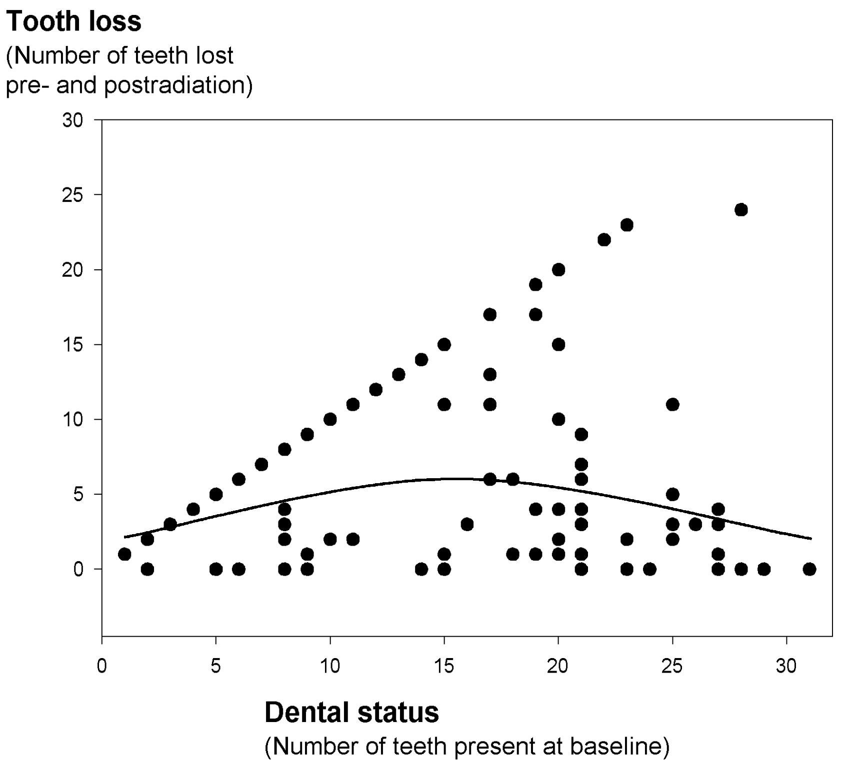

Figure 5.2 The estimated association of tooth loss with dental status. Each black circle represents a patient. Those on the diagonal represent patients who became edentulous as the result of pre- and/or postradiation tooth extractions. The dome-shaped line represents the fitted Poisson regression line, with covariate values: gender = male, and age = 60.

Logically, we may conclude that this substantial tooth loss is initiated by the circumstance that these patients underwent radiotherapy for a head and neck malignancy. Dental intervention in these cancer patients is important because dental pathology is a potentially significant problem.(17) There is a strong need for dental treatment including tooth extractions, which is usually not perceived by the patients themselves,(45) in order to prevent oral sequelae of radiotherapy.(10)

The results of the Poisson regression analysis indicate that tooth loss was statistically significantly associated primarily with dental status at baseline and the number of high DRFs, and secondarily with factors concerning radiotherapy. This finding compares to our earlier conclusion that the decision policies of dental clinicians seem to be based primarily on dental factors, and to a lesser extent on factors concerning radiotherapy.(18) It was noted that the association between dental status and tooth loss has a shallow dome-shape function form (see Fig 5.2). Thus, the amount of tooth loss increases when the number of retained teeth increases. However, the amount of tooth loss gradually decreases in patients who have more than 15 teeth, although these patients have more teeth that are "at risk" for potential tooth loss. It is plausible that patients who did not experience substantial tooth loss in the past have better levels of dental health(46) and therefore required less dental treatment, including tooth extraction, prior to radiotherapy.

The incidence of postradiation tooth loss (161 teeth, which is 27% of total tooth loss) and amount of radiation caries requiring extensive dental treatment including tooth extractions at the time of the follow-up evaluations was rather high. Possible explanations for postradiation tooth loss are that for practical considerations, tooth extraction of teeth not within the high-dose radiation field was postponed until after radiotherapy. In addition, poor patient compliance could have resulted in failure to adhere to dental treatment and oral hygiene recommendations. This may also explain the rather high levels of radiation caries at the time of the follow-up evaluation.

Patterns of non-compliance for dental treatment in head and neck cancer patients have been reported by several investigators.(4-9) A review of the medical and dental literature by Ainamo & Ainamo(47) shows that patients with chronic illness tend to comply poorly, especially when the treatment time is lengthy or the complexity high. Typical reasons for non-compliance are, among others, stressful life events,(48) depression,(49) and alcoholism.(50) In addition, the lack of social network and social support, low interest in oral health, and "external locus of control" have been suggested as reasons for non-compliance. (9,51,52) Whereas "internal locus of control" means that a person takes charge of his or her own health-care situation, an "external locus of control" is determined by the individual's perception that various environmental factors are beyond his/her control. It has been shown that patients with head and neck cancer tend more toward external locus of control.(9) Non-compliance with dental care and oral hygiene is an important issue that deserves further attention.

The findings of this clinical survey also indicate that when a head and neck cancer patient presents with reduced dentition and/or with poor dental health at the preradiation oral screening, substantial tooth loss may result. Moreover, patients who have remaining teeth during irradiation are at risk of developing new dental pathosis, such as radiation caries. Subsequent to the radiation, a patient who presented initially with poor dental health may again need extensive dental treatment, including tooth extractions. Consequently, the preradiation treatment plan, enhanced by dental decision-making, should include this anticipation. Uncompromising preradiation dental intervention is therefore warranted. However, we believe that our findings justify undertaking a survey study that would further define the relationship between a head and neck cancer patient's perceptions regarding the need for dental rehabilitation and his or her ability to comply with the recommended dental treatment and oral hygiene measures. This could result in better-targeted recommendations, leading to optimization of dental and oral-hygiene care regimens in patients with head and neck cancer.

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CHAPTER 6

SCREDENT, a system for dental decision support in patients with head and neck cancer

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Submitted

Abstract

Objectives

To construct and test a computer-based system for dental decision support in patients with head and neck cancer.

Methods

Findings from our previous studies concerning pretherapy dental decision-making in patients with head and neck cancer were used to develop and test SCREDENT, a decision support system. Dental health status, radiotherapy conditions, and tooth loss in a sample of 209 patients were modeled in an iterative approach, using the aiNet-software, a probabilistic neural network application. ROC curve analysis, measures of accuracy, and logistic regression analysis were used to assess SCREDENT's performance in predicting tooth loss/ tooth extraction.

Results

Modelling and prediction procedures of the aiNet software were relatively simple and rapid. In all training, testing, and validation sequences, SCREDENT was able to reach a solution. Altogether, approximately 1660 vectors (representing teeth under examination) were processed. The results show that in almost 95% of the cases, SCREDENT's predictions for tooth extraction (conditional probability cut-off value: 0.5) agree with the actual tooth extractions carried out as part of the preradiation oral screening.

Conclusions

SCREDENT accurately predicts whether tooth extraction is the most favorable option for preradiation intervention. By means of feeding all appropriate decisions made on the basis of SCREDENT's predictions back into the training set, this system offers a framework for continuous updating and adjusting of the decisions process and therefore not only allows evidence-based decision-making, but also may be a component of a quality control system. A further attractive feature of SCREDENT may be its use for training inexperienced clinicians.

Introduction

High-dose radiotherapy to the head and neck, which includes oral and maxillofacial structures and salivary glands, may result in serious side effects. The short-term effects are mucositis, loss of taste and smell, secondary or "opportunistic" infections, and reduced salivary function. The long-term effects include persistence of reduced salivary function, radiation caries (Fig 6.1), progression of pre-existing periodontal disease activity, limited mouth opening (trismus), soft-tissue breakdown and failure to heal, and radiation bone injury, which in its severest form develops as osteoradionecrosis. As a secondary effect, patients with head and neck cancer experience significant tooth loss, prior to and following radiotherapy.(1,2)

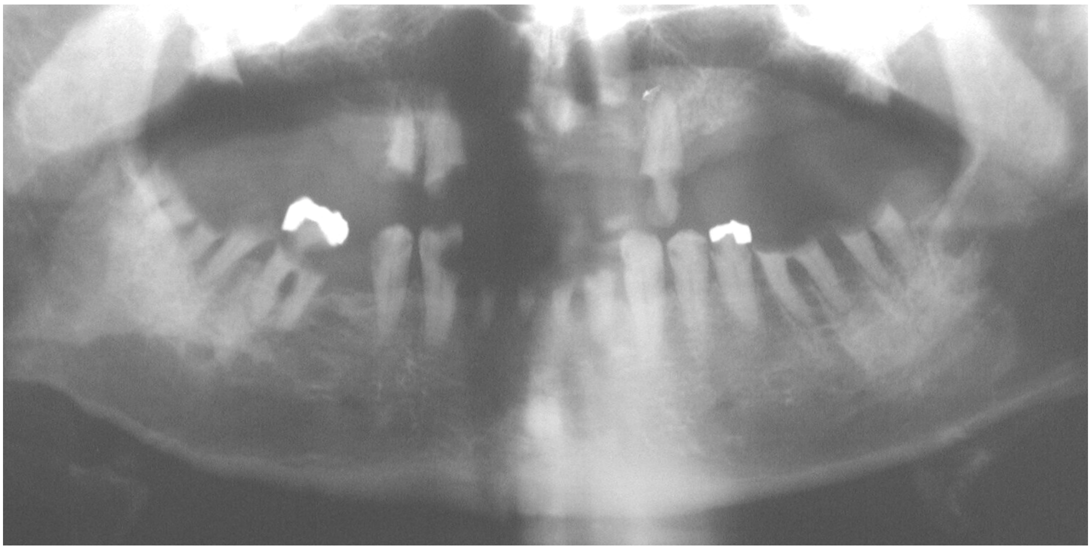

Figure 6.1 Orthopantomogram showing massive radiation caries, two years after radiotherapy for an oropharyngeal squamous cell carcinoma. Note the circumferential spread of the lesions, which resulted in amputation of clinical crowns.

To reduce oral sequelae of head and neck cancer therapy, extensive dental preventive and treatment measures before, during, and after cancer therapy are mandatory. (1,3-5) Implicit in the preventive approach is pretherapy oral screening to identify and eliminate dental risk factors for oral complications.(4) The current standards for dental care before radiation therapy include extraction of those teeth with significant bone loss, extensive caries, and/or extensive periapical lesions. In addition, partially impacted or incompletely erupted teeth and residual root tips not fully covered by bone and/or showing radiolucency to x-rays should be removed.(2,4,6-8)

Important factors in the dental management include, among others, the following considerations.(2,5,9)

(1) anticipated radiation field and dose;
(2) pretherapy dental status, dental hygiene, and retention of teeth that will be exposed to high-dose irradiation;
(3) patient's motivation and ability to comply with preventive measures.

Although several studies strongly support the efficacy of the pretherapy oral screening,(6,10,11) evidence-based clinical guidelines(12-14) to aid clinicians in deciding which options for dental intervention suit these patients best are not yet widely available. In view of the risk that results from high-dose irradiation, special attention to preradiation dental planning appears critical.(2,5) Each case must be managed individually; a single-formula approach for all patients is contra-indicated.(2) The key to control may be the implementation of a dental decision support system, derived from an evidence-based approach.

Evidence-based medicine is an approach to clinical judgment and decision-making in which the clinician uses the best evidence available to decide upon the intervention that suits an individual patient best.(15) This approach involves the rigorous evaluation of the effectiveness of health-care interventions, dissemination of the results of evaluation, and application of these findings toward improvement of clinical practice.(16) Good clinicians use both individual clinical expertise and the best available external evidence, and neither alone is enough. External clinical evidence can inform but can never replace individual expertise. Evidence-based medicine is therefore not an obligatory "cookbook" approach.(17)

This survey forms part of an international research project on dental decision support in patients with head and neck cancer.(5,9,18) The aim of the current survey was to construct and test a system to support dental decision-making, prior to radiotherapy for head and neck cancer. We first summarize some characteristics of decision support systems. We then propose "SCREDENT," a system for dental decision support in head and neck cancer patients.

Decision support systems are interactive, computer-based systems that aid users in judgment and decision-making. They provide data storage and retrieval and support framing, modeling, and problem solving, as depicted in Fig 6.2. Decision support systems are especially valuable in situations in which confidence and reliability are of importance. There are several types of decision support system, such as belief networks, influence diagrams, probabilistic expert systems, and artificial neural network applications.(19) We used a software package to emulate a neural network(20) as formal constructional technique for SCREDENT.

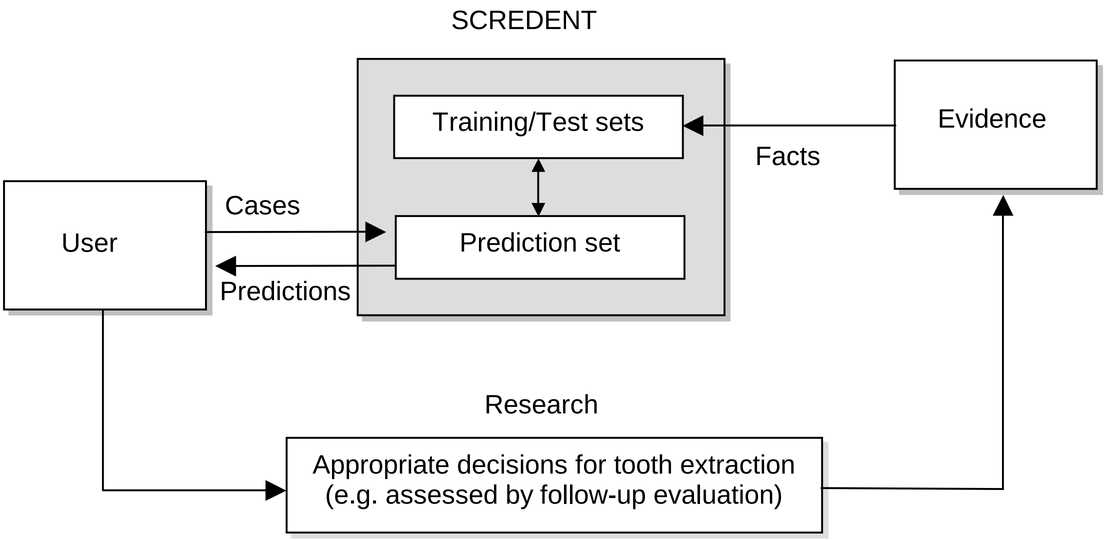

Figure 6.2 Diagram of SCREDENT, a computer-based decision-support system. The gray box represents the part of SCREDENT that is modeled using the probabilistic neural network (aiNet software). The predictions from SCREDENT are conditional probabilities for tooth loss/ tooth extraction. All decisions for tooth extraction that proved to be appropriate should be re-entered into SCREDENT's training set, assuring an evidence-based approach.

The potential benefits of neural-network software seem obvious to those who design them but are often less clear to the end user.(21) Many clinicians are suspicious of these network applications and look upon them as "black boxes". The benefits of analyses using neural networks over more conventional methods, especially for analysis of complex and noisy data, must therefore be clearly demonstrated. In addition, according to Cross et al.,(21) useful software applications must be, among others things, robust and easy to use. While the quality and reliability of decision support systems are important, the most crucial aspect is their user interface. Systems with cumbersome or unclear user-interfaces are rarely useful.

Artificial neural networks have been extensively studied and applied.(20,22-25) This has resulted in numerous research reports in this area. The most common neural-network learning algorithm in biomedical applications is "back-propagation" in "multilayer perceptrons."(26) We used a type of neural network with a different architecture, the Probabilistic Neural Network (PNN). This type of neural network acts as a classifier or predictor that overcomes many of the problems of back-propagation. It has self-organizing properties(27) and trains virtually instantaneously. At present, although there have been relatively few applications of PNN modelling in biomedical situations, all have performed well.(28) Readers looking for more information on neural networks are referred to comprehensive introductory texts.(20,21,29-37)

Materials and methods

The subjects came from a previous clinical study, conducted in 1999.(18) These patients (n=209) had undergone head and neck cancer therapy at the Otorhinolaryngology department and allied departments of University Medical Center Utrecht, The Netherlands, between 1993 and 1998. Patients selected for inclusion in that clinical survey were required to satisfy the following conditions: they (1) were in the regular cancer follow-up schedule; (2) had undergone primary cancer treatment, including radiation therapy, for squamous cell carcinoma in head and neck, one to five years previously; (3) were treated with the intention of curing the disease (patients receiving only palliative treatment or patients with active disease were not included for ethical reasons); and (4) had undergone preradiation dental screening. A second, more recent patient sample was analyzed in order to further validate SCREDENT. This sample consisted of 30 patients who were treated in the University Medical Center Utrecht in the year 2000. Informed consent was acquired from the patients who were found to meet the criteria for inclusion in the study protocol.

Data on dental health status and tooth loss were obtained via pretherapy oral screening. We used a specially designed dentition assessment form- the SCREDENT form- that together with comprehensive instructions and a "getting started" document, is available for download from the Internet.[1] The "SCREDENT, getting started" document also presents an example of a clinical case, illustrating how the findings from the preradiation oral screening should be recoded and entered into SCREDENT in order to make predictions for tooth extraction.

The SCREDENT data collection form was designed and tested using the results from our previous studies. Among other variables, such as type, location, and stage of head and neck tumor, the following, fully described in the SCREDENT instruction document, were recorded:

Input variables:

(1) "*dmftot*": the number of teeth retained
(2) "*drftot*": the total number of high Dental Risk Factors(5)
(3) "*upper*" / "*lower*": the location of the tooth
(4): "*molar*" / "*bicusp*" / "*cusp*" / "*incis*": the type of tooth
(5) "*gland*": major salivary glands in high-dose irradiation field
(6) "*trx*": tooth in high-dose radiation field
(7) "*patfact*": patient's dental IQ

Output variable:

(8) "*tloss*" : tooth extraction/ tooth loss

Using these eight variables, the decision problem analyzed in this paper was modeled graphically, as depicted in Fig 6.3. The solid arrows indicate the correlations between variables which were the scope of the present study. The dotted arrows indicate correlations that are present but were not further specified.

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[1] Available for download at the Internet at http://www.mexsys.net. *(See also Appendices 2,3.)*

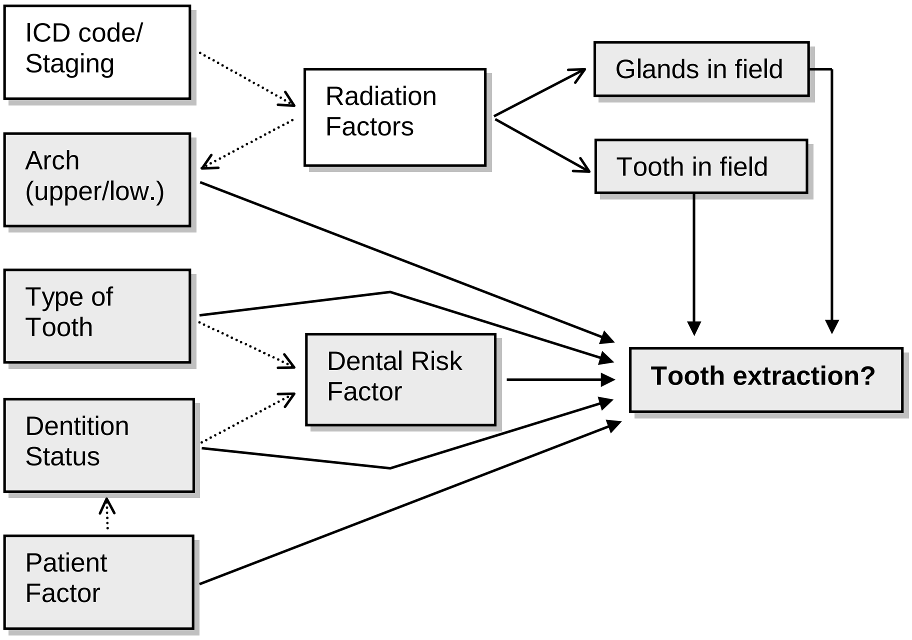

Figure 6.3 Schematic representation of the variables involved in the decision problem. The solid arrows indicate the correlations between the variables that are modeled using aiNet software.
(*ICD code*: International Classification of Diseases, Ninth Revision, Clinical Modification, as published by the U.S. Public Health Service and Health Care Financing Administration)

The next phase of the analysis was the neural-network computing. We used the aiNet software package (aiNet for Windows, version 1.25, aiNet, Celje, Slovenia) to run the PNN on a personal computer.[2] All sets of eight variables, including the known output variables ("*tloss*") were recoded into 2 discrete and 11 binary variables. This process resulted in sets of 13 variables, the so-called "training vectors." aiNet has a spreadsheet-type interface, depicted in Fig 6.4, to enter and store the "training set." The procedure of modeling, data encoding, and data entering is thoroughly described and illustrated with examples in aiNet's manual and in the "SCREDENT, getting started" document. Interested readers are invited to download the SCREDENT files in order to try out the system.

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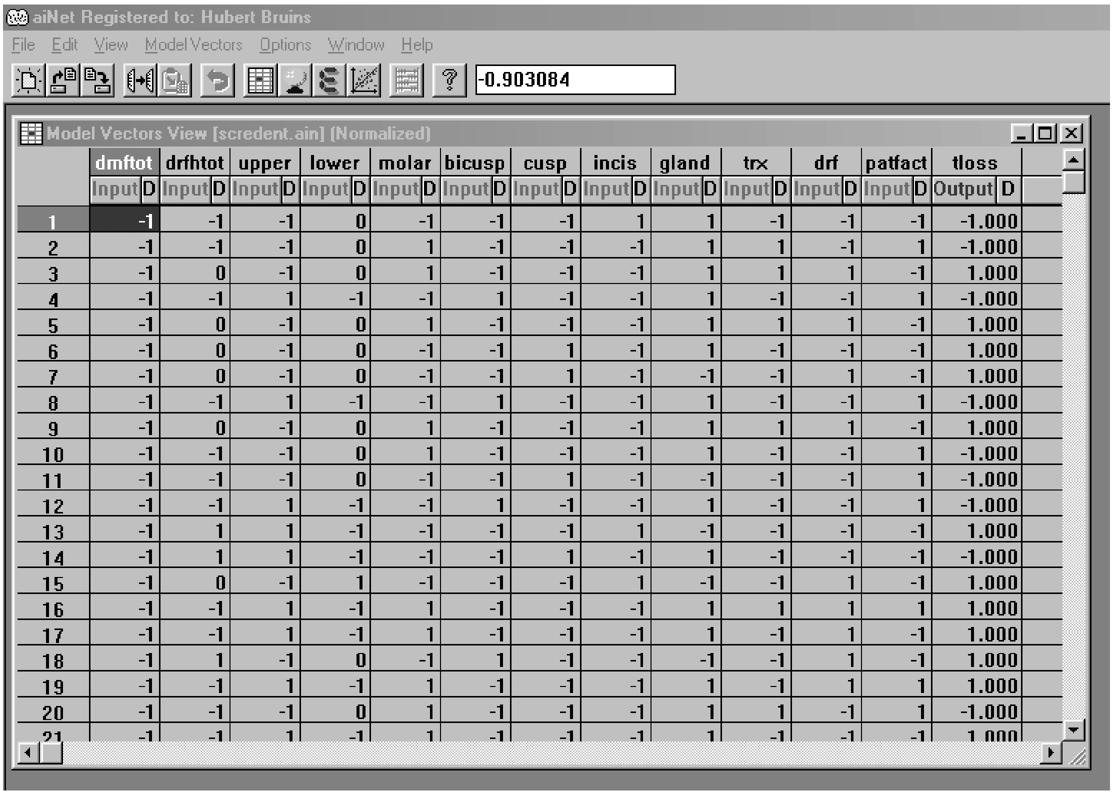
[2] A full working version of aiNet (version 1.25), including online help files, examples, and a comprehensive manual in Microsoft Word format (Microsoft Corporation, Redmond, Washington, WA), can be obtained through download from the Internet. (http://www.ainet-sp.si/NNdownload.htm).



aiNet Registered to: Hubert Bruins

-0.903084

Model Vectors View [scredent.ain] (Normalized)

	dmftot	drfhtot	upper	lower	molar	bicusp	cusp	incis	gland	trx	drf	patfact	tloss
	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Output D
1	-1	-1	-1	0	-1	-1	-1	1	1	-1	-1	-1	-1.000
2	-1	-1	-1	0	1	-1	-1	-1	1	1	-1	1	-1.000
3	-1	0	-1	0	1	-1	-1	-1	1	1	1	-1	1.000
4	-1	-1	1	-1	-1	1	-1	-1	1	-1	-1	1	-1.000
5	-1	0	-1	0	1	-1	-1	-1	1	1	1	-1	1.000
6	-1	0	-1	0	-1	-1	1	-1	1	-1	-1	-1	1.000
7	-1	0	-1	0	-1	-1	1	-1	-1	-1	1	-1	1.000
8	-1	-1	1	-1	-1	1	-1	-1	1	-1	-1	1	-1.000
9	-1	0	-1	0	1	-1	-1	-1	1	1	1	-1	1.000
10	-1	-1	-1	0	1	-1	-1	-1	1	-1	-1	1	-1.000
11	-1	-1	-1	0	-1	-1	1	-1	-1	-1	-1	1	-1.000
12	-1	-1	1	-1	-1	1	-1	-1	1	-1	-1	1	-1.000
13	-1	1	1	-1	-1	-1	-1	1	-1	-1	-1	-1	1.000
14	-1	1	1	-1	-1	-1	1	-1	1	-1	-1	-1	-1.000
15	-1	0	-1	1	-1	-1	-1	1	-1	-1	1	-1	1.000
16	-1	-1	1	-1	1	-1	-1	-1	1	1	1	1	1.000
17	-1	-1	1	-1	1	-1	-1	-1	1	-1	1	-1	1.000
18	-1	1	-1	0	-1	1	-1	-1	-1	-1	1	-1	1.000
19	-1	-1	1	-1	1	-1	-1	-1	1	-1	1	1	1.000
20	-1	-1	-1	0	1	-1	-1	-1	1	1	-1	1	-1.000
21	-1	-1	1	-1	1	-1	-1	-1	1	-1	-1	-1	1.000

Figure 6.4 aiNet's model vector view illustrating the first 20 model vectors of SCREDENT's training set (approximately 1660 model vectors).

To test SCREDENT's performance, six separate samples of 60 training vectors (test sets) were randomly retracted from the training set and used to make predictions. The values of the known output variable ("*tloss*") were deleted, so these samples consisted of only the 12 input variables. Each row comprising the 12 input variables with the missing output variable is called a "test vector." Running aiNet's prediction option, the missing output variable ("*tloss*") of each test vector was predicted on the basis of the data in the training set. The prediction is given as the conditional probability that the tooth under examination should be extracted or will be lost. The value of this conditional probability lies between 0 (no tooth extraction) and 1 (tooth extraction). Next, these predictions were compared to the actual output variables, the tooth extractions that were or were not carried out as part of the pretherapy dental screening. Receiver Operating Characteristic (ROC) curve analysis, described in detail elsewhere,(38-40) was used to assess SCREDENT's performance. In addition, true-positive, true-negative, false-positive, and false negative values and "overall accuracy" were computed. Overall accuracy is defined as true positives plus true negatives divided by total sample size. In addition, we compared SCREDENT's performance to logistic regression analysis, using the aggregation of test sample 1-6. This aggregated sample is designated "test sample 7" (see Table 6.1).

To further validate the model, a validation set consisting of the second patient sample was used to repeat SCREDENT's predictive accuracy. Again, a ROC analysis was carried out and accuracy was assessed.

Results

Modeling and prediction procedures of the aiNet software were relatively simple and rapid. In all training, testing, and validation sequences, SCREDENT was able to arrive at a solution. Altogether, approximately 1600 vectors (representing teeth under examination) were processed.

Table 6.1 Summary of SCREDENT test samples

SCREDENT Sample	*True pos.*	*False pos.*	*True neg.*	*False neg.*	*Sensitivity*	*Specificity*	*Area under the ROC Curve*[1]	*Accuracy (%)*
test 1	9	1	47	3	0.75	0.97	0.967	93
test 2	17	3	39	1	0.89	0.98	0.979	93
test 3	17	5	36	2	0.89	0.87	0.945	88
test 4	17	4	34	5	0.77	0.89	0.941	85
test 5	13	0	45	2	0.86	1.00	0.987	97
test 6	21	2	34	3	0.87	0.94	0.970	92
Validation n = 417	185	6	213	13	0.93	0.97	0.987	95
Overall n = 777	279	21	448	29	0.90	0.95	0.968	94
SCREDENT test 7	94	14	236	16	0.85	0.94	0.955	92
Logistic regression test 7	85	10	240	25	0.77	0.96	0.953	90

[1] Area under the ROC curves: asymptotic significance level, p <0.001

The results show that in almost 95% of the cases, SCREDENT's predictions for tooth extraction (conditional probability cut-off value: 0.5) agree with the actual tooth extractions carried out as part of the preradiation oral screening. True-positive, true-negative, false-positive, and false negative values are shown in Table 6.1, along with sensitivity and specificity values. Fig 6.5 displays ROC curves. The areas under the ROC curves of the test samples ranged from 0.941 to 0.987 (mean 0.964), which also demonstrates a very high predictive accuracy. The area under the ROC curve of the validation sample was 0.987, which was the second highest of all ROC curves. It should be noted here that SCREDENT's specificity is slightly better than its sensitivity. This means that SCREDENT predictions are more accurate when a tooth should not be extracted or will not be lost than when a tooth requires extraction.

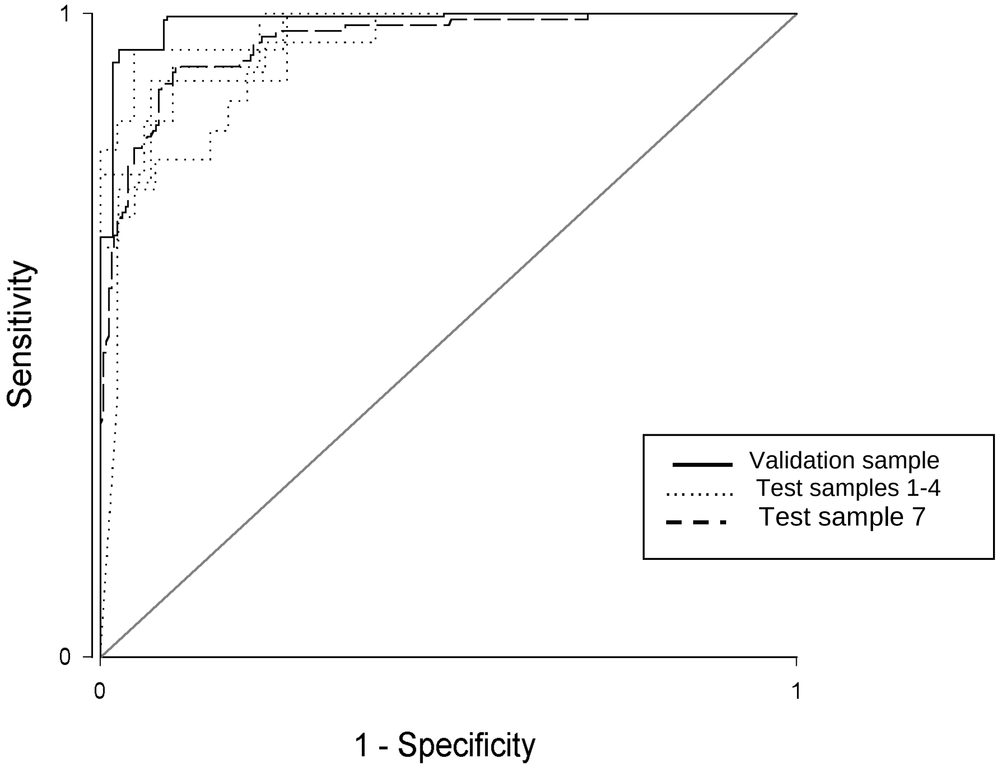
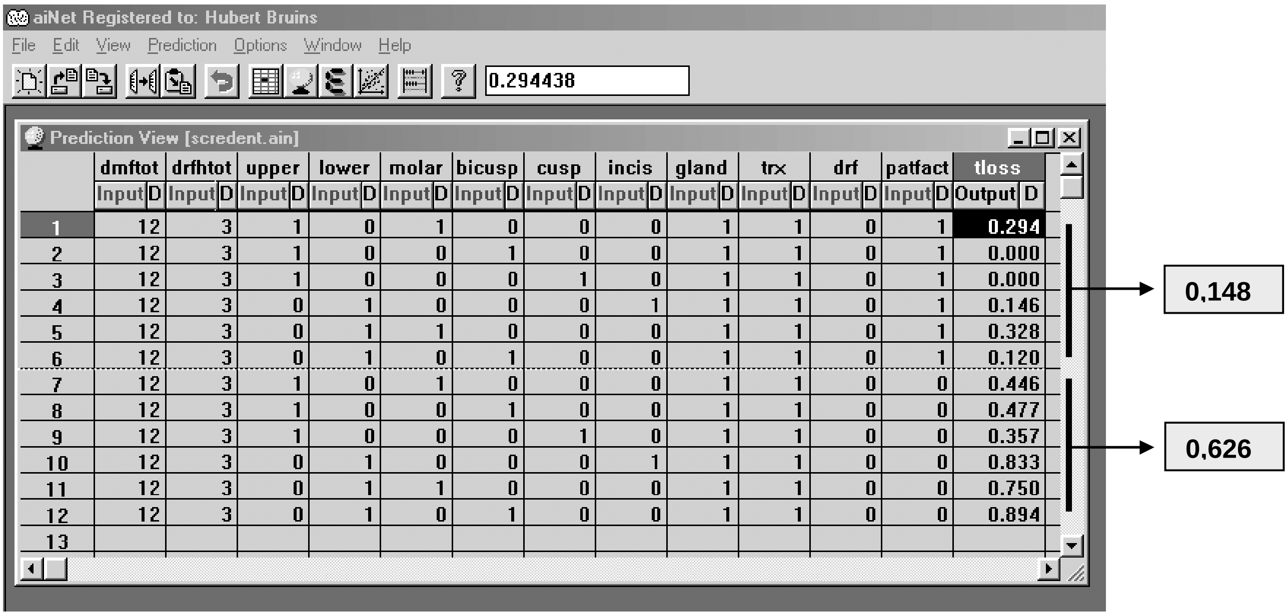


Figure 6.5 Receiver Operating Characteristics (ROC) curves.

SCREDENT predictions revealed that the patient factor "*patfact*" has a major influence on the prediction values. A hypothetical prediction example is depicted in Fig 6.6. The output values (conditional probabilities) in the column "*tloss*" were predicted on the basis of the model vectors in the training set with known outputs. Rows 1-6 represent teeth (together with dental health status and radiotherapy conditions) of a patient with a high 'dental IQ' (*patfact*=1). The overall 'mean' conditional probability for tooth loss (dental extraction) is 0,148. Rows 7-12 represent the same teeth, but now for a patient with unfavorable "dental IQ" (*patfact*=0). The overall "mean" conditional probability for tooth loss is now 0.626, that is 4.2 times higher, which shows that the mean probability of tooth loss (column "*tloss*") in patients with "*patfact*" = 1 (high dental IQ), in rows 1-6, is 4.2 times higher than in cases with "*patfact*" = 0 (average/low dental IQ), in rows 7-12.



	dmftot		drfhtot		upper		lower		molar		bicusp		cusp		incis		gland		trx		drf		patfact		tloss	
	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Input	D	Output	D
1	12		3		1		0		1		0		0		0		1		1		0		1		0.294	
2	12		3		1		0		0		1		0		0		1		1		0		1		0.000	
3	12		3		1		0		0		0		1		0		1		1		0		1		0.000	
4	12		3		0		1		0		0		0		1		1		1		0		1		0.146	
5	12		3		0		1		1		0		0		0		1		1		0		1		0.328	
6	12		3		0		1		0		1		0		0		1		1		0		1		0.120	
7	12		3		1		0		1		0		0		0		1		1		0		0		0.446	
8	12		3		1		0		0		1		0		0		1		1		0		0		0.477	
9	12		3		1		0		0		0		1		0		1		1		0		0		0.357	
10	12		3		0		1		0		0		0		1		1		1		0		0		0.833	
11	12		3		0		1		1		0		0		0		1		1		0		0		0.750	
12	12		3		0		1		0		1		0		0		1		1		0		0		0.894	
13																										

Figure 6.6 SCREDENT's prediction view of a hypothetical sample, further explained in text

Discussion

Many clinical decisions are based primarily on values or beliefs and on various resources: opinion-based decision-making. At present, more and more attention is being given to evidence derived from research: evidence-based decision-making.(15,17) As stated before, good clinicians use both individual clinical expertise and the best available external evidence. In this paper, we propose SCREDENT, a system to support dental decision-making in patients with head and neck cancer. The rationale for constructing SCREDENT came from the understanding that decision-making in this area is often critical while evidence-based guidelines were not yet available.(5,9)

SCREDENT incorporates a patient factor, describing patient's "dental-mindedness" or "dental IQ,"(41) that significantly influences the outcome of the prediction. The patient factor stresses the importance of the patient's overall dental health at the time of the pretherapy dental screening, as noted in our previous study.(18) We have found that, when a head and neck cancer patient presents with poor dental health at the pretherapy oral screening, there will be substantial preradiation tooth loss. Moreover, if these patients have remaining teeth during irradiation, they are more likely to continue to develop dental pathosis following radiotherapy than are patients who present with satisfactory dental health.(42) Subsequent to the radiation, they will need extensive dental treatment, including tooth extractions. Consequently, the initial treatment planning, enhanced by SCREDENT, should include the anticipation that the remaining dentition of patients presenting with poor dental health may continue to deteriorate. In these cases, SCREDENT accurately predicts whether tooth extraction is the most favorable option for preradiation intervention.

Comparing SCREDENT's performance to the logistic regression model shows that SCREDENT performs slightly better (accuracy 92%, versus 90% for the logistic regression model). However, unlike the logistic regression model, SCREDENT can handle missing or inaccurate data,(22) and the explicit form of the relationships between the input variables and the output does not have to be specified in neural network models.(43)

A very important issue is to verify whether the predictions are applicable to the patient under examination. Additional considerations, such as the lack of clinical or financial resources, may require adjustment of the overall treatment plan. In addition, timing considerations are very important. If the interval between the preradiation oral screening and the start of the radiotherapy is limited, dental intervention involving extensive dental treatments is usually not possible. On the other hand, teeth requiring extraction, as indicated by SCREDENT, can be left in place until later if they are NOT in the high-dose radiation field. This demonstrates that a decision support system is not prescriptive. SCREDENT can inform, but it can never replace individual expertise.

The fact that the validation sample produced the second highest accuracy result may reveal a form of bias. Developing SCREDENT obviously provided feedback to the decision-making authors. Analysis of the decision problem yielded additional knowledge. In effect, it may have influenced the decision-makers' opinion and degree of belief in the appropriateness of the dental intervention decisions, leading to decisions that were more congruent with SCREDENT's predictions. This also illustrates the dynamic property of decision support systems.(27,32,44) By means of feeding all appropriate decisions made on the basis of SCREDENT's predictions back into the training set, a framework is created for continuous updating and adjusting of the decision process. This not only allows evidence-based decision-making but also may be a component of a quality control system. A further attractive feature of SCREDENT may be its use for training inexperienced clinicians.

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CHAPTER 7

SUMMARY, GENERAL DISCUSSION, AND CONCLUSIONS

Summary and general discussion

This thesis presents a series of studies that investigated preradiation dental decision-making in patients with head and neck cancer. In ***Chapter 1***, it is ascertained that in view of the risk for oral sequelae resulting from high-dose radiotherapy, special attention to preradiation dental planning appears critical. Each case must be managed individually on the basis of the patient's needs, the status of the tumor, and the risks for dental health in irradiated tissues; a single-formula approach for all patients is contra-indicated.(1)

In accordance with the evidence-based approach that forms the basis of the health-care paradigm of this new millennium,(2,3) the main subject of this thesis is to develop and to test a decision support system, in order to enhance dental decision-making in patients with head and neck cancer. More specifically, studies were conducted to:
(1) Identify the decision dilemma and perform a clinical decision analysis;
(2) Analyze the decision policies of clinicians familiar with and experienced in preradiation dental screening in order to describe how dental- and radiotherapy-related risk factors influence their decision-making;
(3) Propose a method for judgment analysis, in order to identify the characteristics of individual judgment policies of dental clinicians with respect to the prophylactic extraction of teeth;
(4) Develop and test "SCREDENT," a system for dental decision support in patients with head and neck cancer.

In the studies underlying this thesis, three different approaches to analyzing judgment and decision-making were used: ***normative***, ***descriptive,*** and ***contextual***. These approaches to analyzing judgment and decision-making relate to two of the four decision strategies introduced in Chapter 1, which were applied in this thesis. This is summarized in a simple matrix.

	DECISION STRATEGY (see Chapter 1)	
	COMPUTATIONAL	JUDGMENTAL
STUDY APPROACH	*NORMATIVE (Chapter 2)* *CONTEXTUAL (Chapter 6)*	*DESCRIPTIVE* *(Chapters 3,4,& 5)*

Normative approach

The ***normative*** approach attempts to answer the question, "How should decisions be made?" It seeks to identify the decision problem and separate it into manageable components that are usually better defined and understood. Studying a complex system built out of such components can subsequently be aided by a theoretically sound analyzing technique. The process of decomposing and formalizing a problem is called "modeling," which allows for exploring, explaining, and arguing about a decision problem. The normative approach is used to study a decision situation in which a computational strategy(4) should be adopted for decision-making. This applies if there is good insight into the decision problem and satisfactory levels of certainty on causation and outcome preferences.

How should decisions be made? The answer is revealed by the formal technique of Clinical Decision Analysis,(5,6) which involves "*a priori decomposition*" of the decision process. It refers to separating the decision process into its components before the decision is made.(7) Such components include (a) the *probabilities* or likelihood of occurrence of each alternative considered and (b) the *utility* attached to each alternative. Construction of a *decision tree* prior to the decision is an easy way of simplifying the decision process because it forces clarification of all the bases for the decision. Only four types of information are needed in order to construct a decision tree:

(1) What are the possible courses of action?
(2) What are the events that might follow from those actions?
(3) What is the probability of occurrence of each event?
(4) What is the outcome value (utility) of each event?

Generating this information makes possible the analysis of the decision problem in a much more organized and thoughtful way than would otherwise be the case.(5-8)

Model for pretherapy decision support

In ***Chapter 2***, Clinical Decision Analysis was used to design and test a Model for Pretherapy Dental Decision Support (MDDS). The considerations that underlie the decision problem are outlined in detail. In order to construct the decision tree, the Dental Risk Factor (DRF), the Malignancy-Related Risk Factor (MRRF), and the Outcome Value (OV) are introduced. The major difficulty encountered in constructing the decision tree was assessment of probabilities and utilities. When results from evidence-based research are available, reasonable probabilities can often be deduced. This was not the case with regard to the decision-making problem underlying this thesis, as explained in Chapter 2. Current clinical standards are descriptive in nature and do not involve straightforward probabilities. To compensate for the lack of these evidence-based probabilities, baseline estimates are used instead, resulting in what is therefore called a *base-case analysis*.(5) The estimates are than quantified through the use of direct ranking methods, using simple comparison scales. These hierarchical scales produce good levels of consistency and are very appropriate for making comparisons.(9-13)

However, the use of estimates implies a degree of *un*certainty and susceptibility to biases. For the purpose of testing the robustness and the coherence(14) of the MDDS, probabilistic sensitivity analyses were performed using second-order Monte Carlo simulations.(15) The sensitivity analyses show that in general, the decisions supported by the model are robust and the model is coherent (using 10,000 simulations, and a 95% confidence interval). The overall conclusion is that the MDDS is a useful tool for the development of evidence-based guidelines.

The MDDS points out that in selected cases (favorable complementary decision factors, i.e. adequate clinical and financial resources, and satisfactory levels of patient compliance) and under certain risk conditions (especially, moderate risk conditions), it is worthwhile, with regard to better patient outcomes, to accept some degree of risk of an adverse outcome. Here, the model reveals the area in which further clinical research may be most valuable: how would clinicians use or "weight" the components of the decision tree in making pretherapy dental decisions? Do they accept some risk or do they avoid risky choices? These questions were solved using a descriptive approach.

Descriptive approach

The second approach in this thesis to analyzing Judgment and Decision-Making (JDM) is ***descriptive***. The descriptive approach to JDM attempts to answer the question, "How do people make decisions?" It recognizes that people do not always follow normative rules and therefore tries to characterize their actual behavior and beliefs.(16-18) This descriptive approach is used to study a decision situation in which a judgmental strategy(4) for decision-making should be adopted.

How do clinicians make judgments and decisions? The answer may be revealed via Clinical Judgment Analysis (CJA),(14,19) which involves "*a posteriori decomposition*" of the judgment process.(7) If a priori decomposition implies decomposing the decision process prior to its occurrence, then a posteriori decomposition obviously implies that decomposition will take place after a series of judgments have been made. It is meaningful to recall the definitions of judgment and decision-making introduced in Chapter 4: clinical judgment is based on the weighting and combining of information so as to arrive at conclusions that can serve as a basis for clinical decision-making. The latter process involves selecting courses of clinical action in order to achieve optimum outcomes.

As outlined in Chapter 3 and 4, the judgment policies of a group of clinicians ("between-judges") and of individual judges ("within-judge") can be captured after judgments are made regarding paper cases; the results may then be used to set up a survey to analyze clinical cases (Chapter 5).

Judgment analysis survey

The findings of the international survey using a consensus questionnaire (***Chapter 3***) support the assumption made in Chapter 2 that policies in this field seem to be based primarily on clinical experience and opinions rather than on evidence-based guidelines. Nonetheless, opinion-based and experience-based decision-making are essential components of the clinical thought process,(3,7) as explained in Chapter 1.

Findings from the survey show a high correlation between the aggregated policies of the clinicians and the MDDS (correlation coefficient: 0.85; $p < 0.01$), indicating that this model may be appropriate in further solving the decision problem.

As a cue for decision-making, the Dental Risk Factor (*DRF*) was far more important than either the irradiation factor (*RTX*) or tooth functionality (*STRAT*). Yet, clinicians' degree of certainty in the appropriateness of their decisions is significantly influenced ($R= 0.69$; $p<0.01$) by only the radiation dose on teeth (*RTX*) and not by dental conditions (*DRF*) or by tooth functionality (*STRAT*). This finding may be explained as follows: the dental intervention decision prior to irradiation is triggered by the fact that a high radiation dose will be delivered to the oral structures. Clinicians are quite certain of the necessity and appropriateness of this dental intervention. Anticipating irradiation, they subsequently make their judgments and decisions based mainly on dental health characteristics. As explained in Chapter 5, a parallel applies for tooth loss in these patients. Tooth loss is initiated by irradiation but is primarily correlated to dental factors.

The findings in Chapter 3 apply to the aggregated policies of all forty-four clinicians, which were analyzed at group level. It is important to note here that a simple aggregation and a "majority rule" were used prior to the statistical analysis, in order to combine the independent judgments of multiple clinicians. Mean levels of clinicians' consensus show great similarity in their policies. However, this similarity is lower in the case of moderate dental risk conditions. Moreover, tooth functionality was not an important factor in clinicians' extraction decisions. One explanation might be that, particularly in these patients, clinicians found it difficult to acknowledge the functional impact of missing teeth. In adults and older persons, it has been shown that oral function problems increase when the number of retained teeth decreases.(20-25) In head and neck cancer patients, oral function problems relate primarily to the type and extent of tumor therapy.(26-30) The functional impact of the dental status is therefore most likely an additional factor and of less concern to a majority of, or perhaps to all, clinicians.

The low importance of tooth function as a cue for preradiation dental decision-making may also be related to "risk aversion." Many decision theorists have described individual differences in attitudes toward risk. It has been shown that one's willingness to accept risk (or willingness to gamble) is dependent on specific outcome dimensions(9,31,32) (in the problem domain of this thesis: oral complications, oral functioning), and on personal experiences.(17) For example, a clinician familiar with one or more cases of osteoradionecrosis induced by post-irradiation dental extractions is more likely to reduce his level of risk-taking by extracting more teeth prior to irradiation. Accordingly, the decision-maker seems less prepared to consider the "expected utility" or benefit of retaining functional teeth.(33,34) However, as the judgment analysis in Chapter 3 was carried out at group level, these individual differences in the perception of risks and anticipated benefits could not be detected by this method.

Several authors note that an aggregation of independent judgments is more accurate than individual responses.(35-38) In fact, the accuracy of an aggregate is a function of the number of raters and the agreement between raters.(39,40) cited by (35) However, several experiments have shown that the quality of answers improves with increasing group size up to about 13, after which the law of diminishing returns takes over(41,42) and "regression to the mean" may become apparent. This leads to another assumption, that analysis of *individual* judgment policies *before* they are compared and aggregated may reveal additional information.

JANNET

These assumptions concerning the need for analysis on an individual basis resulted in the development of JANNET (***Chapter 4***). JANNET, Judgment Analysis by Neural NETwork, was designed to be used when the assumptions underlying multiple regression analysis, the principle analysis method for Judgment Analysis,(14,19) are not met. For each individual clinician, JANNET produced the Likelihood Ratio (LR) of each type of dental intervention for strategic teeth versus non-strategic teeth. Hence, the JANNET approach made possible the recognition of probabilistic "patterns" in individual judgment policies. Using the K-means cluster analysis based on the LR of each response option resulted in 4 clusters. A summary profile of the clusters is given in Chapter 4 (Table 2 and Figure 5). In contrast to the LR's response options "*tooth extraction*" and "*dental treatment*," the LR of response 3 ("*no-action*") failed to contribute significantly to the clustering of the judges.

Using the results from the clustering allows the judgment making of the clinicians to be analyzed more precisely than is allowed by the between-judge analysis in Chapter 3. As discussed previously, such an improved insight into this particular area of "nonlinear" judgment and decision-making could be helpful for the development of evidence-based guidelines and for training of clinicians.(43) For example, it has revealed that certain clinicians tend to avoid risky choices, and that others are willing to take some risk by retaining teeth in the anticipation of better outcomes in terms of oral function.(44)

Cohort study

The cohort study (45,46) described in ***Chapter 5*** involved a retrospective and follow-up evaluation of 209 patients treated with radiation for cancer of the head and neck. This study was designed to investigate the association of tooth loss with dental status (number of retained teeth), dental risk factors (DRFs), and radiotherapy-related factors respectively. A further objective was to study the incidence of radiation caries and osteoradionecrosis.

The results of the analyses indicate that the level of tooth loss was statistically significantly associated with dental status and the number of high DRFs at baseline, and also with radiotherapy factors (number of teeth and/or the major salivary glands in the high-dose radiation field). These findings compare to the conclusions made in Chapter 3 that the decision policies of clinicians seem to be primarily based on dental factors, including patients' overall dental health, and also on factors concerning radiotherapy.

The findings of this clinical survey indicate that when a head and neck cancer patient presents with reduced dentition and/or with poor dental health at the preradiation oral screening, substantial tooth loss may result. It is concluded that tooth loss in the patients in this sample is considerably higher than the amount of tooth loss described in epidemiological studies concerning the general population. (47-64) Moreover, patients who have remaining teeth during irradiation are at risk of developing new dental pathosis, such as radiation caries, following radiotherapy. Subsequent to the radiation, a patient who presented initially with poor dental health may again need extensive dental treatment, including tooth extractions. Consequently, the preradiation treatment plan, enhanced by dental decision-making, should include this anticipation. Uncompromising preradiation dental intervention is therefore warranted. A survey study that would further define the relationship between a head and neck cancer patient's perception regarding the need for dental rehabilitation and his or her ability to comply with the advised dental treatment and oral hygiene measures is recommended.

Contextual approach

The third and final approach to analyzing judgment and decision-making is ***contextual***. Occasionally, the term "prescriptive" is used to outline how we can help clinicians make better decisions. "Prescriptive" implies a degree of obligation and inflexibility. As explained in Chapter 1, good clinicians use both individual clinical expertise and the best available external evidence. External clinical evidence can inform, but can never replace individual expertise. Since evidence-based medicine is therefore not an obligatory 'cookbook' approach,(65) in this thesis the term "*contextual*" is introduced. This term should be interpreted as: "within the context of the decision problem," but also as: "from the context or approach of evidence-based decision making." The former interpretation implies that the decision maker not only understands but also takes into account all components of the decision-making process. The latter interpretation of the term "*contextual*" relates to the paradigm of evidence-based decision-making. As explained by Muir Gray, an evidence-based approach initiates strategies to increase the good-to-harm ratio of therapies, resulting in an increase in the effectiveness of healthcare.(3)

SCREDENT

In ***Chapter 6***, SCREDENT, a computer-based system for dental decision support in patients with head and neck cancer, is presented. Using methods of probability and decision theory, this system is capable of modeling dental decision problems. It allows for combining expert opinions with observational data and processes the information to support decision-making. SCREDENT is especially valuable in situations in which confidence and reliability are of primary importance.

The findings from the first four studies in this thesis reveal that dental factors, radiation conditions, and patient's dental IQ are the most important variables in the decision process. The outcome value in terms of oral functioning seems of secondary importance in the decision process and has therefore not been included.

SCREDENT was easy to train, and making predictions using the spreadsheet type "prediction view" is a straightforward procedure. The software allows data to be added or deleted from the training set without lengthy retraining. As with human experience, artificial neural network learning is often a continuous process.(66) Additional input data collected during operation can improve the performance because it can be fed back into SCREDENT without difficulties.

Testing of SCREDENT revealed high levels of accuracy, indicating that the system is capable of modeling preradiation dental extraction decisions in patients with head and neck cancer. However, what is the advantage of SCREDENT, if any, over the decision-tree model, the MDDS?

Decision-tree model (MDDS) versus SCREDENT

Clinicians often weight (parts of) clinical data in a *nonlinear* fashion.(14) In general, nonlinear phenomena are pervasive in the medical domain.(67) The association between dental status and tooth loss, outlined in Chapter 5 and depicted in Fig 5.2 on page 77 is a good example of such a nonlinear phenomenon. Another simple example may illustrate these nonlinear phenomena. As shown in Chapter 3, the periodontal condition of a tooth, assessed by measuring the depth of a periodontal pocket using a special probe, is a significant cue for dental extraction prior to radiation therapy. If we plot the risk level or "level of concern" against the pocket depth we can clearly identify the sigmoidal shape of the curve (nonlinear equation), see Fig 7.1. Thus, the difference in pocket depth of 1 mm has major implications only when the pocket depths are in the interval of 4-7 mm. If a pocket depth is 11 mm instead of 8 mm, in this interval, the difference of 1 mm has virtually no consequences for the decision.

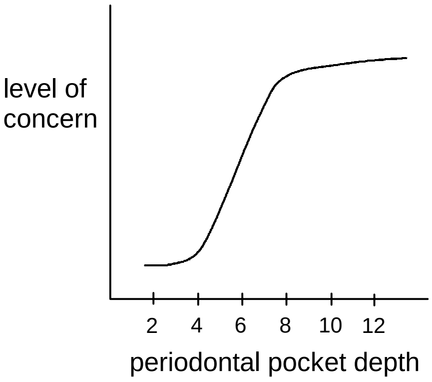

Figure 7.1

Calculating expected values (EVs) by means of "folding back and averaging out" a decision tree (Chapter 2) is in fact a *linear* process with a limited number of outcomes. For example, the decision tree presented in Chapter 2 has 2^3 branches and 2 outcome variables, resulting in sixteen different Expected Values (Evs). Instead, the probabilistic neural network application not only easily handles a large number of conditions but also models nonlinear phenomena. The same applies to the neural network approach to clinical judgment analysis outlined in Chapter 4. The JANNET method enabled analysis of individual judgment policies when the technique of multiple regression analysis could not be applied because the linearity and normality assumptions underlying this technique were not met.

Moreover, missing data of one or more decision-tree components (e.g. missing nodes or missing probabilities) fully corrupt the process of "folding back and averaging out." SCREDENT, however, can handle missing data very well. The system is capable of *generalization*: similar inputs produce similar predictions despite small deviations in the input data. Generalization in neural networks may be viewed as multidimensional interpolation.(66,68)

Another important advantage of using SCREDENT over the decision-tree model is that the former is self-organizing and is capable of learning the most complicated relationships between the training vectors ("training vectors" are further explained in Chapters 4 and 6, and in Appendix 3) and their correct classification.(66,69-72) Here, one of SCREDENT's major potentials becomes clear: by feeding all appropriate decisions made on the basis of SCREDENT's predictions back into the "knowledge domain" comprising the training vectors, this system allows for continuous updating and adjusting of the decisions process and therefore not only permits evidence-based decision-making, but also may be a component of a quality control system in this problem domain.

Conclusions

(1) The Model for Pretherapy Dental Decision Support (MDDS) in patients with head and neck cancer identifies and structures dental decision problems, and appears a useful tool for the development of evidence-based guidelines in this domain.

(2) The preradiation dental decision policies of a group of experienced oral-maxillofacial surgeons and hospital dentists seem to be based primarily on clinical experience and opinions rather than on evidence-based guidelines; the policies are mainly determined by dental risk factors; the certainty concerning the appropriateness of the decisions depends only on irradiation factors.

(3) The JANNET approach, which looks promising and should be further tested, makes possible the recognition of probabilistic "patterns" in nonlinear judgment policies and the subsequent grouping of clinicians with related decision policies together.

(4) A majority of the clinicians participating in the international survey do not use tooth functioning as a significant factor in the preradiation decision making process; instead, they appear to avoid possible adverse outcomes by extracting teeth prior to irradiation, which may be interpreted as "risk aversion."

(5) Tooth loss in patients with head and neck cancer is statistically significantly associated with preradiation dental-health status, the number of high dental risk factors, and radiotherapy-related factors; the incidence of radiation caries following radiotherapy is associated with the number of high dental risk factors at the time of the preradiation dental screening.

(6) The initial dental treatment planning in patients with head and neck cancer, enhanced by clinical decision-making, should include the anticipation that the patient's oral health may deteriorate following radiotherapy, especially in cases initially presenting with poor dental health; therefore, uncompromising preradiation dental intervention is warranted.

(7) SCREDENT, a computer-based system for preradiation dental decision support in patients with head and neck cancer, is accurate in predicting tooth loss (i.e. dental extractions); the system can learn from those of its predictions that turned out to be appropriate, and may therefore be useful as tool for the continuous updating of evidence-based clinical guidelines and for quality control in this domain.

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CHAPTER 8

SAMENVATTING EN CONCLUSIES

(SUMMARY AND CONCLUSIONS IN DUTCH)

Samenvatting

Hoofdstuk 1 is de algemene inleiding van dit proefschrift. Hierin worden de probleemstelling, de doelstellingen en de opbouw gepresenteerd. Eerst komen een aantal aspecten van hoofd-halstumoren aan de orde. Vervolgens wordt ingegaan op de orale gevolgen van radiotherapie in het hoofd-halsgebied. Om deze complicaties zoveel mogelijk te beperken zijn preventieve en curatieve tandheelkundige maatregelen voorafgaand, tijdens en na de tumorbehandeling onontbeerlijk. Met de *tandheelkundige screening* die aan de tumorbehandeling vooraf gaat worden tandheelkundige risicofactoren opgespoord. Een op het individu toegesneden behandelplanning, waarbij sterk rekening wordt gehouden met de medische en psychosociale componenten dient hierbij centraal te staan. Het blijkt niet mogelijk om voor het tandheelkundige beleid standaardprocedures toe te passen.

Dit proefschrift zoekt naar een oplossing met behulp van klinische besliskunde. Hierbij worden vier verschillende beslissingsstrategieën geïntroduceerd: (1) de rekenkundige strategie, (2) de beoordelingsstrategie, (3) de compromisstrategie en (4) de gokstrategie. De rekenkundige strategie en de beoordelingsstrategie worden uitgewerkt en toegepast in het proefschrift.

De doelstelling van dit proefschrift is het ontwikkelen en testen van een systeem voor het ondersteunen van tandheelkundige beslissingen voorafgaand aan radiotherapie bij patiënten met een hoofd-halstumor. Dit wordt gerealiseerd door:

(1) Een analyse van de tandheelkundige beslissingen die voorafgaand aan radiotherapie worden genomen;

(2) Een analyse van de besluitvorming van op dit gebied ervaren kaakchirurgen en ziekenhuistandartsen met als doel te beschrijven hoe de tandheelkundige en de aan radiotherapie verbonden risicofactoren hun besluitvorming beïnvloedt;

(3) Het presenteren van een nieuwe methode om te analyseren welke individuele afwegingen kaakchirurgen en tandartsen maken bij de beslissing om gebitselementen voorafgaand aan radiotherapie te extraheren;

(4) Het nagaan in hoeverre gebitsverlies bij patiënten met een hoofd-halstumor verbonden is met de gebitsstatus en de aanwezige tandheelkundige en radiotherapeutische risicofactoren;

(5) Het ontwikkelen en testen van SCREDENT, een systeem dat ondersteuning biedt bij het nemen van tandheelkundige beslissingen bij patiënten met een hoofd-halstumor.

In ***Hoofdstuk 2*** wordt een klinische beslissingsanalyse beschreven die uit vier stappen bestaat:

1. Inventariseren en analyseren van de dilemma’s bij het nemen van beslissingen, gevolgd door het opstellen van een beslisboom;
2. Bepalen van kansen en uitrekenen van de beslisboom;
3. Afwegen van de optimale beslissingen;
4. Sensitiviteitsanalyse waarbij gebruik wordt gemaakt van tweede orde "Monte Carlo" simulaties.

Deze stappen resulteren in een beslissingsmodel (Model for Dental Decision Support --MDDS) voor optimalisatie van tandheelkundige beslissingen. De resultaten van de sensitiviteitsanalyse tonen aan dat het model voldoende robuust is. Het model lijkt daarom geschikt om richtlijnen te ontwikkelen die op wetenschappelijk onderzoek zijn gefundeerd (Eng. *evidence-based guidelines*). De conclusie is dat verdere beoordeling van de validiteit van het model nodig is voordat praktische toepassing mogelijk is.

In ***Hoofdstuk 3*** wordt een internationaal onderzoek beschreven. Het werd uitgevoerd om inzicht te krijgen in de besluitvorming van kaakchirurgen en ziekenhuistandartsen die ruime ervaring hebben met de tandheelkundige screening. Aan in totaal 54 kaakchirurgen en ziekenhuistandartsen in diverse landen werd een vragenlijst toegezonden. Vierenveertig kaakchirurgen en ziekenhuistandartsen retourneerden de vragenlijst (een respons van 81%). Door een zogenoemde "klinische beoordelings-analyse" (Eng. *clinical judgment analysis*) toe te passen op de verzamelde antwoorden van de gehele groep is er sprake van een *inter*-beoordelaarsanalyse (Eng. *between*-judges analysis).

De resultaten van de beoordelingsanalyse tonen aan dat 88% van de genomen beslissingen en 49% van de daarbij ervaren zekerheid kan worden verklaard door de tandheelkundige en radiotherapeutische risicofactoren. Bovendien blijkt de besluitvorming van de kaakchirurgen en de ziekenhuistandartsen in hoge mate gecorreleerd (correlatiecoëfficiënt = 0.85) met het beslisboom-model (MDDS). Slechts 9 van de 44 deelnemers (20%) gebruikten schriftelijke richtlijnen bij de tandheelkundige screening voorafgaand aan de radiotherapie. Dit bevestigt de veronderstelling dat de besluitvorming vooral gebaseerd is op ervaring en persoonlijke standpunten in plaats van op richtlijnen die op wetenschappelijk onderzoek zijn gefundeerd. Geconcludeerd wordt dat het beslismodel (MDDS) een goede basis is voor verder onderzoek. Ook kan het model voor onderwijsdoelen worden gebruikt.

In ***Hoofdstuk 4*** wordt JANNET (**J**udgment **A**nalysis via **N**eural **NET**work) gepresenteerd. Deze nieuwe analysetechniek voor klinische beoordelingsanalyse (Eng. *clinical judgment analysis*) maakt gebruik van een artificieel neuraal netwerk en verschilt daardoor van de meeste klinische beoordelingsanalysen waarbij de analysetechniek gebaseerd is op multiple regressieanalyse. JANNET kan worden toegepast wanneer de aannamen voor multipele regressie analyse ongeldig zijn.

Ter beoordeling van de bruikbaarheid van de analysetechniek wordt JANNET toegepast op de besluitvorming van de kaakchirurgen en ziekenhuistandartsen uit het internationale onderzoek dat in Hoofdstuk 3 wordt gepresenteerd. Omdat JANNET wordt uitgevoerd op individueel niveau en niet op groepsniveau, is er sprake van een *intra*beoordelaars-analyse (Eng. *within*-judges analysis).

Er wordt aangetoond dat met behulp van JANNET bepaalde patronen in de besluitvorming te herkennen zijn. Zo blijkt dat de clinici onderling sterk verschillen in de mate waarin ze de functie van gebitselementen wegen. Geconcludeerd wordt dat deze nieuwe techniek het verdient om verder te worden getest en toegepast.

In ***Hoofdstuk 5*** wordt een onderzoek beschreven bij 209 patiënten die vanwege een hoofd-halstumor met radiotherapie zijn behandeld. Onderzocht wordt de relatie tussen de mate van gebitsverlies en de gebitsstatus alsmede de tandheelkundige en radiotherapeutische risicofactoren. Een nevendoel is om het aantal gevallen van radiatiecariës en osteoradionecrose te bestuderen.

Het totale gebitsverlies in een periode van 1 tot 5 jaar (mediaan: 3 jaar) was in de onderzoekspopulatie veel hoger dan voor de algemene populatie volwassenen is beschreven. De relatie tussen gebitsverlies en de gebitsstatus alsmede de tandheelkundige en radiotherapeutische risicofactoren wordt aangetoond. Tevens wordt vastgesteld dat radiatiecariës optrad bij 45% van de patiënten die tijdens de bestraling een natuurlijke (rest)dentitie hebben. Osteoradionecrose bleef beperkt tot 5 gevallen.

De uitkomsten van het onderzoek ondersteunen de conclusie uit Hoofdstuk 4 dat de besluitvorming van kaakchirurgen en ziekenhuistandartsen op dit gebied voornamelijk wordt bepaald door tandheelkundige factoren. De uitkomsten vormen een belangrijke richtlijn voor tandheelkundige screening. Indien voorafgaand aan de radiotherapie bij een patiënt met een hoofd-halstumor een slechte gebitstoestand wordt aangetroffen, is het waarschijnlijk dat er na de radiotherapie opnieuw omvangrijke gebitspathologie ontstaat. Daardoor zullen er bij radiotherapie vaak uitgebreide tandheelkundige behandelingen, met inbegrip van gebitsextracties, nodig zijn. In het geval van een slechte begintoestand van het gebit is een grondige tandheelkundige sanering noodzakelijk. Hiermee dient bij het opstellen van het tandheelkundig behandelplan grondig rekening te worden gehouden.

In ***Hoofdstuk 6*** wordt SCREDENT beschreven. Dit is een computerprogramma voor beslissingsondersteuning dat gebruik maakt van een artificieel neuraal netwerk. SCREDENT werd ontworpen aan de hand van de resultaten van het onderzoek dat in Hoofdstuk 5 beschreven werd. ROC-curve analyse, predictieve waarde (Eng. *accuracy*) en logistische regressieanalyse werden gebruikt om SCREDENT te testen. De resultaten tonen aan dat SCREDENT in bijna 95 % van de gevallen een juiste voorspelling geeft voor gebitsextractie als beste optie voor tandheelkundige interventie (predicatieve waarde 0.94). Door de mogelijkheid om voorspellingen van SCREDENT die bij evaluatie juist blijken, vervolgens weer naar het kennisdomein (Eng. *knowledge domain*) van het systeem terug te koppelen, wordt het systeem "zelflerend" gemaakt.

Hoofdstuk 7 bevat een samenvatting en een algemene discussie. Ook worden de conclusies van dit proefschrift gepresenteerd.

De wetenschappelijke aanpak in dit proefschrift wordt in dit hoofdstuk geplaatst in het perspectief van een aantal benaderingen voor het analyseren van klinische beoordelingen en beslissingen (Eng. *judgment and decision making*): de ***normatieve***, de ***beschrijvende*** en de ***contextuele*** benadering.

De ***normatieve benadering*** beoogt de volgende vraag te beantwoorden: "*hoe* ***dienen*** *beslissingen te worden genomen*?" Het antwoord wordt in dit proefschrift verkregen met behulp van de in Hoofdstuk 2 uitgewerkte rekenkundige strategie voor het nemen van klinische beslissingen. Met deze strategie wordt een beslisproces van tevoren gestructureerd en geanalyseerd. Door het gebruik van de normatieve benadering ontstond het beslismodel (Model for Dental Decision Support --MDDS) voor optimalisatie van tandheelkundige beslissingen. Het construeren en het testen van dit model riep vervolgens nieuwe onderzoeksvragen op. Hoe wegen ervaren kaakchirurgen en ziekenhuistandartsen de factoren bij het tandheelkundige beslissingsproces dat aan radiotherapie in het hoofd-halsgebied vooraf gaat? Zijn ze bereid om daarbij enig risico te nemen of proberen ze elk risico te vermijden?

Deze vragen worden in de Hoofdstukken 3 en 4 beantwoord met behulp van de ***beschrijvende benadering***. Deze benadering beoogt de volgende vraag te beatwoorden: "*hoe* ***worden*** *beslissingen genomen*?" De beschrijvende benadering maakt gebruik van de in Hoofdstuk 1 geïntroduceerde beoordelingsstrategie voor het nemen van klinische beslissingen.

Met de beschrijvende benadering wordt aangetoond dat de meerderheid van de tandartsen en kaakchirurgen risicovolle beslissingen uit de weg gaat en dat "gebitsfunctie" meestal geen belangrijke factor is bij hun besluitvorming. De meest waarschijnlijke verklaring is dat deze clinici moeite hebben met het inschatten van de gevolgen van gebitsverlies op de orale functie bij dit type patiënten. Maar ook is het mogelijk dat de orale functie door hen ondergeschikt wordt gemaakt aan het vermijden van orale risico's bij hoofd-halsbestraling

De beschrijvende benadering wordt ook toegepast bij het in Hoofdstuk 5 gepresenteerde onderzoek van 209 patiënten die met radiotherapie behandeld zijn vanwege een hoofd-halstumor.

De derde en laatste benadering in dit proefschrift bij de bestudering van klinische beoordelingen en beslissingen is ***contextueel***. Deze term verwijst naar het belang om zoveel mogelijk aspecten bij de besluitvorming te betrekken. De contextuele benadering wordt gebruikt om het in Hoofdstuk 6 beschreven SCREDENT systeem te ontwikkelen en te testen. Net als het beslisboom-model is ook SCREDENT gebaseerd op de rekenkundige strategie

De voordelen die het gebruik van SCREDENT heeft ten opzichte van het beslisboom-model (MDDS) worden ook in Hoofdstuk 7 besproken. In vergelijking tot het beslisboom-model kan SCREDENT een groot aantal condities verwerken en kan tevens niet-lineaire verbanden modelleren. Bovendien kan SCREDENT incomplete gegevens verwerken, en kan tevens generaliseren en gecompliceerde verbanden in het kennisdomein interpreteren. Het grootste voordeel van SCREDENT komt echter voort uit de 'zelflerende' eigenschappen van het systeem. Door terugkoppeling van de resultaten kunnen beslissingen voortdurend worden geoptimaliseerd. Daardoor is SCREDENT een systeem voor het nemen van "evidence-based" beslissingen en verschaft tevens een raamwerk voor kwaliteitscontrole.

Het doel van ***Appendix 1*** is een voorbeeld te geven van het theorema van Thomas Bayes, een dominee en wiskundige uit de 18e eeuw. Het voorbeeld laat zien dat er een verschil bestaat tussen de waarden van voorwaardelijke kansen die mensen intuïtief bepalen en de waarden die met behulp van een rekenkundig methode bepaald worden en hoe het theorema van Bayes deze verschillen kan verkleinen.

Appendix 2 bevat het SCREDENT onderzoeksformulier en de richtlijnen voor het gebruik er van.

Appendix 3 bestaat uit het "SCREDENT getting started" document een handleiding voor de installatie en het gebruik van het SCREDENT computerprogramma.

Conclusies

(1) Met het model voor tandheelkundige beslissingsondersteuning (MDDS) kunnen tandheelkundige risicofactoren bij patiënten met een hoofd-halstumor geïdentificeerd en gestructureerd worden. Het model blijkt bruikbaar als instrument voor het ontwikkelen van "evidence-based" richtlijnen op dit gebied.

(2) De tandheelkundige beslissingen die voorafgaand aan radiotherapie van patiënten met een hoofd-halstumor worden genomen, zijn voornamelijk gebaseerd op klinische ervaring en persoonlijke standpunten in plaats van op wetenschappelijk onderzoek gebaseerde richtlijnen. De besluitvorming wordt vooral bepaald door aanwezige tandheelkundige risicofactoren. De mate van zekerheid hierbij wordt echter primair bepaald door aan de radiotherapie verbonden risicofactoren.

(3) De JANNET methode lijkt veelbelovend en dient verder toegepast en getest te worden. Het biedt de mogelijkheid om kansvoorwaardelijke patronen te herkennen in de besluitvorming van tandartsen en kaakchirurgen. Hierdoor kunnen clinici met overeenkomstig beleid gegroepeerd worden.

(4) De meerderheid van de kaakchirurgen en ziekenhuistandartsen die deelnamen aan het internationale onderzoek gebruiken "gebitsfunctie" niet of nauwelijks als factor in hun besluitvorming. Het blijkt dat ze eventuele complicaties trachten te beperken door ook functionele gebitselementen te extraheren voorafgaand aan radiotherapie in het hoofd-halsgebied, hetgeen als risicovermijding aangemerkt kan worden.

(5) Gebitsverlies bij patiënten met een hoofd-halstumor is statistisch significant geassocieerd met de gebitsstatus, de tandheelkundige risicofactoren en de aan radiotherapie verbonden risicofactoren.

(6) In het tandheelkundige behandelplan dat voorafgaand aan radiotherapie in het hoofd-halsgebied wordt opgesteld dient sterk rekening te worden gehouden met het feit dat bij patiënten waarbij een matige of slechte begintoestand van het gebit wordt vastgesteld, ook na de bestraling een grote kans bestaat op het ontstaan van gebitspathologie. Daarom is bij deze patiënten het noodzakelijk om het gebit voorafgaand aan de bestraling grondig te saneren.

(7) SCREDENT, een geautomatiseerd systeem voor ondersteuning van tandheelkundige beslissingen voorafgaand aan radiotherapie in het hoofd-halsgebied, blijkt accuraat in het voorspellen van gebitsverlies. Het systeem is "zelflerend" en lijkt daarom uitermate geschikt als instrument voor het voortdurend optimaliseren van op wetenschappelijk onderzoek gebaseerde richtlijnen en voor kwaliteitscontrole in dit domein.

APPENDIX 1

BAYES THEOREM, AN EXAMPLE

APPENDIX 1. Bayes Theorem: an example

Thomas Bayes was born in London in 1702 and died in Turnbridge Wells, Kent, England, in 1761. He was a clergyman and mathematician-in spirit. He made important contributions to the theory of probability. His conclusions were accepted by Laplace, and remained unchallenged until Boole questioned them. Over the past decade the value of Baysian methods have become increasingly apparent and has resulted in a "blossoming" of these techniques for reasoning under uncertainty. However, some controversy still remains.

Bayes set out his **theory of probability** in "*Essay towards solving a problem in the doctrine of chances"* published in the *Philosophical Transactions of the Royal Society of London* in 1764. The paper was sent to the Royal Society by Richard Price, a friend of Bayes, who wrote:

> *"I now send you an essay which I have found among the papers of our deceased friend Mr Bayes, and which, in my opinion, has great merit... In an introduction which he has writ to this Essay, he says, that his design at first in thinking on the subject of it was, to find out a method by which we might judge concerning the probability that an event has to happen, in given circumstances, upon supposition that we know nothing concerning it but that, under the same circumstances, it has happened a certain number of times, and failed a certain other number of times."*

The paper described Bayes' statistical technique known as Bayes Theorem. It bases the probability of an event that has to happen in a given circumstance on a prior estimate of its probability under these circumstances. The aim of Appendix 1 is to give an example of Bayes' approach.

Basic definitions of notation

In this Appendix, we will follow the following definitions of probability:

- $P(A)$: probability of event A, which is a number between 0 and 1.
- If A represents a certain event then $P(A)=1$.
- $P(NOT\,A)=1-P(A)$: probability of non-event A.
- $P(AB)$: probability of simultaneous events A and B.
- $P(A\mid B)$: conditional probability: probability of event A given event B.

Bayes Theorem

The foundation of probability theory follows from the following intuitive definition of conditional probability:

- $P(AB) = P(A \mid B) * P(B)$

In this definition events **A** and **B** are simultaneous and have no (explicit) temporal order. Therefore, we can write:

- $P(AB) = P(BA) = P(B \mid A) * P(A)$

This leads us to a common form of Bayes Theorem, the equation:

- $P(A) = \frac{P(A \mid B) * P(B)}{P(B \mid A)}$

which allows us to compute the probability of one event in terms of observations of another and knowledge of joint distributions.

Example: the problem of base-rate neglect

Assume that temporomandibular disorders (TMD) have a prevalence of 1/1000. Next, assume that a test to detect the disorder, for example a questionnaire to assess a person's signs and symptoms, has a false positive rate of 5%. This means that of all persons with a positive test result, 95% has the disorder and 5% has not. Assume that the test diagnoses correctly every person who has the disease (false negative rate 0%).
What is the probability (? %) that a randomly selected person[$] found to have a positive result actually **has** a temporomandibular disorder?

A similar type of question involving heart disease was put to a number of students and staff at Harvard Medical School. Almost half gave the response 95 %. The average answer was 56%. The correct answer was given by less than 10% of the participants.

What is your answer? …%

The correct answer is given on the next page.

[$] Do not select a person from the Special Dental Care department's waiting room because the prevalence of temporomandibular disorders in this group is much higher!

The correct answer that a randomly chosen person (from the general population) found to have a positive test result, actually has the disorder is **2%!**

An informal way of explaining this result is to think of a population of 10,000 people. Given the prevalence of 1/1000, we would expect just 10 people in this population to have the disorder. If you test everybody in the population then the false positive rate means that, in addition to the 10 people who do have the disorder, another 500 will be wrongly diagnosed as having it. In other words, only about 2% (10/510 x 100%) of the people diagnosed positively actually have the disorder.

When people give a high answer like 95%, they are ignoring the very low probability of having the disease (base-rate = 0.1%). In comparison, the probability of a false positive test is relatively high (5%).

The formal way of explaining the result, using Bayes Theorem, is as follows:

Let A be the event "person has the disorder."

Let B be the event "positive test."

We wish to calculate $P(A \mid B)$, where A is "having a TMD disorder", and B is "a positive test result."

In fact, it is easier to calculate $P(NOT\,A \mid B)$.

Therefore, we note that: $P(A \mid B) = 1 - P(NOT\,A \mid B)$

Using Bayes Theorem:

$$P(NOT\,A \mid B) = \frac{P(B \mid NOT\,A) * P(NOT\,A)}{P(B)} = \frac{P(B \mid NOT\,A) * P(NOT\,A)}{P(B \mid A) * P(A) + P(B \mid NOT\,A) * p(NOT\,A)}$$

Now, we know the following:

$P(A)$= 0.001

$P(NOT\,A) = 1 - P(A)$ = 0.999

$P(B \mid NOT\,A)$ = 0.05

$P(B \mid A)$ = 1 (remember, the false negative rate of the test was 0%)

Hence,

$$P(NOT\,A \mid B) = \frac{0{,}05 * 0{,}999}{0{,}001 + 0{,}05 * 0{,}999} = 0{,}09804$$

Hence, $P(A \mid B)$ = 1- 0.09804 is approximately 0.02 (2%)

Conclusions

This example illustrates the gap between the judgments people make intuitively and the probabilities yielded by explicit calculation or empirical observations. As early as 1954, Meehl stated that many clinical predictions could best be made by statistical rather than by intuitive means. Slovic et al., (1976) concluded on the basis of diverse research findings that people systematically violate the principles of rational decision making when judging probabilities, making predictions, or otherwise attempting to cope with probabilistic tasks. As shown in this example, a Bayesian approach provides a mathematical rule that may enhance rational judgment and decision making.

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SCREDENT DENTITION ASSESSMENT FORM (Bruins, Jolly & Koole, 1999)

Patient code number	**Date of Birth** Day Month Year	**Gender** M = 1 F = 2	**Date of Oral Screening** Day Month Year

---

Type of head & neck tumor[1]			**Location of tumor**: ICD code[1]	**CTNM stage**[1] T	N	M	**AJCC Stage**[1] (1,2,3 or 4)
SCC	Benign Salivary Gland						

Tumor record

First	Second/ recurrence

Goal of tumor therapy:

Cure	Palliation	?

Type of tumor therapy: (more than one entry possible)

Surgery	Radiation	Chemo	?

Major salivary glands in radiation field? (Bilaterally, > 50%): yes / no

Patient's Dental IQ / Compliance: high / average-low (please check guidelines)

Dentition Status (Tooth numbering according FDI system)

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	17	28
STATUS																
DRF																
TRX																
TREATM.																

	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
STATUS																
DRF																
TRX																
TREATM.																

Prosthetic Status

Upper	Lower

0 = No prosthesis
1 = Bridge
2 = More than one bridge
3 = Partial denture
4 = Both bridge(s) /Part.dent.
5 = Full removable denture
9 = Not recorded

Reminder Dentition Status Codes[1]

Tooth STATUS:
0 = Sound
1 = Decayed
2 = Filled, with decay
3 = Filled, no decay
4 = Missing
5 = Dental implant
6 = Bridge abutment / crown / implant
7 = Bridge abutment/ crown, with decay
8 = Unerupted tooth / unexposed root
9= Not Recorded

DRF: 0 = medium or low, 1= High

TRX: 0 = tooth **not** in radiation field (>50Gy.)
1 = tooth in radiation field (>50Gy.)

TREATM.: 0 = None, 1 = Dental treatment, 2 = Extraction

---

[1] see guidelines document

SCREDENT Dentition Assessment Form: guidelines for dental clinicians

The SCREDENT form for oral health assessment of patients with head and neck cancer is designed for collection of information to support pretherapy dental decision-making, by means of the SCREDENT system. The form is designed to facilitate computer processing of the findings. How to recode and enter the data into the SCREDENT system is described in the "SCREDENT getting started" document (see Appendix 3).
To minimize the number of errors, all entries must be clear and unambiguous. Please, fill in the boxes and/or mark/circle one or more of the printed response options within with a black pencil, e.g.:

Gender	**Goal of tumor therapy**:		
2	[✓ Cure]	Palliation	?

The form includes the following sections:

- Patient identification information;
- Head and neck cancer information;
- Dentition status and treatment need;
- Prosthetic status.

The following should be recorded:

- Survey and patient identification information

- ~ **Patient code number**: a string of figures and or letters to identify the patient, e.g. patient's hospital ID number: "AB123456"
- ~ **Date of birth**: format: day month year, e.g. "05 12 1953"
- ~ **Gender**: male is coded as "1", female as "2"
- ~ **Date of oral screening**: format: day month year, e.g. "01 02 1999"

- Head and neck cancer information

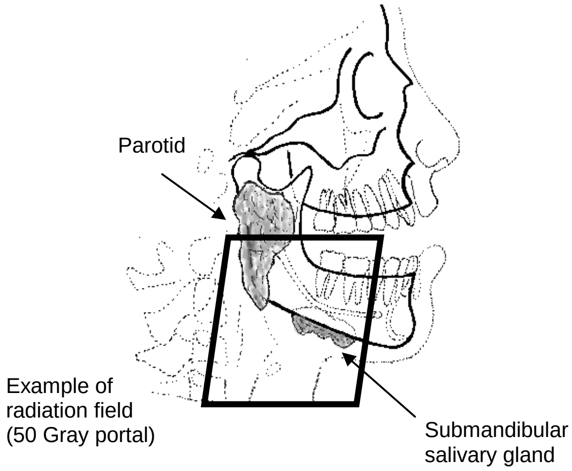
- ~ **Type of head & neck tumor:** refers to the histopathology. Approximately 90% of all malignant neoplasm of the oral cavity, pharynx, and larynx are: SCC - Squamous Cell Carcinoma. If so, mark/circle "SCC"
  If it concerns a benign salivary gland tumor, e.g. a pleomorphic adenoma: circle "Benign Salivary Gland". If it concerns a different type of malignant neoplasm, please enter its description in the blank box, e.g. "malignant melanoma" or "lymphoma"
- ~ **Location of tumor:** Please enter *ICD code* (According to the International Classification of Diseases, Ninth Revision, Clinical Modification, as published by the U.S. Public Health Service and Health Care Financing Administration). A comprehensive code list can be found on: http://www.eicd.com/EClass/2htm
- ~ **CTNM stage:** the TNM classification system to be used is that of the American Joint Committee for Cancer (AJCC)(1), see page 129,130.

~ **Tumor record:** "*First*" has to be used for primary malignant neoplasm's. "*Second/ recurrence*" is for patients who have had prior surgery and/or radiation for a head and neck malignancy in the past

~ **Goal of tumor therapy:** record "*cure*" if the intention is to cure the patient. Record "*palliation*" or the "*?*" (unknown) if this applies for the case judged.

~ **Type of tumor therapy**: more than one entry possible, e.g. if the treatment regiment consists of a combination of surgery and radiation, record both "*Surgery*" and "*Radiation*"

~ **Major salivary glands in radiation field?** Record "*Yes*" if the major salivary glands (parotid and submandibular gland) are both, bilaterally, for at least 50% in the radiation field of 50 Gy or more (see figure). To get this information, please check simulation radiographs/CT scans and/or consult with the radiotherapist.



- Patient's Dental IQ/Compliance:

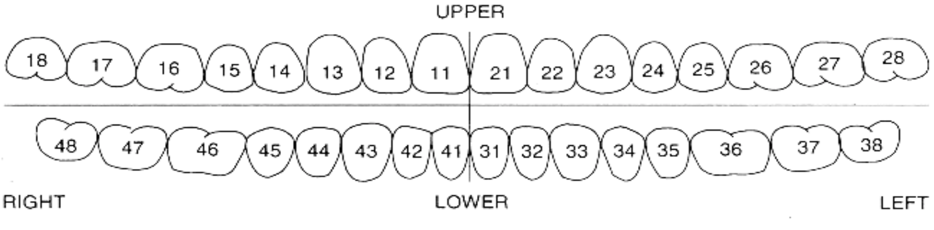
~ Record "*High*": if

- * patient's level of oral hygiene is satisfactory, **and**
- * he or she visits a dentist at least one a year, **and**
- * if the overall level of oral health is satisfactory (the total number of DRF's should **not** be higher than 4), **and**
- * if there are no financial limitations for comprehensive dental care.

~ Record "*average-low*" if patient's dental IQ/Compliance does **not** meet the criteria of "*High*".

- Dentition status

~ tooth codes according to the system used by the International Dental Federation



WHO 96217

~ **Status:** refers to tooth status (modified from WHO, 1997)(2)

*** Code "0"**: Condition = *sound*, if a tooth (crown and/or root) shows no evidence of treated or untreated caries (clinical and/or radiographic). The stages of caries that precede cavitation, such as white spots and/or stained pits or fissures, as well as other conditions similar to the early stages of caries, are excluded because they cannot be reliably diagnosed.

*** Code "1"**: Condition = *decayed*: when a lesion in a pit or fissure, or on a smooth tooth surface, has a unmistakable cavity, undermined enamel, or a detectable softened floor or wall, which feels soft or leathery to probing with a dental probe.

* **Code "2"**. Condition = *filled with decay*: when the tooth has one or more permanent restorations and one or more areas that are decayed.

* **Code "3"**. Condition = *filled, with no decay*: a tooth is considered filled, without decay, when one or more permanent restorations are present and there is no caries anywhere on the tooth.

* **Code "4"**. Condition = *missing tooth*: as result of caries or for any other reason.

* **Code "5"**. Condition = *dental implant*: when a missing tooth (otherwise coded as "4") has been replaced by a dental implant

* **Code "6"**. Condition: *bridge abutment*, *special crown or veneer*, *with decay*: when a tooth forms part of a fixed bridge, i.e. is a bridge abutment, or has a crown (e.g. gold/porcelain/acrylic crown), or veneer (laminate), covering the labial surface of a tooth and has one or more areas that are decayed.

* **Code "7"**. Condition: *bridge abutment, special crown or veneer, with no decay*: when a tooth forms part of a fixed bridge, i.e. is a bridge abutment, or has a crown (e.g. gold/porcelain/acrylic crown), or veneer (laminate), covering the labial surface of a tooth and there is no caries anywhere on the tooth.

* **Code "8"**. Condition = *unerupted crown or unexposed root*: used for a tooth space with an unerupted permanent tooth, or a root (fragment, 'radix relictae') not exposed (covered with mucosa and or bone). A decayed root with missing crown should be coded as "1". A root resulting from decapitation of a tooth (e.g. an abutment to support an "overdenture") should be coded as "1", "2", or "3", depending on its condition.

* **Code "9"**. Condition = *not recorded*: this code is used for any tooth or root that cannot be examined for any reason (e.g. because of orthodontic bands, severe hypoplasia etc.)

~ **DRF**: refers to Dental Risk Factor, as defined by Bruins et al.1998(3)

Table summarizes dental conditions and weightings to assign the DRF score:

* **Code "0"**. Condition = *low/medium risk*. This code should be used when a tooth has:

- one or more dental conditions (see table) with a "low" weighting, and/or
- one or two dental conditions with a 'medium' weighting, and
- no conditions with "high" weightings.

* **Code "1"** Condition = *high risk*. This code should be used when a tooth has:

- three or more dental conditions with a "medium" weighting, and/or
- one or more dental conditions with a 'high' weighting.

~ **TRX:** refers to wether or not the tooth judged is in the radiation field over 50 Gray and or is in a short distance to a radioactive source for brachytherapy. The latter is a method of radiation treatment in which sealed radioactive sources are used to deliver the dose by interstitial (direct insertion into tissue), intracavitary (placement within a cavity), or surface application.(8)

*** Code "0"**, if the tooth is not in the radiation field of 50 Gy or more.

*** Code "1"**, if the tooth judged is within the radiation field of 50 Gy or more.

To obtain this information, please check the simulation radiographs/CT scans and/or consult with the radiotherapist.

~ **Treatment need**: refers to the indicated treatment of a tooth.

* **Code "0"**. Criterion = *no treatment*: this code is recorded if it is decided that a tooth should not receive any treatment.

* **Code "1"**. Criterion = *treatment, no extraction*: if a tooth need any form of dental treatment, including root planing, surgical periodontics, surgical endodontics etc.

* **Code "2"**. Criterion = *extraction*: if it is decided to extract a tooth, including surgical removal. (This code also applies if an erupted tooth or unexposed root -Status code "8"- should be surgically removed).

- Staging for head and neck cancers

The TNM classification staging system to be used for the SCREDENT form is that of the American Joint Committee for Cancer (AJCC) (1) See Blair & Callender, 1994(9) for additional information.

The staging system is a clinical system, based on the best possible estimate of the tumor extent, before treatment. The assessment of the primary tumor is based on inspection and palpation when possible and by both indirect mirror examination and/or direct endoscopy. Information on tumor extent usually is obtained by consulting the oncologist and from patient's hospital records.

-The T stage is an anatomic description of the extent of the primary tumor. The T-stage varies according to site of origin (see Table 2a).

-The N stage (see Table 2b) is based on extent of regional lymphatic metastasis (cervical lymph nodes)

-The M stage (see Table 2c) represents presence or absence of distant metastasis.

Stage groupings recommend by the AJCC are as follows:

Stage 1: T1N0M0
Stage 2: T2N0M0
Stage 3: T3N0M0; T1, 2, or 3, N1, M0
Stage 4: T4N0 or N1; any T, N2 or N3; any T, any N, with M1.

Table 1 Dental Conditions to assign Dental Risk Factor (DRF) Score

Clinical and Radiographic Findings[a]	Weighting	
PERIODONTAL DISEASE		
Probing depth / Proximal bone loss:[b] 3 to 6 mm	Medium	
Probing depth / Proximal bone loss: > 6mm		High
Gingival recession: 3 to 6 mm	Medium	
Gingival recession: > 6 mm		High
Bleeding upon probing	Medium	
Spontaneous gingival bleeding		High
Furcation involvement / Bone loss in furcation area		High
Mobility 1-2 mm side to side	Medium	
Mobility > 2 mm side to side and/or 1 mm vertical		High
PULPAL DISEASE AND PERIAPICAL LESIONS		
Abnormal response to tests,[c] no previous endodontic treatment, no rarefying osteitis[d]	Medium	
Abnormal response to tests, and no previous endodontic treatment, rarefying osteitis		High
Swellings and/or sinus tracts		High
Rarefying osteitis, ∅ < 3mm, with adequate root canal filling[e], without (percussion) pain	Low	
Rarefying osteitis, ∅ < 3mm, with inadequate root canal filling[e], with (percussion) pain		High
Rarefying osteitis, ∅ >3 mm		High
Condensing osteitis [f]/hypercementosis[g] with normal reactions to tests	Low	
Condensing osteitis with abnormal reactions to tests	Medium	
Internal/external root resorption		High
EXTENSIVE CARIES		
Primary caries < 2/3 of the clinical crown	Medium	
Primary caries ⩾ 2/3 of the clinical crown/pulpal involvement		High
Defective restoration[h] with secondary caries[i], no pulpal involvement	Medium	
Root caries < 1/2 of root circumference, no pulpal involvement	Medium	
Root caries ⩾ 1/2 of root circumference		High
NON FUNCTIONAL TEETH		
Partially impacted (incompletely erupted) teeth or permucosal residual roots		High
Residual root tips not fully covered by alveolar bone and /or showing periodontal ligament or radiolucency		High
Fully impacted teeth, without follicle enlargement and fully covered by bone	Low	
Fully impacted teeth, with follicle enlargement and/or not fully covered by bone		High

[a] Identified at tooth level, which means tooth-related.

[b] The radiographic standard for interpretation of bone proximal bone loss is that the alveolar crestal bone must be greater than 3 mm from the CEJ.(4)

[c] Pulp sensitivity: cold, heat, electric (EPT) and percussion tests.

[d] Rarefying osteitis: radiolucent periapical bone destruction communicating with the periodontal ligament space via a discontinuity in the lamina dura. (5)

[e] Criteria for assessment of root canal obturation: The prepared and filled canal should contain the original canal and should be filled completely (0.5-2mm from radiographic apex). No space between canal filling and canal wall should be seen. No canal space should be visible beyond the end point of the root canal filling. The whole canal system/ all roots should be obturated (6).[43]

[ff] Condensing osteitis: hypersclerotic trabeculi in the bone adjacent to the periapical region and communicating with the periodontal ligament space.(5)

[9] Hypercementosis: distortion of the apical third of the tooth root characterized by increased width while the periodontal ligament space and lamina dura remain unaltered.(5)

[h] Restorations are defective if any of the following conditions are present: marginal discrepancies >0.5 mm, part of the restoration missing, bulk fracture, or marginal staining of composites suggesting leakage.(7)

[i] True radiographic secondary (i.e., recurrent) caries and/or residual caries.(7)

Table 2a T staging of primary head and neck tumors

Site	Stage	
All sites		
	TX	Primary cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
Oral cavity		
	T1	Two cm less in greatest dimension
	T2	More than 2 cm but not more than 4 cm in greatest dimension
	T3	Tumor is greater than 4 cm in greatest dimension
	T4	Tumor invades adjacent structures, such as cortical bone, muscle of tongue, skin, maxillary sinus
Nasopharynx		
	T1	Tumor limited to one sub site of nasopharynx
	T2	Tumor invades more than one sub site of nasopharynx
	T3	Tumor invades nasal cavity and/or oropharynx
	T4	Tumor invades skull and/or cranial nerves
Hypopharynx		
	T1	Tumor confined to the site of origin
	T2	Extension of tumor to adjacent site region, without fixation of the hemilarynx
	T3	Extension of tumor to adjacent site region, with fixation of the hemilarynx
	T4	Massive tumor invading cartilage, bone, or soft tissue of neck
Larynx - supraglottis		
	T1	Confined to site of origin with normal vocal cord movement
	T2	Involving adjacent supraglottic sites without glottic fixation
	T3	Limited to the larynx with fixation or extension to postcricoid area, medial wall of piriform, or pre-epiglottic space
	T4	Massive tumor extending beyond the larynx to involve oropharynx, soft tissues of the neck, or destruction of the thyroid cartilage
Larynx - glottis		
	T1	Confined to the vocal cord(s) with normal mobility
	T2	Supraglottic or subglottic extension with normal or impaired vocal cord mobility
	T3	Confined to larynx with fixation of vocal cord
	T4	Massive tumor with cartilage destruction and/or extension beyond the larynx or both
Larynx - subglottis		
	T1	Confined to subglottic region
	T2	Extended to the vocal cord(s) with notmal or impaired cord mobility
	T3	Confined to the larynx with cord fixation
	T4	Massive tumor with cartilage destruction and/or extension beyond the larynx or both

Table 2b T staging of primary head and neck tumors (regional lymph nodes)

Stage	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Table 2c M staging of primary head and neck tumors (distant metastasis)

Stage	
MX	Presence of metastasis cannot be assessed
M0	No distant metastasis
M1	distant metastasis present

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Getting started with SCREDENT

1. Preliminaries

1.1. Introduction

This "getting starting" document introduces how SCREDENT (Beta-1 version) may be used to predict tooth extraction/ tooth loss in patients with head and neck cancer. The SCREDENT application runs within aiNet, a software package that emulates a probabilistic neural network on a personal computer. Please, check the aiNet manual for comprehensive information on the program. After familiarization with aiNet and SCREDENT, predicting tooth loss will take only a few minutes. This enables chair-side decision support. We believe that in addition, SCREDENT's primary role may be to offer a framework for continuous updating and adjusting of the decisions process, as explained in Chapter 6, and therefore to allow evidence-based decision-making; it may thus be a component of a quality control system.

After further testing, we will develop plans for a new version of SCREDENT that combines the SCREDENT dentition assessment form and the prediction function, by means of a specially designed interface with pop-up menus and database facilities to store the cases. In addition, SCREDENT will be extended to all other situations where dental screening of medically compromised patients is mandated.

1.2. Where to get the aiNET software?

From the MEXSYS website at **http://www.mexsys.net** follow the link to the SCREDENT download page.

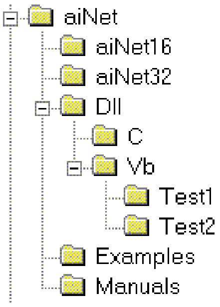
1.3. Hardware and Software Requirements

aiNet requires the following minimal configuration:

- a PC with the 386 processor
- a minimum of 4 MB of RAM
- about 5 MB of hard disk space,
- Microsoft Windows95, Windows NT or as a minimum, Microsoft Windows 3.
- a VGA graphics card (aiNet does not support Hercules mono and EGA graphics, although Windows does).

1.3.1. Installation

aiNet is supplied in a compressed format: AINETXX.ZIP. This ZIP.file contains all of the documentation and software. Decompressing the AINETXX.ZIP will result in the following subdirectory structure:



Correct aiNet sub-directory structure

2. SCREDENT

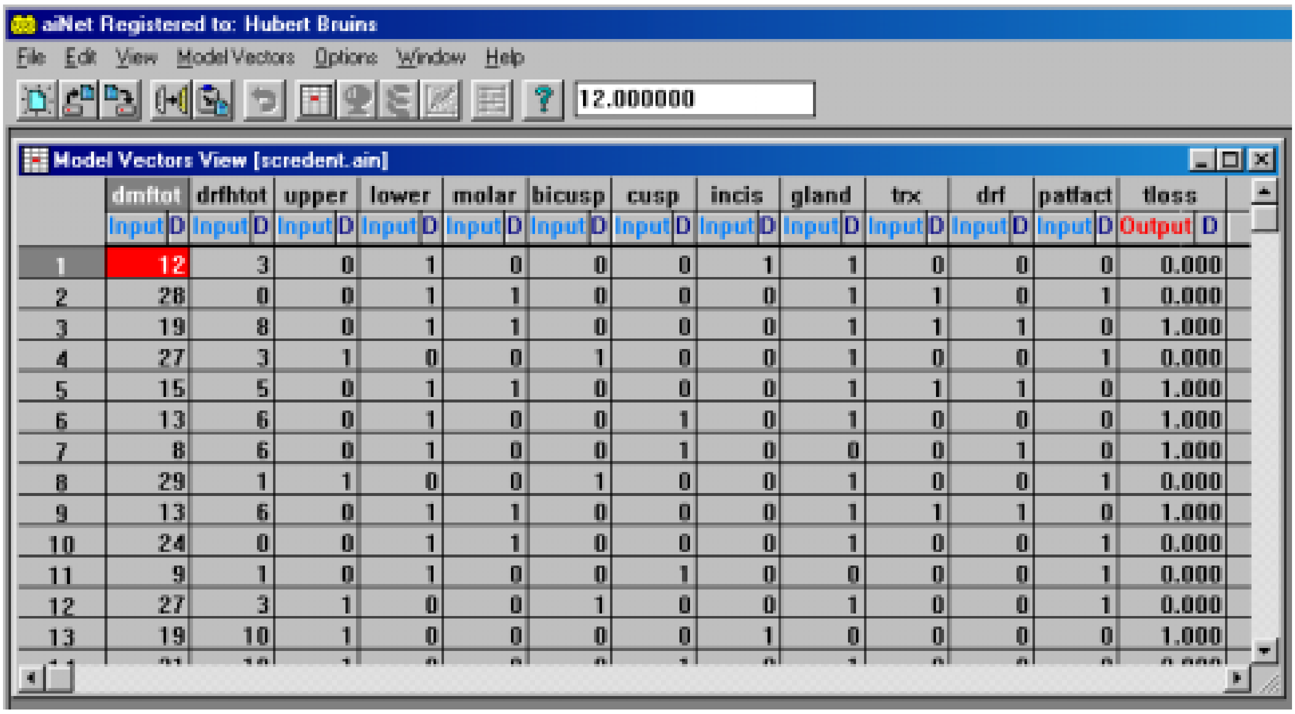
2.1. Downloading the scredent.ain file

To be able to run the SCREDENT application (Beta-1 test version) in aiNet, you first have to download the ***scredent.ain*** file from the MEXSYS.NET website at **http://www.mexsys.net.** Store the file in a new directory, for example in: C:\My documents\SCREDENT\scredent.ain

2.2. Open the scredent.ain file

- Start aiNet and Click on in the aiNet's menu bar at the top of the screen to open the ***scredent.ain*** file (follow the path to the scredent.ain file, for example: C:\My documents\SCREDENT\scredent.ain).

After opening the ***scredent.ain*** file, your screen should look like this:



	dmftot	drfhtot	upper	lower	molar	bicusp	cusp	incis	gland	trx	drf	patfact	tloss
	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Output D
1	12	3	0	1	0	0	0	1	1	0	0	0	0.000
2	28	0	0	1	1	0	0	0	1	1	0	1	0.000
3	19	8	0	1	1	0	0	0	1	1	1	0	1.000
4	27	3	1	0	0	1	0	0	1	0	0	1	0.000
5	15	5	0	1	1	0	0	0	1	1	1	0	1.000
6	13	6	0	1	0	0	1	0	1	0	0	0	1.000
7	8	6	0	1	0	0	1	0	0	0	1	0	1.000
8	29	1	1	0	0	1	0	0	1	0	0	1	0.000
9	13	6	0	1	1	0	0	0	1	1	1	0	1.000
10	24	0	0	1	1	0	0	0	1	0	0	1	0.000
11	9	1	0	1	0	0	1	0	0	0	0	1	0.000
12	27	3	1	0	0	1	0	0	1	0	0	1	0.000
13	19	10	1	0	0	0	0	1	0	0	0	0	1.000

Figure A 3.1

NOTE: the model vectors are 'de-normalized' and 'unlocked', indicating that model vectors can be changed, deleted, and/or entered. First, make a copy of the scredent.ain file. From the menu, select: *File* | *Save as* and enter the name of the new scredent file name, for example: ***scredent1.ain.***

- Next, normalize and lock the model vectors. From the menu, select: *Model vectors* | *Normalize+lock*

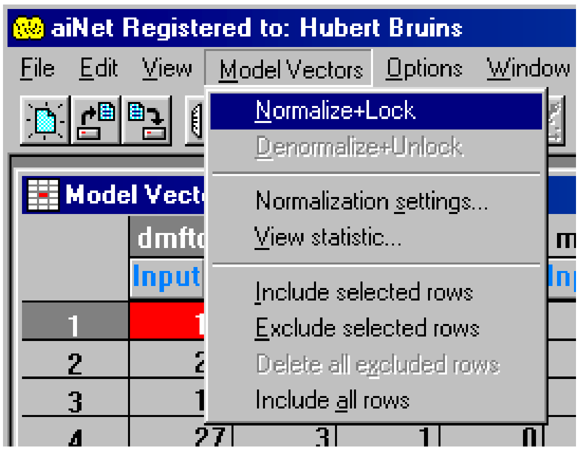


Figure A-3.2

- Make sure that you use: *Normalization settings…* normalization method: **regular**

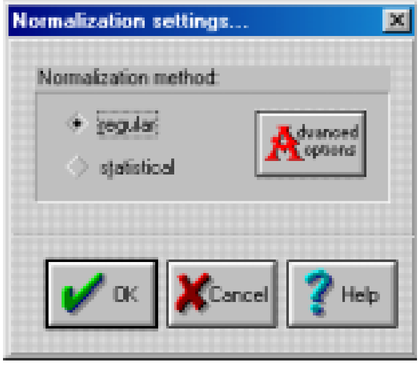
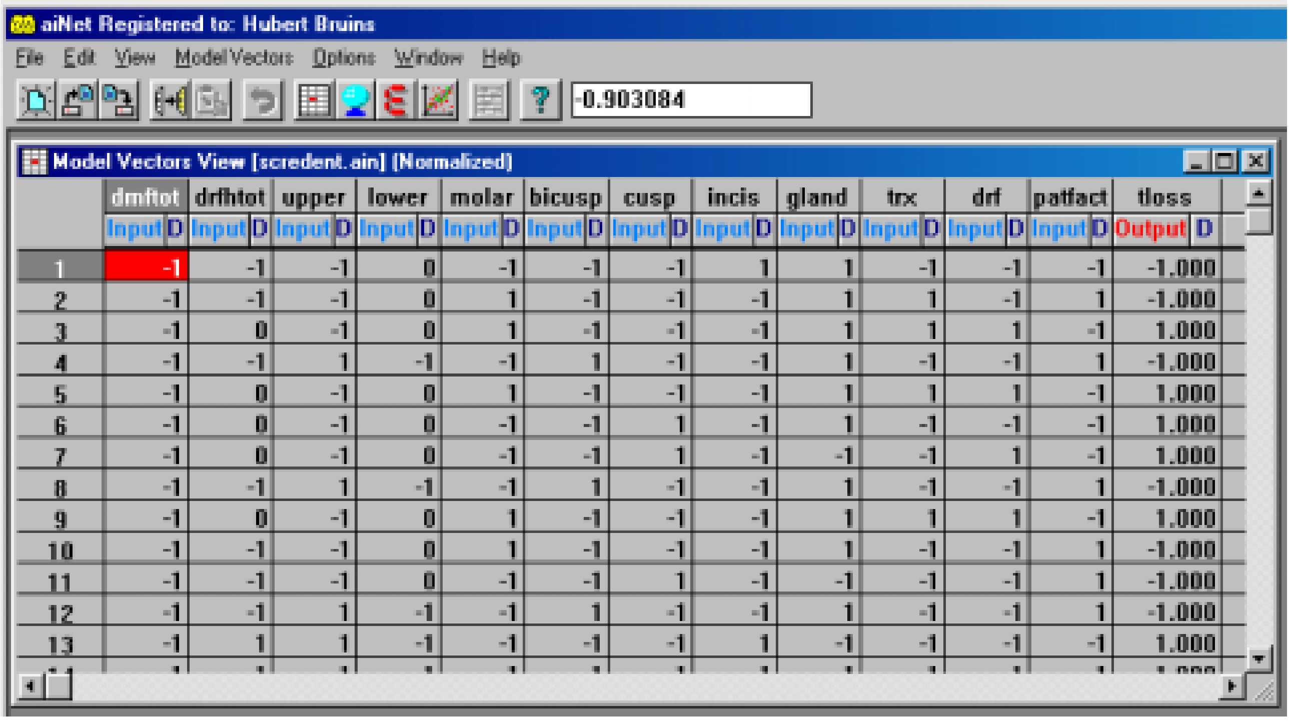


Figure A-3.3

NOTE: the result should look like this:



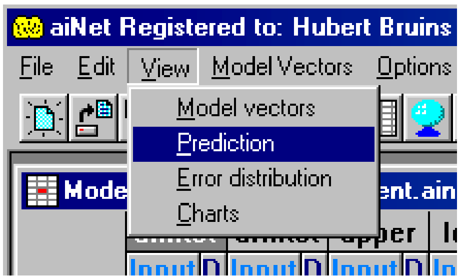
-0.903084

Model Vectors View [scredent.ain] (Normalized)

	dmftot	drfhtot	upper	lower	molar	bicusp	cusp	incis	gland	trx	drf	patfact	tloss
	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Output D
1	-1	-1	-1	0	-1	-1	-1	1	1	-1	-1	-1	-1.000
2	-1	-1	-1	0	1	-1	-1	-1	1	1	-1	1	-1.000
3	-1	0	-1	0	1	-1	-1	-1	1	1	1	-1	1.000
4	-1	-1	1	-1	-1	1	-1	-1	1	-1	-1	1	-1.000
5	-1	0	-1	0	1	-1	-1	-1	1	1	1	-1	1.000
6	-1	0	-1	0	-1	-1	1	-1	1	-1	-1	-1	1.000
7	-1	0	-1	0	-1	-1	1	-1	-1	-1	1	-1	1.000
8	-1	-1	1	-1	-1	1	-1	-1	1	-1	-1	1	-1.000
9	-1	0	-1	0	1	-1	-1	-1	1	1	1	-1	1.000
10	-1	-1	-1	0	1	-1	-1	-1	1	-1	-1	1	-1.000
11	-1	-1	-1	0	-1	-1	1	-1	-1	-1	-1	1	-1.000
12	-1	-1	1	-1	-1	1	-1	-1	1	-1	-1	1	-1.000
13	-1	1	1	-1	-1	-1	-1	1	-1	-1	-1	-1	1.000

Figure A-3.4

- Next, open the prediction view:select: *View* | *Prediction* or, alternatively, click on the icon



NOTE: the result should look like this:

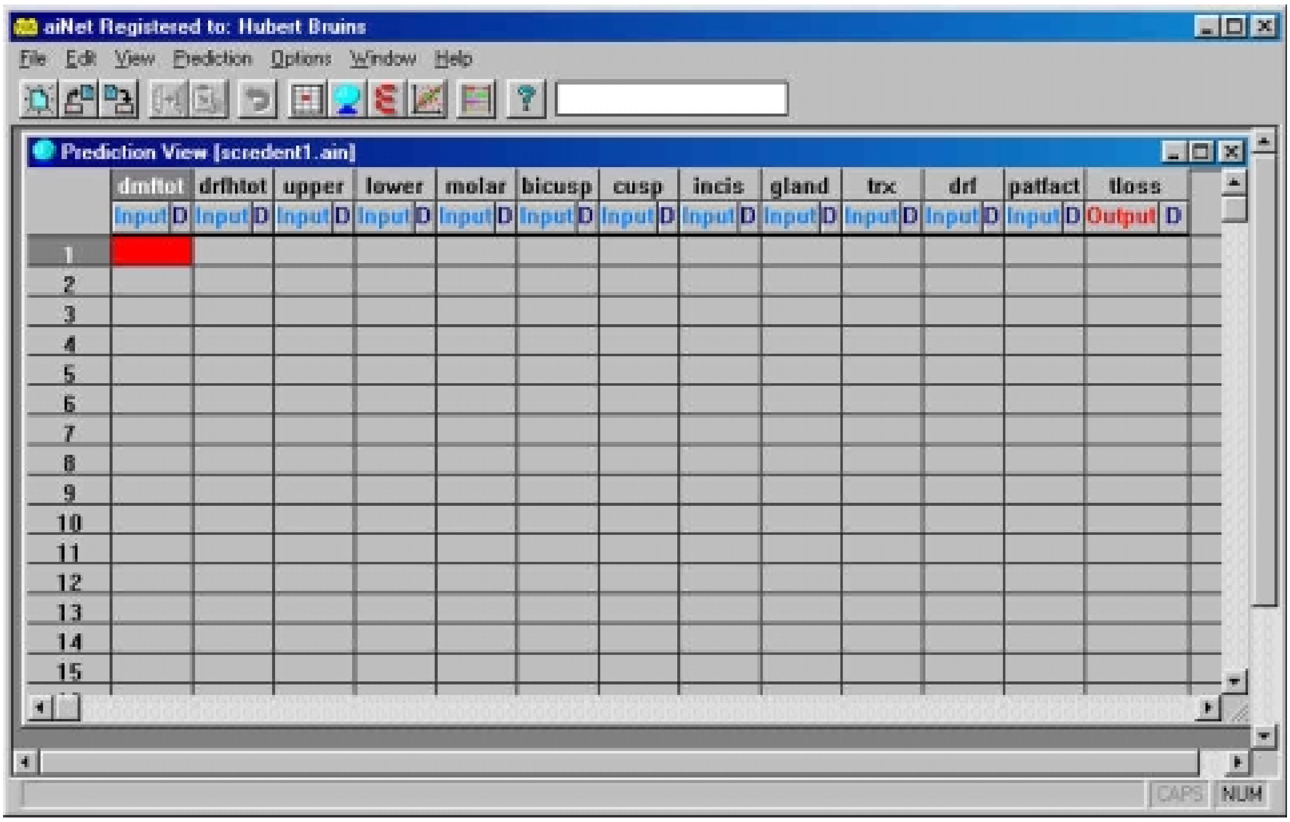


Figure A-3.5

NOTE: the Prediction view is a spreadsheet-type interface. Each row represents a 'prediction vector' and has 12 input variables and 1 output variable. Before you can make predictions for tooth extraction (tooth loss), you first have to enter the input variables. An example (case presentation) will be given in the next section.

2.3. SCREDENT, prediction of tooth extraction: a case presentation

The preradiation dental screening was performed according to accepted standards (see Bruins, Koole & Jolly, 1998). The SCREDENT dentition assessment form was used according to the guidelines described in the SCREDENT guidelines document. Please check this document for a comprehensive description of all clinical variables. The completed form is depicted on page 138 (example data displayed in blue.) The orthopantomogram/Panorex is displayed on page 137.

- Open the ***scredent1.ain*** file. Next, save the file using a new file name representing the patient's name or number, or alternatively, chose any other file name.
- Open SCREDENT's Prediction View, as explained above (see Figure A-3.5).
- Recode the data from the SCREDENT form and enter the data into the Prediction View spreadsheet. Each row in the Prediction View represents a tooth. Therefore, in this example, we need 12 Prediction Vectors (rows) in order to make predictions in the case of this particular patient.

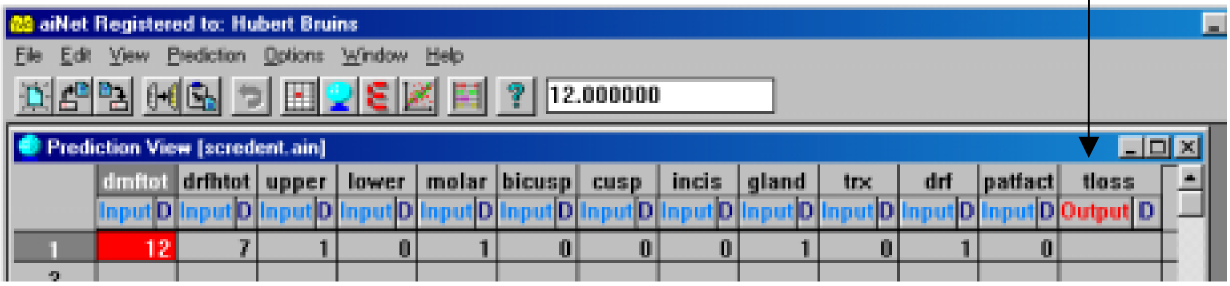
- ROW 1 of the prediction view represents tooth # 17 (the input is displayed in **blue**):

- *dmftot* = number of teeth present (retained teeth) = **12**
- *drftot* = number of high Dental Risk Factors(DRF=1) = **7**
- *upper* = upper arch (yes=1/no=0) = **1**
- *lower* = lower arch (yes=1/no=0) = **0**
- *molar* (yes=1/no=0) = **1**
- *bicusp* (yes=1/no=0) = **0**
- *cusp* (yes=1/no=0) = **0**
- *incis* (yes=1/no=0) = **0**
- *gland* (in high dose radiation field >50% = 1 / not in field > 50% = 0) = **1**
- *trx* (tooth in high dose radiation field =1 / not in field= 0) = **0**
- *drf* (high dental risk factor, yes=1/no=0) = **1**
- *patfact* (dental IQ, high=1 / average-low=0) = **0**

Thus, the first Prediction Vector is: {12,7,1,0,1,0,0,0,1,0,1,0,…}

NOTE: The output value, the conditional probability of tooth extraction/tooth loss, must not be entered. As explained before, SCREDENT will make this prediction for you.

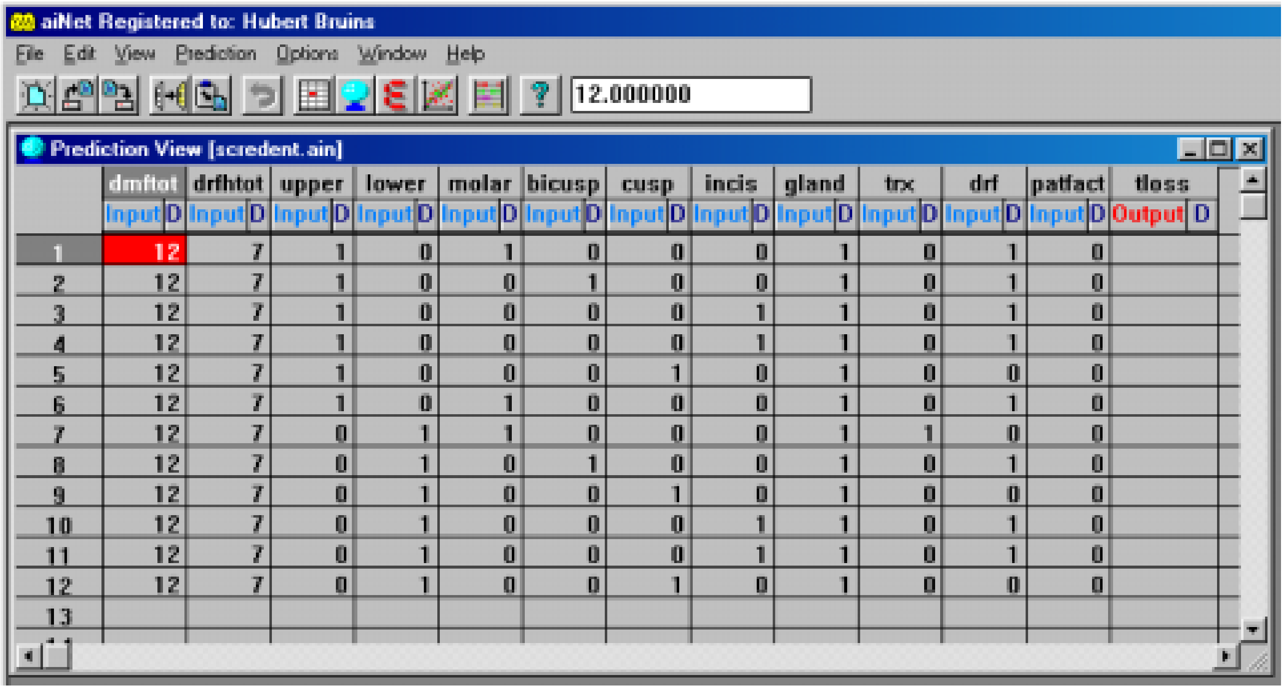
NOTE: the first row should look like this:



	dmftot	drfhtot	upper	lower	molar	bicusp	cusp	incis	gland	trx	drf	patfact	tloss
	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Output D
1	12	7	1	0	1	0	0	0	1	0	1	0	

Figure A-3.6

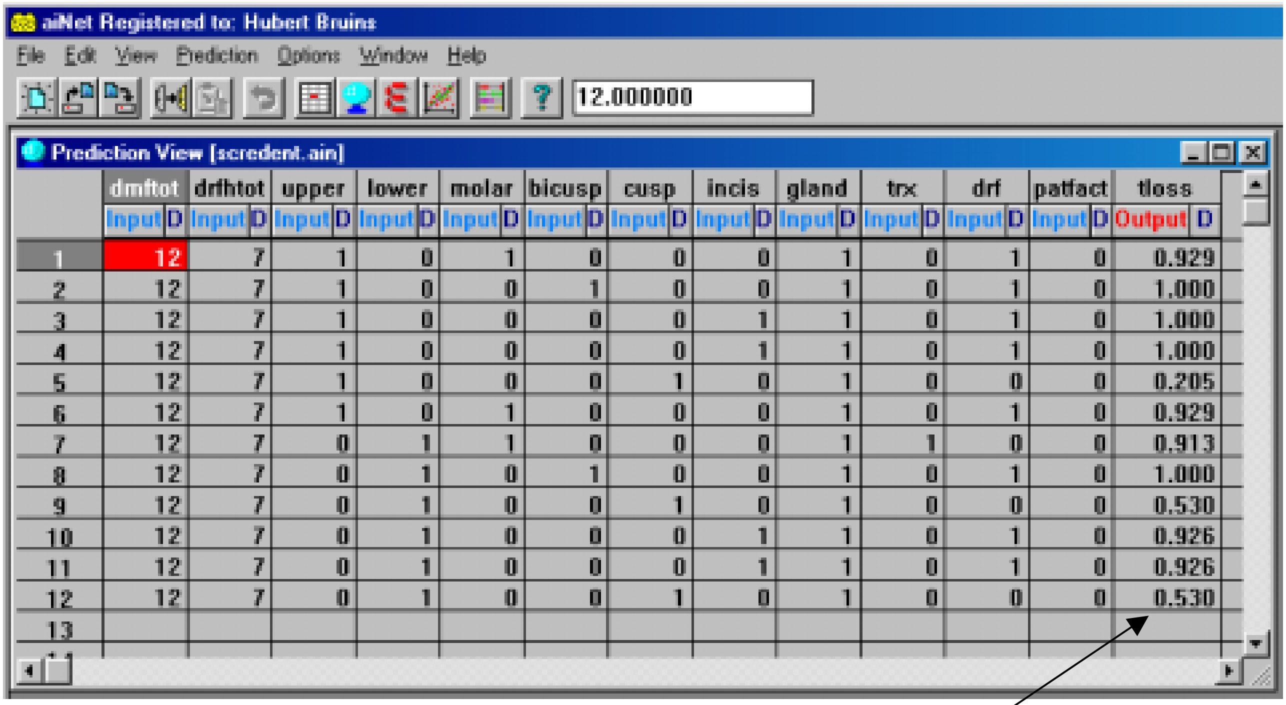
- Repeat the process for the other 11 teeth. Note that the variables '*dmftot*', '*drftot*', '*gland*', and '*patfact*' are not tooth-bound, but patient-bound. Thus, the values of these 4 variables are the same for every tooth. The result of entering all 12 teeth in SCREDENT's Prediction View should look like this:



	dmftot	drfhtot	upper	lower	molar	bicusp	cusp	incis	gland	trx	drf	patfact	tloss
	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Output D
1	12	7	1	0	1	0	0	0	1	0	1	0	
2	12	7	1	0	0	1	0	0	1	0	1	0	
3	12	7	1	0	0	0	0	1	1	0	1	0	
4	12	7	1	0	0	0	0	1	1	0	1	0	
5	12	7	1	0	0	0	1	0	1	0	0	0	
6	12	7	1	0	1	0	0	0	1	0	1	0	
7	12	7	0	1	1	0	0	0	1	1	0	0	
8	12	7	0	1	0	1	0	0	1	0	1	0	
9	12	7	0	1	0	0	1	0	1	0	0	0	
10	12	7	0	1	0	0	0	1	1	0	1	0	
11	12	7	0	1	0	0	0	1	1	0	1	0	
12	12	7	0	1	0	0	1	0	1	0	0	0	
13													

Figure A3-7

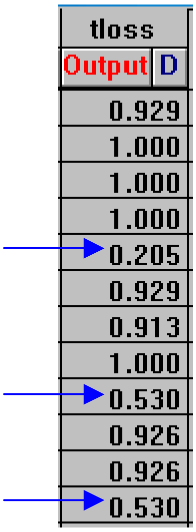
- Next, predictions for '*tloss*' are made. To calculate these predictions, select the *Prediction|Calculate Prediction* command from the menu, or alternatively, press F5.



	dmftot	drfhtot	upper	lower	molar	bicusp	cusp	incis	gland	trx	drf	patfact	tloss
	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Input D	Output D
1	12	7	1	0	1	0	0	0	1	0	1	0	0.929
2	12	7	1	0	0	1	0	0	1	0	1	0	1.000
3	12	7	1	0	0	0	0	1	1	0	1	0	1.000
4	12	7	1	0	0	0	0	1	1	0	1	0	1.000
5	12	7	1	0	0	0	1	0	1	0	0	0	0.205
6	12	7	1	0	1	0	0	0	1	0	1	0	0.929
7	12	7	0	1	1	0	0	0	1	1	0	0	0.913
8	12	7	0	1	0	1	0	0	1	0	1	0	1.000
9	12	7	0	1	0	0	1	0	1	0	0	0	0.530
10	12	7	0	1	0	0	0	1	1	0	1	0	0.926
11	12	7	0	1	0	0	0	1	1	0	1	0	0.926
12	12	7	0	1	0	0	1	0	1	0	0	0	0.530
13													

NOTE: the '*tloss*' column displays the predictions for tooth extraction / tooth loss. These values are conditional probabilities. 1.000 means that tooth loss is 100% certain; 0.000 means that tooth loss is 0 % certain (= tooth retention is 100% certain, follow-up period 3 years, see Chapter 5)

NOTE: a closer look at the '*tloss*' column reveals the following:

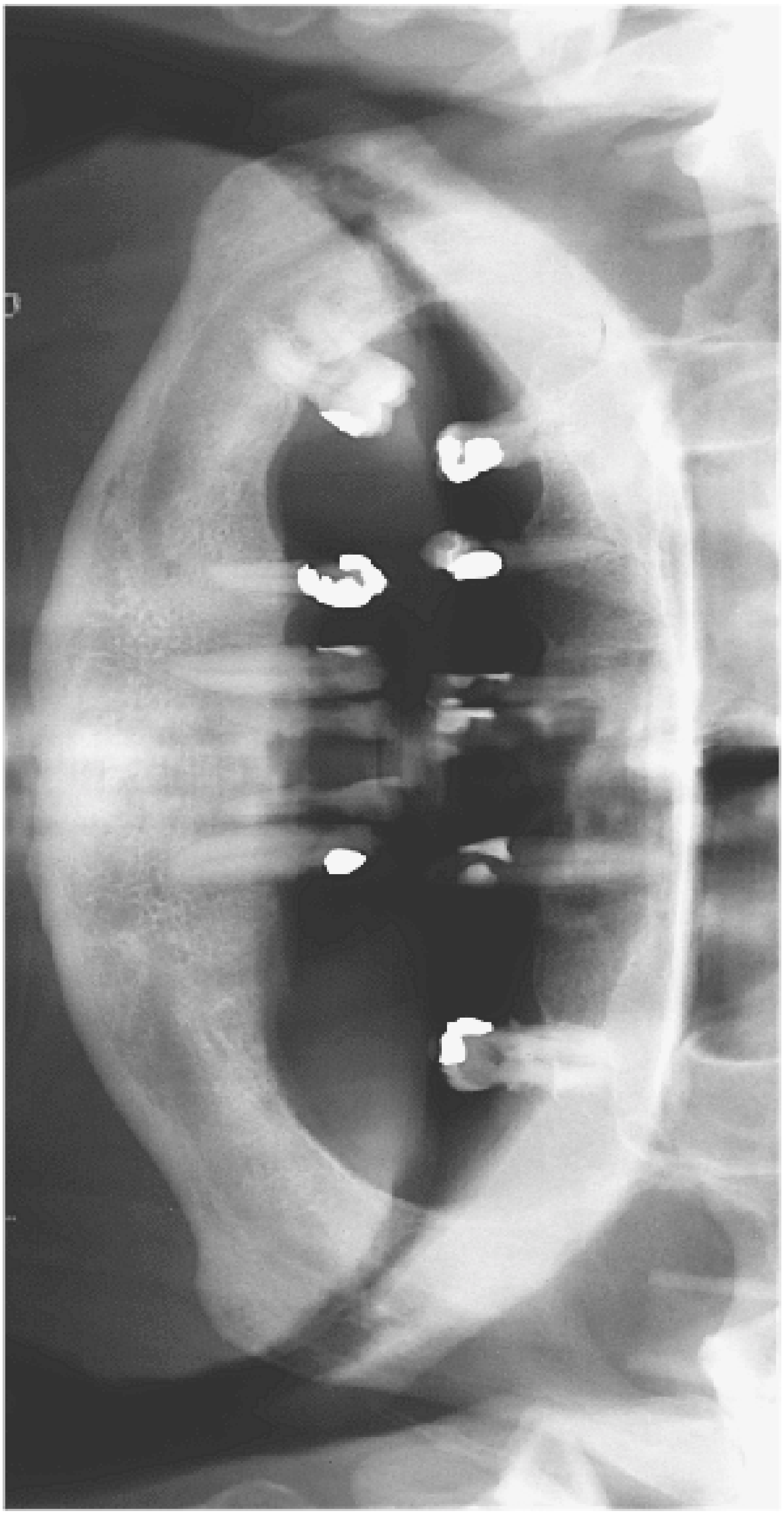


tloss
Output D
0.929
1.000
1.000
1.000
0.205
0.929
0.913
1.000
0.530
0.926
0.926
0.530

Most conditional probabilities are higher than 0.9, indicating a high chance for tooth extraction/tooth loss. The **blue arrows** point at conditional probabilities that are medium or low, indicating that in these cases the chance for tooth loss is between 17.9 % - 53 %. Thus, 9 of the total of 12 teeth that are present are likely (probability > 90%) to be extracted. The other 3 teeth (#23, #43, #33) may be retained.

HOW should we interpret these results? Please note that this prediction from SCREDENT can inform, but can never replace individual expertise. Remember, evidence-based medicine is not an obligatory 'cookbook' approach. Additional decision factors, such as timing considerations, are very important. For example, the conditional probability for tooth extraction of tooth # 48 (prediction vector in row 7) is 0.913. Tooth #48 is the only tooth within the high dose radiation field. Therefore, it is important that this tooth is extracted before radiation starts, allowing an adequate healing time of at least 14 days. The other eight teeth with high conditional probabilities for tooth extraction are not in the high dose radiation field and can be left in situ until later. In addition, the dental treatment planning should include 'normal' dental considerations. For example, in this particular patient, a full mouth clearance could be opted for, or alternatively, the decision could be for an over-denture on teeth #33 and #43. However, because the dental IQ of this patient is poor and because xerostomia is anticipated (salivary glands in high dose radiation field), the conditional probability for tooth extraction/tooth loss for both cuspids in the lower jaw is 0.530 (rows 9 and 12), indicating a 50% change that these cuspids will be lost within 3 years following radiation therapy (see Chapter 5).

3. Example case OPG (the example SCREDENT form is depicted on page 138)



SCREDENT DENTITION ASSESSMENT FORM (Bruins, Jolly & Koole, 1999)

Patient code number	Date of Birth Day Month Year	Gender M= 1 F = 2	Date of Oral Screening Day Month Year
123AA	17 07 1936	1	24 03 1999

Type of head & neck tumor			Location of tumor ICD code[1]	CTNM stage T	N	M	AJCC Stage (1,2,3 or 4)
SCC	Benign Salivary Gland		161.1	2	0	0	2

Tumor record

First	Second/ recurrence

Goal of tumor therapy:

Cure	Palliation	?

Type of tumor therapy:

Surgery	**Radiation**	Chemo	?

Major salivary glands in radiation field? (Bilaterally, > 50%): **yes** / no

Patient's Dental IQ / Compliance: high / **average-low** (please check guidelines)

Dentition Status (Tooth numbering according FDI system)

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	17	28
STATUS	4	3	4	2	4	4	2	2	4	4	3	4	4	4	3	4
DRF	-	1	-	1	-	-	1	1	-	-	0	-	-	-	1	-
TRX	-	0	-	0	-	-	0	0	-	-	0	-	-	-	0	-
TREATM.	-	?	-	?	-	-	?	?	-	-	?	-	-	-	?	-

	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
STATUS	3	4	4	3	4	2	2	4	4	2	2	4	4	4	4	4
DRF	0	-	-	0	-	0	1	-	-	1	0	-	-	-	-	-
TRX	1	-	-	1	-	0	0	-	-	0	0	-	-	-	-	-
TREATM.	?	-	-	?	-	?	?	-	-	?	?	-	-	-	-	-

Prosthetic Status

Upper	Lower
3	3

0 = No prosthesis
1 = Bridge
2 = More than one bridge
3 = Partial denture
4 = Both bridge(s) /Part.dent.
5 = Full removable denture
9 = Not recorded

Reminder Dentition Status Codes (see guidelines)

Tooth STATUS:

0 = Sound
1 = Decayed
2 = Filled, with decay
3 = Filled, no decay
4 = Missing
5 = Dental implant
6 = Bridge abutment / crown / implant
7 = Bridge abutment/ crown, with decay
8 = Unerupted tooth / unexposed root
9= Not Recorded

DRF: 0 = medium or low, 1= High

TRX: 0 = tooth not in radiation field (>50 Gy.)
1 = tooth in radiation field (>50 Gy.)

Curriculum Vitae

The author of this thesis was born in Amsterdam on December 5, 1953. He finished high school (HBS-B, 6-year curriculum) in 1972, but was unsuccessful that year in the "lottery" that governs dental school admissions in the Netherlands. Instead, he followed an introductory course in Philosophy at the University of Utrecht. In 1973, he was admitted to the Dutch Film and Television Academy in Amsterdam, where he obtained a bachelor of arts degree in the summer of 1977. In this period, and in the following year, he served as cinematographer for numerous film productions.

As his interest in dentistry was still strong, he started courses in this field at the University of Amsterdam (6-year curriculum) in September 1978. He obtained a bachelor's degree (cum laude) in 1980, a Master's degree (cum laude) in June of 1983, and his dentist's degree (awarded cum laude), in October of 1983.

In April of 1984, he started a general dental practice in Naarden, the Netherlands. From 1988 to 1997, he worked part-time as nursing-home dentist in Verpleeghuis Naarderheem, and from 1990 to 1995, also in Verpleeghuis Zonnehoeve. This stimulated his interest in "special dental care,", and as it developed further, he left the general dental practice in 1989 and started working in the dental clinic of a convalescent institutional complex (Groot Klimmendaal, Arnhem, the Netherlands). In the same year, he also served as part-time research assistant in the field of geriatric dentistry under Prof. Dr. W. Kalk and Prof. Dr. C. de Baat at the Dental School of the University of Nijmegen.

From 1992 to the end of 1994, he worked at a special dental care clinic ("Stichting Bijzondere Tandheelkunde") in Amsterdam under Dr. P. Makkes, where he treated patients suffering from dental phobia and handicapped patients.

Since January 1995, he has been employed as a dentist at the Department of Special Dental Care of the University Medical Center Utrecht. A portion of his activities have been directed toward hospital dentistry and clinical research. In addition, in 1997, he joined the medical staff of the St. Antonius Hospital in Nieuwegein, mainly treating children under general anaesthesia (day care). At the beginning of 2001, he was appointed Chef de Policlinique of the Department of Special Dental Care of the University Medical Center Utrecht.

Acknowledgments

At the completion of this thesis, I am very pleased to take the opportunity to thank all those who contributed to this work. I am greatly indebted to so many people who have given their generous support that the list seems endless. Although I can't refer to you all by name, I would like to mention the following persons in particular.

First, I would like to express my sincere gratitude to my promotores, ***Prof. Dr. R. Koole*** and ***Prof. Dr. C. de Putter***, who gave me the opportunity to set up the research project and who helped me to overcome many obstacles. Ron and Cees, your enthusiasm and friendly support have been very important to me, **thanks**!
In addition, I want to express my special gratitude to my co-promotor, ***Prof. Dr. D.E. Jolly*** of the College of Dentistry of the Ohio State University. When we first met in Philadelphia in 1988, neither of us could have expected that our future cooperation through the Internet was going to shrink our geographical distance while expanding our scientific horizons. Yet, our "face-to-face" collaboration proved to be incredibly fruitful. Dan, thanks very much for your creative attitude, and your time and effort.

I would like to thank ***Prof. Dr. F. Bosman***, ***Prof. Dr. P.Egyedi, Prof. Dr. D.E. Grobbee***, ***Prof. Dr. G.J. Hordijk***, and ***Prof Dr. W.P.Th.M. Mali*** who all encouraged and inspired me greatly.
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Without the leading work of ***Prof. Dr. R. Cooksey*** of the University of New England, Australia, "Clinical Judgment Analysis" would still be a "closed book" to me. Ray, thank you very much for the education of JANNET.

I also thank ***Dr. A. Krajnc*** of aiNet, Slovenia, for letting me use his outstanding probabilistic neural network software. Alec, thanks for the quick e-mail responses in all the cases where, not your excellent software but I myself got stuck.

I am also grateful to ***Prof. Dr. C. de Baat*** for his support during so many years. Cees, when in the Acknowledgements to your own thesis (1990) you wrote "*je kunt erop rekenen dat ik je zal 'terugbetalen'*," I was not yet aware that my "investment" was going to be so profitable.

I wish to express my special thanks to ***Dr. Ir. J.A.J. Faber*** of the Department of Biostatistics of the University of Utrecht, for his outstanding contributions and vibrant discussions on statistics.

My deepest admiration goes to ***everyone*** at the Departments of Special Dental Care, Oral-Maxillofacial Surgery, and Otorhinolaryngology at the UMCU and to ***all others*** who during the course of my research project showed their interest and assisted me to "get the jobs done."

Without the language skills and patience of ***Elizabeth Krijgsman***, the English of this thesis would not be as fluent as it is. Liz, thanks very much for your care for the manuscripts. I will not forget it!

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I am much indebted to my big brother ***Bart Bruins***, who gave me lots of "constructional behavioral" advice and took care of our business during all that time I had a "good excuse," Bart, many thanks! It is now my turn to assist you in completing your own research project.

Finally, I 'm speechless when it comes to expressing my deepest gratitude to my friend and wife ***Angèle***. Without her support, care, and love it simply would not have been possible to complete this dissertation. Also to my fantastic children ***Isabelle***, ***Xander***, and ***Stéphanie***: it looks like I've finally finished my "homework", ***so let's go……………***

………………………………………………… !!!