Evidence-Based Decision Making in Dentistry

Multidisciplinary Management of the Natural Dentition

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This book is dedicated to the memory of Steve Michael Nemcovsky, son of Shulamit and Carlos, who tragically passed away in November 2015.

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1 Introduction to Evidence-Based Decision-Making in the Multidisciplinary Management of the Natural Dentition

Eyal Rosen, Carlos E. Nemcovsky, and Igor Tsesis

Abstract

The ultimate goal of conservative dental treatment is to preserve the natural dentition. In complicated cases where a complex multidisciplinary treatment approach may be required, serious dilemmas may rise, and possible further complications and tooth prognosis might be unpredictable. Application of evidence-based approaches in the multidisciplinary management of the natural dentition could result in reduction of mistakes in the clinical decision-making.

This book is aimed to provide dental practitioners with evidence-based knowledge and practical tools that may be incorporated in their daily practice. The principles of evidence-based decision-making in endodontology, periodontology and oral rehabilitation, as well as common clinical dilemmas such as the decision on whether to preserve a natural tooth or extract and replace it with an implant, and future trends in dentistry and how they may affect the clinical decision-making are discussed.

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The decision whether and how to preserve the natural tooth by endodontic, periodontal, and prosthetic treatments, or to extract and replace it with an alternative such as fixed partial dentures or dental implants, seems to present a frequent dilemma [*1*, *2*]. Complicated cases may require a complex multidisciplinary treatment approach in order to preserve the natural tooth, and the possible further complications, as well as the

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prognosis of the tooth, may be unpredictable, thus challenging the practitioner's decision-making. In addition, it should be recognized that not every complication will necessarily lead to failure [*1*, *3*–*5*]. The treatment outcome may not be compromised as long as the main treatment goals are achieved. However, in cases where complications compromise the main treatment goals, less predictable outcomes may be anticipated [*5*–*8*].

A contemporary principle in dentistry is that every reasonable effort should be made to preserve natural teeth. The basic goal of dental implants is to replace missing teeth or those definitely indicated for extraction, but implants are not meant to replace present teeth [*1*, *2*, *6*].

When considering treatment alternatives, some clinical trials may use "success" as the exclusive outcome variable, based on strict clinical and radiographic evaluations. In contrast, others may use "survival," defined as the "retention of the tooth or implant, depending on the intervention," as the outcome variable. This may lead to a confusion when attempting to compare between different treatment modalities [*2*]. Therefore, the comparison between different treatment modalities cannot be solely based on outcome measurements [*5*, *9*]. Other factors such as long-term prognosis, specific prosthetic/periodontal/endodontic considerations, possibilities offered by modern dental treatments, alternative treatments (especially in case of treatment failure), and the patient's preferences should all be recognized and incorporated in the practitioner's decision-making [*1*, *2*, *5*, *6*] (Fig. 1.1).

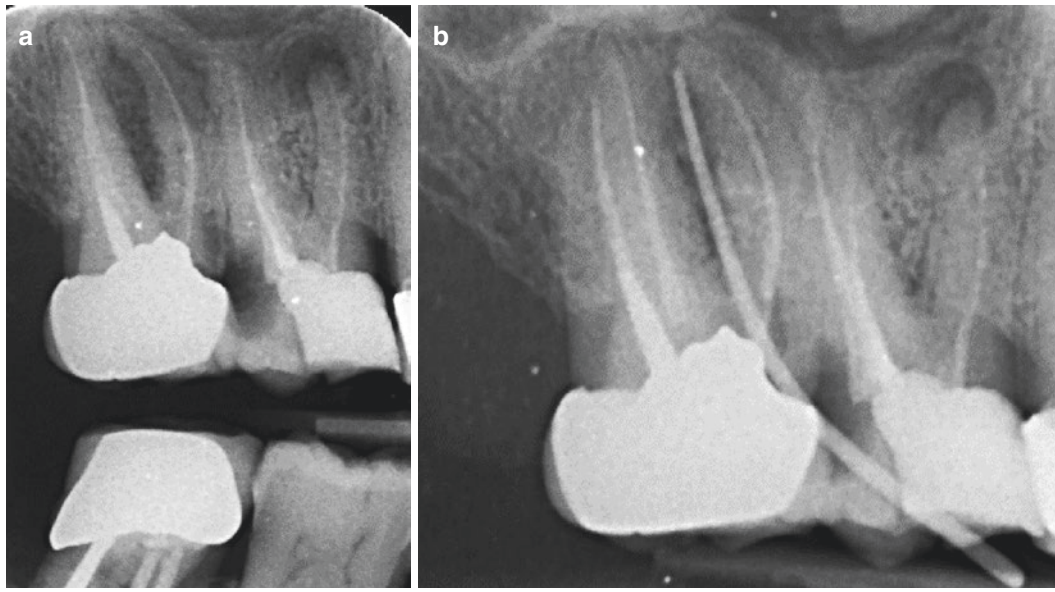

Fig. 1.1 A complex endodontic, periodontal, and prosthetic case

A 55-year-old male, with no reported personal or family disease history of interest, presented with a complaint of pain and discomfort at the right maxillary molar area (a). The first molar was diagnosed with extensive caries, supporting bone loss, periodontal pockets, and asymptomatic apical periodontitis. The second molar (b – radiographed while placing a #50 gutta-percha point in a deep buccal periodontal pocket in order to radiographically trace the source of the infection) was diagnosed with a chronic apical abscess and a suspected vertical root fracture. Although this case seems an ordinary daily case, it encapsulates many decision-making dilemmas regarding the treatment choices:

What is the prosthetic, periodontal, and endodontic prognosis of these teeth?

How should these factors be integrated in the decision-making process?

Would a cone beam computed tomographic examination contribute to the decision-making process?

Is it beneficial to preserve these natural teeth by additional treatments? Or is it better to extract and replace one of them or both of them with implants?

What are the available modern endodontic, periodontal, and prosthetic treatment modalities relevant to this case?

In case of extractions, what are the available biological and technological strategies for alveolar bone regeneration? And how would future trends in dentistry affect the clinical decision-making in such cases?

The required additional maintenance treatments and the patient's quality of life should also be taken in consideration. For example, endodontically treated natural teeth may provide more effective masticatory function compared to implant-supported restorations [*10*]. In addition, although the success of endodontically treated teeth and implants may be comparable, the latter may require more postoperative maintenance [*11*]. Thus, natural endodontically treated teeth may provide better dental function and less subsequent treatments than implants [*5*, *6*, *10–12*].

As part of the clinical decision-making process, specific patient- and practitioner-related matters should also be considered [*5*, *6*]:

- Are my patients similar to those presented in the literature (e.g., in terms of motivation, socioeconomic status, systemic considerations)?
- Is the treatment modality feasible in my setting?
- Will the potential benefits of a treatment outweigh the potential risks for a certain case?

Certain practitioners may tend to institute their clinical approach to complicated cases on personal experience, which in some cases may imply "Making the same mistakes with increasing confidence over an impressive number of years" [*13*]. On the other hand, *evidence-based dentistry (EBD)* is an approach to oral healthcare that integrates the best available clinical evidence to support a practitioner's clinical expertise for each patient's treatment needs and preferences [*14–16*] and should be routinely adopted by practitioners [*5*, *6*].

Evidence-based dentistry is based on the process of systematically finding, apprising, and using research findings as the basis for clinical decision-making. *Systematic reviews* constitute the basis for EBD [*5*, *13–15*, *17–20*]. The application of an evidence-based approach for the management of the natural dentition should result in reduction of mistakes in the clinical decision-making process [*5*, *6*, *14–16*, *21*].

In a clinical scenario, the evidence assessment requires a definition of a specific clinical question (e.g., determine the patient characteristics, the clinical intervention, the comparison methods, and the clinical outcome of interest), followed by a comprehensive literature search in order to identify as much of the relevant literature as possible. Then, review and synthesis of the evidence are performed by using explicit methodology aimed at minimizing bias and addressing the completeness, quality, and combinability of the identified evidence [*5*, *6*, *13–15*, *17–20*]. Eventually, evidence-based conclusions can be made [*5*, *6*] (Fig. 1.2).

One of the main goals of the evidence-based decision-making process is to appraise the available evidence in order to "separate the wheat from the chaff." The available literature should be graded by the strength of evidence [*14–21*], and a cornerstone of this process is the use of hierarchical systems of classifying the evidence. This hierarchy is known as the *levels of evidence (LOEs)* [*22*].

One of the earliest reports of an LOE hierarchical system was published in 1979 by the Canadian Task Force on the Periodic Health Examination [*22*, *23*]. Since the introduction of LOE, several other organizations have adopted variations of the classification system, while most of them share a lot in common [*14–23*]. As an example, in practically all LOE classification systems, *randomized controlled trials (RCT)* are considered as a high level of evidence, as opposed to *case reports* and *narrative reviews* that are considered as a low level of evidence [*14–24*]. To date, classification systems such as the one presented by the "Oxford Centre for Evidence-Based Medicine" [*24*] provide comprehensive hierarchical systems for classifying scientific evidence [*14–24*].

Systematic reviews use these hierarchical systems of classifying evidence and may lead to surprising conclusions that may contradict common concepts and even demonstrate *a reverse pyramid of scientific evidence*, i.e., when there are scarce high LOE relevant studies and many low LOE nonrelevant studies, there might be a misconception that a certain clinical topic is scientifically well supported [*25*]. This situation stresses the need for strict evidence-based analysis of the available data [*14*, *15*, *17*, *26*]. An example to a "reverse pyramid of scientific evidence"

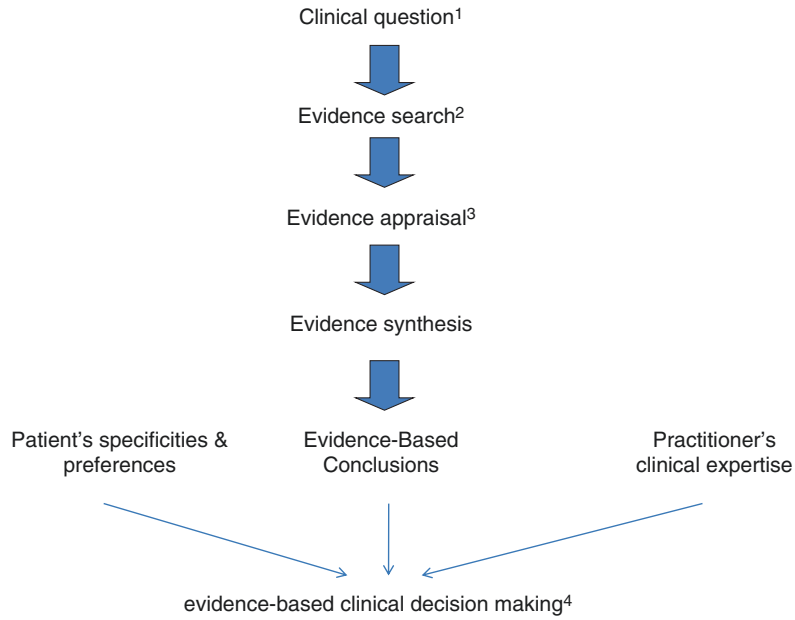

Fig. 1.2 The evidence-based decision-making algorithm for the management of the natural dentition
[1]Specific clinical question defining the patient characteristics, the clinical intervention, the comparison methods, and the clinical outcome of interest.
[2]Wide-range evidence search using search engines and hand search.
[3]Evaluation of the evidence validity, clinical usefulness, quality, and combinability using strict inclusion criteria.
[4]Evidence-based decision-making integrates the best available clinical evidence to support a practitioner's clinical expertise for each patient's treatment needs and preferences

that will be elaborated in a separate chapter of the book is the currently available evidence to support the efficacy of cone beam computed tomography in dentistry.

Systematic review of the available literature regarding a certain clinical scenario may lead to a conclusion that there is no available relevant data, and therefore further research is indicated to elucidate that particular clinical question [*5*, *6*]. On the other hand, in other cases, when sufficient high-quality and combinable data has been retrieved during the systematic review process, a meta-analysis of the results across the studies may be performed and can even lead to new insights regarding that particular clinical question [*5*, *6*, *14–16*, *20*, *25*].

This book will provide dental practitioners with knowledge and practical tools for an evidence-based approach to incorporate in their daily decision-making process in the management of the natural dentition.

The principles of evidence-based decision-making will be discussed, followed by particular chapters that will focus on specific endodontic, periodontal, and prosthetic considerations that should be integrated in the decision-making process. In addition, common clinical dilemmas such as the decision whether to preserve the natural tooth or to extract and replace it with an implant, case selection for the use of cone beam computed tomography in dentistry, as well as future trends in dentistry and how they may affect the clinical decision-making will also be elaborated. Clinical figures and case presentations accompany the text to support efficient application in daily practice.

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Principles of Evidence-Based Decision-Making

2

Massimo Del Fabbro, Stefano Corbella, and Silvio Taschieri

Abstract

Evidence-based medicine is defined as "the conscientious, explicit and judicious use of current best evidence about the care of individual patients integrated with clinical expertise and patient values to optimize outcomes and quality of life".

In the hierarchy of study designs used in clinical research, randomized controlled trials (RCTs), prospective controlled trials (CTs) and meta-analyses or systematic reviews (SRs) of RCTs are considered to provide the highest level of evidence. Conversely, uncontrolled studies like case series and case reports, as well as retrospective studies, due to the features of the study design and many methodological aspects that may somehow affect the outcomes, are considered to have a higher level of bias as compared to RCTs. The latter are specifically designed to minimize the experimental bias in any steps of the study procedures, so as to provide the most reliable possible outcomes.

Since the volume of published information is steadily increasing, it is extremely important to assess the level of evidence of the publications, in order to discern which information should be relied upon to formulate an evidence-based treatment plan and provide the patients with the most accurate, up-to-date and trustworthy information.

The purpose of this chapter is to provide the basis of the evidence-based dentistry in order to facilitate clinicians in their daily decision-making process.

2.1 Introduction: Treatment Choices in Modern Dentistry

The development of new techniques, instrumentation and biomaterials used in medicine has made possible the extension of the clinical indications for most treatments. However, with

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the increase of healthcare costs, there has been a paradigm shift in healthcare towards evidence-based research. Many manufacturers and corporations tend to use effective marketing strategies rather than peer-reviewed studies to promote their technological and biological advances. This trend can create a confusing picture for clinicians, who have the responsibility for recommending the most appropriate treatment approach using a conscious critical analysis based on accurate diagnostic path. When a clinician discusses treatment planning with a patient, it is necessary to provide the patient with information related to the efficacy and long-term outcome of the various treatment options. These data are needed for informed decisions [1]. Since medical knowledge is steadily increasing, previously accepted facts rapidly become outdated, and it seems impossible for a clinician to follow such explosion of scientific information, due to the time required for reading and critically appraising all of them and the usual shortness of time available. Therefore, busy clinicians need to read selective, efficient and patient-driven research. Thus, in order to discern which information should be relied upon to formulate an evidence-based treatment plan and provide the patients with the most accurate, up-to-date and trustworthy information, it is extremely important to assess the level of evidence of the publications. The evidence-based medicine (EBM) movement started in 1981 with the aim of advising physicians on how to evaluate the medical literature. In recent years, the concept of evidence-based dentistry has thus increasingly become widespread. Today, it is of utmost importance to improve the quality of scientific research to obtain "unbiased" information, simplifying the choice of the most appropriate, effective and possibly less invasive therapies, with the resulting positive impact on patients' health. In particular, the decision as to whether a questionable tooth should be removed and replaced by an implant versus conventional endodontic treatment and restorative therapy can be challenging [2–5].

2.2 Algorithms for Decision-Making in Patient Management: Historical Perspectives and Evolution

Medical decision-making in patient management substantially evolved during the last century: until the end of 1970, it was based on trial and error and involved high levels of problem-solving, being, therefore, predominantly intuitive and anecdotal; in the 1980s the empirical medicine emerged, involving pattern recognition and less problem-solving, and it was evidence-based probabilistic. In this paternalistic model, physicians would be solely responsible for clinical decision-making, and the patient's preferences and opinion were rarely, if ever, taken into consideration. Conversely, today this process is dominated by the personalization and customization of healthcare: the patient and the health professional work together in order to achieve the most satisfactory treatment decision for the patient, creating a balance between the preferences of the former and the expertise of the latter. Jointly decisions with reliable EBM are referred to as shared decision-making (SDM) and aim to enhance knowledge about the options and outcomes that is relevant to arrive at the most satisfactory treatment decision for the patient. SDM is available in various forms, e.g. brochures, booklets, interactive software and videos or decision tables. These aids in decision-making essentially consist of applying known patient conditions and preferences to an algorithm of the disease and treatment course based on EBM. A medical algorithm is any computation, formula, score, scale, diagram, survey or look-up table useful to improve the delivery of healthcare [6–8]. Medical algorithms are used by clinicians and medical researchers, significantly improving the quality and cost-effectiveness of medical care, but, unfortunately, although being a valuable resource in healthcare, they are underutilized. One fundamental characteristic is that algorithms can be programmed: data are entered and processed according to formulas derived from the source material and result in useful output. Errors

can arise in the area of medical algorithms; therefore, centralizing and automating them are one way to reduce planning, calculation, execution, errors, etc., and to share information among a wide range of clinical care provider. For this purpose the Medical Algorithms Project (MEDAL) was developed by John Svirbely in 1998 in order to provide a collection of medical algorithms in a format that supports clinicians, programmers and validators.

2.3 Evidence-Based Medicine and Its Application into Clinical Practice

Evidence-based medicine (EBM), also termed evidence-based practice (EBP) (which takes into account the practice healthcare setting and circumstances), originated in the second half of the nineteenth century, by a group of clinical epidemiologists at McMaster University (Hamilton, Ontario, Canada), led by David Sackett. The actual term "evidence-based medicine" was first coined by Gordon Guyatt, one of Sackett's mentees, and despite its ancient origins, it remains a relatively young discipline in continuous evolution and adaptation. EBM has been defined by Sackett et al. as "the conscientious, explicit and judicious use of current best evidence about the care of individual patients integrated with clinical expertise and patient values to optimize outcomes and quality of life" [2]. The revised and improved definition of EBM is a systematic approach to clinical problem-solving which allows the integration of the best available research evidence with clinical expertise and patients' values (Fig. 2.1), where practice of evidence-based medicine means the integration of the clinician's individual clinical expertise with a critical evaluation of the best available external clinical evidence from systematic research and individual clinical expertise means the ability, the dexterity and the skills that each single clinician acquires during years of clinical experience and practice [3–5]. In this definition, best available external clinical evidence is meant clinically relevant research, usually from the basic science of medicine and patient-centred clinical research [9].

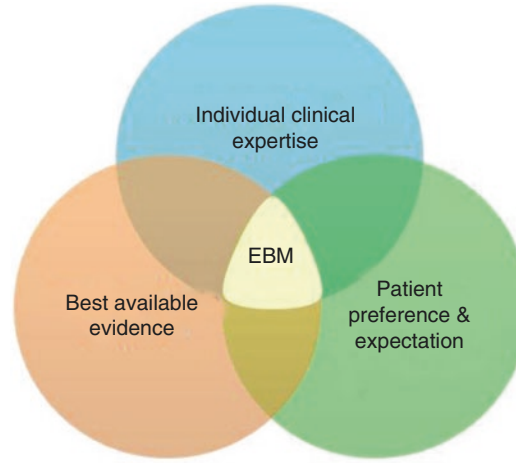

Fig. 2.1 Evidence-based medicine triad

Individual clinical expertise can never be replaced by external clinical evidence, even if the latter can be informative, and it decides whether the external evidence applies to the individual patient and how it should be integrated into a clinical decision. In terms of study designs, the best scientific evidence from primary studies (i.e. studies made on patients that present results for the first time, as it will be explained later) is represented by randomized controlled clinical trials conducted on patients from which data that can demonstrate the effectiveness, the safety or the harm and the inefficacy of a tested drug or therapy are obtained. Since evidence-based medicine involves tracking down the best external evidence necessary to answer the clinical questions, it is not restricted only to randomized studies and meta-analyses but also comes from the basic sciences. Clinicians practising evidence-based medicine identify and apply the most effective interventions to maximize the quality of life for individual patients. For example, a recent Cochrane review by Del Fabbro et al. [10] comparing endodontic surgery and orthograde endodontic retreatment for addressing periapical disease found no significant differences in clinical and radiographic outcomes between the two

treatment modalities after up to 4 years of follow-up. Therefore, in such a case, the treatment choice needs to be based on other than the treatment outcomes and will take into account, for example, the condition of the crown (presence or absence of leakage), the general health state of the patient (the American Society of Anesthesiologists (ASA) status for assessing if he/she is able to undergo a surgical procedure or not), the patient's expectations and wishes, the expertise of the clinician, the overall costs, etc.

2.4 Types of Research Design: Advantages and Shortcomings

The scientific literature in the medical field represents the main source of information for researchers and clinicians. However, the scientific value of different publications may vary enormously from a qualitative point of view, and this may lead to considerable confusion and decreased usefulness for all beneficiaries. How may I ensure that the article I am reading is good? How trustful is the information? How reliable is the take-home message of the article? These are everyday questions from the clinicians that wish to keep updated and acquire the best knowledge from the literature about topics of interest; so, answers to the above questions are due.

In the last few years, the international scientific community has felt the need to provide clear and reproducible criteria for objectively "weighing" a scientific publication. In other words, an article should give the reader a clear message and accurate information based on concrete, reproducible and verifiable evidence. A clinical article should also specify the range of applicability of the results, that is, the type of patients the study results are worth for. This is also called generalizability or external evidence. A study with a high generalizability possesses a major clinical weight compared to one whose results are applicable to a limited category of patients with specific characteristics.

Different types of clinical trials are available, and each type of study possesses precise characteristics in order to provide specific indications to external audience and to researchers. Different types of studies answer different types of questions; for example, to test the efficacy of drugs, surgical procedures or other therapies, one type of study must be used, while to demonstrate the validity (Is the result correct? Is it true?) and reliability (Can the correct result be achieved every time? Is it reproducible by any operator following the same procedure?) of a new diagnostic test, other types of studies are necessary.

From a schematic point of view, the scientific studies can be divided into three main categories:

1. In vitro and in vivo studies (preclinical research)
2. Primary clinical research
3. Secondary clinical research

2.4.1 Preclinical Research

The main purpose of preclinical studies is to assess the general safety and feasibility of new treatments, using standardized in vitro and in vivo models that mimic the target condition as closely as possible. These studies are often time-consuming as they serve to set up and identify the best possible approach to treating the target condition, a process that usually requires multiple changes to the original approach, each bringing some improvements to the developing protocol.

In vitro *models* use biomolecules, cell cultures, tissues and organs to perform studies in a controlled, artificial environment outside of a living organism. The main advantages of in vitro studies using cell cultures are the homogeneity of the isolated culture, the relatively low cost (depending on the type of analysis the researcher is aiming to perform that may require more or less sophisticated instrumentation), a timeline of well-defined events and a reproducible growth of different cultures. One of the limits and weaknesses of in vitro experiments is that they fail to replicate the precise cellular conditions and interactions with other cells and soluble signalling molecules dynamically present into a tissue environment of a living organism.

In vivo *models* refer to studies using a whole, living organism, as animal studies and clinical

trials. In vivo research is preferred over in vitro testing since it can provide information about biological processes on a living subject before the clinical application. Despite the many reasons to believe that in vivo studies have the potential to offer conclusive insights about the nature of medicine and disease, the transferability of information derived from animal experiments depends mainly on how much the model is biologically similar to humans. In vivo testing of patients, on the contrary, has extremely limited possibilities because of the numerous ethical implications involved. Indeed, though one might believe that any type of experimental procedure and investigation is allowed when using animal models, most countries have established strict rules governing the use of experimental animals, aimed at guaranteeing their safety and comfort throughout the experimental procedures, as well as at applying ethical principles similar to those applied for human beings, and minimizing the amount of animals needed for any experimentation. These rules are known worldwide as the "principle of the three Rs", where the latter stands for "Reduction" (minimizing the number of animals, though keeping a sufficient number for giving statistical significance to the study), "Replacement" (replacing—where possible—species provided with higher sensitivity and intelligence with inferior species that may serve as well for experimental purpose), and "Refinement" (if it's not possible to give up using animals, the best possible experimental conditions and anaesthetic and analgesic administration (and antibiotics where indicated) must be provided, for avoiding any type of suffering during and after the experimental treatment, as well as optimal animal housing conditions, food and beverage ad libitum, and frequent controls by specialized veterinary personnel, in order to detect early signs of discomfort).

2.4.2 Primary Clinical Research

The *primary* or *original research* is defined as a research in which data are collected and analysed for the first time. Among the studies that belong to the primary research are:

1. *Case report/case series*: they describe the medical history of a single patient (*case report*) or of a series of patients (*case series*). These studies are useful to describe rare complications or adverse events that may allow to formulate a hypothesis of cause-and-effect association (e.g. two newborns present deformed limbs (phocomelia) and both the mothers took a new drug (thalidomide) or the implant removal from an atrophic jaw caused its fracture) but are inappropriate to describe the efficacy of a treatment. Such hypothesis is anyway important to design specific studies in order to verify them.
2. *Cross-sectional survey*: a representative sample of subjects is examined in order to answer a specific clinical question, such as the prevalence of a condition at a given time period. This study does not require subjects to be followed over time. It is like a photograph of a given situation. For example, how many endodontically treated teeth present a periapical lesion one year after the therapy? Or what is the prevalence of teeth extracted due to root fracture in the population of endodontically treated teeth? A cause-and-effect relationship cannot be established.
3. *Case–control study*: "case" subjects (those having the condition under investigation) are matched with appropriate "control" subjects (those without the condition), regardless of the presence or absence of risk factors suspected of determining the status. The aim of this type of study is, for example, to understand the aetiology of the condition (how it is caused and not how to treat it) or to detect the presence and strength of the association between putative risk factors and a given observed condition. It is less reliable than the cohort prospective study, but it could be the only study choice for rare conditions (cases). This study is retrospective, since it is conducted after the occurrence of the disease and retrospectively evaluates the possible risk factors (e.g. can thalidomide cause limb deformations at birth? A phocomelic group of babies is retrospectively matched to a healthy newborn group, also considering the number

of mothers who took the drug during pregnancy for each group). It can lead to important results in relatively short time with a relatively limited commitment of resources, but it is very prone to result distortion due to the different bias, in particular, related to the control group selection.

4. *Cohort study*: two or more groups of persons are selected based on differences in their exposure to a particular risk factor and are prospectively followed in order to see how many people will develop a particular condition or will respond to a given treatment. The control group can be absent, but it is necessary to follow a large number of subjects for several years. Control subjects must be contemporary, since historical controls (control subjects who have had the disease or the treatment to be evaluated at an early period than that of the study group) provide less reliable results. Cohort study is ideal to determine the prognosis of a particular condition (i.e. what is likely to happen to a subject with this condition) and the possible cause-and-effect relationship. For example, in 1950 in England, 40,000 physicians were divided into 4 cohorts (non-smokers and light, moderate and heavy smokers) and followed for over a decade, and a dose–response relationship was found: those who smoke more have a greater chance to develop a lung cancer.
5. *Randomized controlled clinical trial* (RCT): it is a prospective study (i.e. the study protocol is defined in advance) that compares two treatments (test and control) and in which participants randomly receive one of the two treatments to be evaluated, avoiding that subjects with a favourable prognosis may be preferentially inserted into one of the study groups. RCT is the ideal study to evaluate the efficacy of a therapy, since randomization is the only way to control all those factors, unknown or nonmeasurable, so as to minimize experimental bias (subjects are impartially distributed into the different groups). Groups of patients, patients or parts of them (teeth, eyes, implants, etc.) can be randomized. Despite the methodological excellence that characterizes the RCT, this study type is fairly complex to being designed and performed, often requiring the use of considerable human and instrumental resources, sometimes for a long period. For these reasons they are quite rare in the biomedical disciplines and are often performed in specialized research centres, universities and advanced clinics that may have the necessary resources. In many occasions such trials are supported by industry that can provide resources to researchers, which are asked for testing the efficacy and safety of the products the company wishes to commercialize. However, in this cases of industry-sponsored trials, there is the spectral risk that some form of conflict of interest arises (which might affect the reliability of the findings and their interpretation); therefore, the latter must be clearly disclosed when presenting the study results for publication, by overtly mentioning any kind of support to the study. Also, it should also be specified who prepared the study protocol, if it is the researcher or the sponsor. In fact the latter might somehow design the study in a way to maximizing the positive effects of their products and at the same time minimizing the detection of any adverse effect [11].

2.4.3 Secondary Research

The *secondary research* is based on the careful selection and analysis of data collected in primary studies of high quality, in particular RCT, providing the scientific community with updated and reliable information on a specific topic (*reviews of the literature*). However, it should be highlighted that not all reviews of the literature possess the same reliability level and the same purpose. In fact, we must distinguish between revisions carried out with a systematic and predetermined method, which aim to provide clear guidelines, and revisions that simply aim to describe a subject in an exhaustively way. There are different types of secondary research.

1. *Narrative or traditional review*: It is the summary of different original study results in order to draw conclusions about a treatment or a disease or just provide a thorough description. It gives an overview of a particular topic that generally deals with every aspect. Often, it lacks objectivity in assessing the scientific evidence, and it is not always clear why some studies have been taken into account, while others did not: indeed, the choice of included studies depends exclusively on the individual author presenting the studies, which have come to knowledge in a given time period, but these studies represent only a portion of all the knowledge within the medical literature. Next, the author selects the studies on the basis of subjective criteria and provides only a qualitative description.
2. *Systematic reviews* (SRs): The analysis is focused on specific aspects of a certain pathology or medical intervention by addressing few and well-defined clinical questions. Rigorous and pre-established criteria are used to identify, critically evaluate and synthesize data and quality of studies that will be included in the analysis, in order to achieve evidence-based conclusions (i.e. sound proofs). A systematic review can include one or more *meta-analyses* that are a specific statistical technique that aggregates data from different studies, in order to estimate the combined effect of these studies with greater accuracy. SRs are especially helpful when study results give conflicting indications about a therapy efficacy and/or when the number of subjects in each study (sample size) is insufficient to detect a statistically significant difference [12].
3. *Clinical guidelines* (GL): Ideally, these consist of recommendations developed by means of a systematic literature review process in order to assist physicians and patients in deciding what diagnostic and therapeutic investigations to adopt in specific clinical conditions. Such reviews usually are examined during a consensus conference in which a panel of experts meet in order to discuss, consider the current evidence produced by systematic reviews and produce a document (the GL) with the purpose to formulate clear recommendations that should drive and influence the clinical practice. Unfortunately, it often happens that the position statements with GL are based on narrative reviews rather than on SR, which may derive on the absence of evidence-based primary studies or, most commonly, on the inappropriate approach in addressing the topic. Thus, their reliability is greatly compromised.

2.5 Bias

In general the level of evidence of a study is considered as inversely related to its level of bias. The latter can be defined as any uncontrolled trait of the experimental design that may affect the outcome, therefore producing a distorted result, which may not reflect the true effect of a given treatment. On a statistical point of view, the term bias is defined as a systematic, as opposed to a random, distortion of a statistic as a result of a noncasual sampling procedure. Therefore, any trend in the choice of a sample, the making of measurements on it and the analysis or the publication of findings that tends to give or communicate an answer that differs systematically from the true answer is a bias. It represents a systematic error that produces outcomes that differ unpredictably from those expected in the absence of bias and that might be avoided by optimizing the study design. There are a number of possible biases in an experimental study, and it is practically unfeasible to avoid or control all of them. Though, it is essential to know the most common ones as the control of any potential source of distortion is an important measure of the validity of the study results. The most frequent biases are the selection bias (bias at entry: the patients are not selected according to an appropriate random procedure), the detection bias (bias in outcome assessment: e.g. the evaluator knows which group the patient that is going to be evaluated belongs to), the performance bias (the efficacy of a product may be increased if the producer is the sponsor of the study) and the

publication bias (a study is published more easily if it demonstrates positive results of a given treatment rather than shows no or negative results).

2.6 Level of the Evidence

Since the volume of published information is steadily increasing in many fields of medical sciences, it is extremely important to assess the level of evidence of the publications, in order to discern which information should be relied upon to formulate an evidence-based treatment plan and provide the patients with the most accurate, up-to-date and trustworthy information. Ranking the available evidence into different levels and grades of recommendation was first described by Fletcher and Sackett more than 25 years ago, to give an idea of the quality of the evidence on the basis of the level of bias and flaws of the various types of study design adopted in the biomedical research. In general the level of evidence of a study is considered as inversely related to its level of bias. The latter can be defined as any uncontrolled trait of the experimental design that may affect the outcome, therefore producing a distorted result, which may not reflect the true effect of a given treatment.

In the hierarchy of study designs used in clinical research (Fig. 2.2), randomized controlled trials (RCTs), prospective controlled trials (CTs) and meta-analyses (MAs) or systematic reviews (SRs) (taking into consideration RCTs or controlled clinical trials) are considered to provide the highest level of evidence. In terms of qualitative weight, systematic reviews are at the top of scientific evidence and, therefore, must be considered as fundamental in clinical procedures' validation. Conversely, uncontrolled studies like case series and case reports, as well as retrospective studies, are associated with a lower level of evidence. In other words, the latter types of investigation, due to the features of the study design, such as the choice of the patients, the allocation of treatments, the absence of blinding procedures and many other methodological aspects that may somehow affect the outcomes, are considered to have a higher level of bias compared to randomized controlled studies. RCTs are specifically designed to minimize the experimental bias in any steps of the study procedures, so as to provide the most reliable possible outcomes.

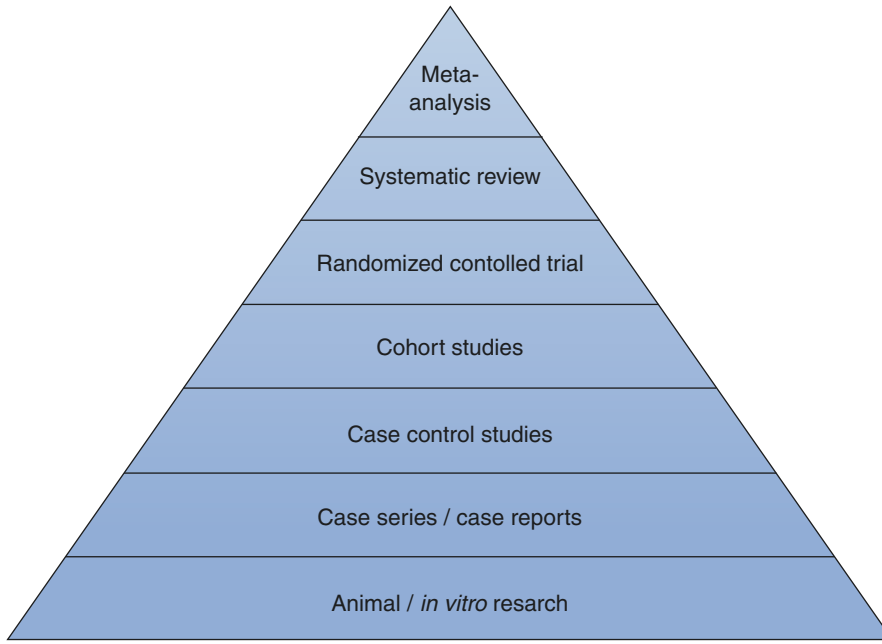

Fig. 2.2 Levels of evidence pyramid

2.7 The Journal's Impact Factor (IF)

The most accredited tool for evaluating the weight of evidence, in addition to the type of study design, is the journal impact factor (IF), which is provided by the Institute for Scientific Information (ISI) by means of the Journal Citation Reports (JCR). Since 1975, the latter publication makes available quantitative tools to classify, evaluate, divide into categories and compare the several journals included (indexed) into the ISI database to the scientific community. IF was first proposed in 1955 by Eugene Garfield (one of the ISI founding members) and indicates the average frequency of citations received by an article in a given indexed journal [13–15]. Citations must be received in a given year and must refer to the articles published in the previous two years in that journal. The IF of the given year is calculated by dividing the total number of citations received in that year by the total number of articles cited and published in the two previous years (leaving out editorials, commentaries, congress abstracts). The higher the number of citations received by a journal, the higher the impact of the journal in the scientific community, which is considered as related to the importance and the reliability of the information provided by the articles published. Since the latter are normally chosen based upon a rigorous selection process called peer review, it is believed that the best quality journals have a manuscript review process able to select the best quality information to be published and that, consequently, they have a high probability of receiving a high number of citations. Though the use of IF as an index of quality of the journals is still a matter of debate among scientists, in the absence of an alternative reliable index, the IF is currently adopted as a marker of the value of published scientific information. Nevertheless, while in most cases there might be a correlation between IF of the journal and the quality of published articles, the IF does not stand as criteria for an individual study. The weight of evidence should not depend on the journal the study was published in. Similarly, scientists and clinicians able to have their studies published on a high IF journal are considered as valuable researchers, independent of the number of citations that their specific articles will receive. Indeed, the use of impact factor as a tool to evaluate the value of individual researchers is highly criticized, and different bibliometric indexes have been developed, based on the actual citations received by the researcher's articles and on the prestige of the citing journals. The most known is the Hirsch index (H-index) which represents the number of articles published by a researcher that have received at least an equal number of citations.

2.8 The PICO Question: How to Start Well a Systematic Review

Systematic reviews are true research projects that synthesize and critically evaluate, in a single document, the results of all experimental studies about a specific and well-defined clinical or healthcare-related question. In order to minimize the risk of error, each review must follow a standardized scientific approach, identified in different steps.

The first step of any research is formulating an answerable clinical question. This is very important because the more the review question is clear and focused, the more likely the review is to achieve relevant results. The process of formulating a good research question is known in evidence-based healthcare as "the well-built clinical question". Good clinical question must be clear, directly focused on the problem and answerable by searching the medical literature. One way of formulating your search question starts with the patient and presents four essential structured components known as *PICO* question [16]. The PICO acronym stands for:

Patient or Population or Problem
Who are the relevant patients? What kind of problem are you trying to solve? What are the most important characteristics of the patient/population/problem? This may include the primary problem, disease or coexisting conditions. The type of population (sex, age or race of a patient) and the environment (private, public, specialized clinic, etc.) might be relevant to the diagnosis or treatment of a disease.

Intervention
What main intervention/treatment are you considering as test? What is the management strategy, diagnostic test or exposure (drugs, diagnostic test, food or surgical procedure)?

Comparison
What is the main control or alternative intervention/treatment/management strategy to be compared, if any? The treatment(s) of interest (test) must be specified, and the treatment for the comparison (control–gold standard–placebo) must be decided. The clinical question does not always have a specific comparison. If the comparison is the current best treatment, the study will aim at evaluating the efficacy of a treatment in relation to control (*relative efficacy*); otherwise, if the comparison is a placebo, the study will evaluate the *absolute efficacy* of a treatment.

Outcome
What are the patient-relevant consequences of the exposure we are interested in? What are you trying to do for the patient? Relieve or eliminate the symptoms? Reduce the number of adverse events? The outcomes with a real clinical significance for the patient must be decided (primary outcomes), and it is necessary to avoid misleading the reader with low relevance outcomes (secondary outcomes). The potential complications have also to be considered, possibly dividing them by the degree of severity.

There is another additional element that is essential for the well-built clinical question, helping in focusing the question and determining the most appropriate type of clinical evidence: *the type of clinical question*. The most common type of clinical question is how to treat a disease or a condition and is:

- Questions about interventions
- Questions about aetiology and risk factors
- Questions about frequency and rate
- Questions about diagnosis
- Questions about prognosis and prediction
- Questions about cost-effectiveness
- Questions about phenomena

After identifying the well-built clinical question, the next step is to search for relevant information (published and unpublished studies) about the issue in question and then to systematically select the eligible studies on the basis of predefined inclusion criteria. Critical assessment of the collected data is a process that involves careful reading and analysis of methodology, contents and conclusion. The final step is the discussion of the reasons for correlation and/or discordance of findings with results of different studies.

During a systematic review process, only if the conditions of homogeneity among patients and investigated treatments exist, a meta-analysis can be performed, that is, a statistical technique to combining the weighted results of different studies and quantitatively treating the data, as they belonged to a single large study. This increases the importance of the statistical comparison, allowing to give more precise results. Not all the SRs can thus lead to a meta-analysis: when studies are highly heterogeneous (in the experimental design, patient characteristics, inclusion criteria, methods, results, etc.), the systematic review should give priority to a qualitative approach, stressing the differences between included studies and suggesting the need for performing further studies with a high level of evidence in order to answer the original SR question.

2.9 Scientific Information: How to Find It (the Literature Databases)

In health disciplines there are numerous sources of information that may be of assistance for clinicians to keep updated with the new scientific knowledge and that can be divided into traditional and electronic sources. Traditional sources are books, communication with colleagues, courses, congresses, grey literature and biomedical journals, while the electronic ones include electronic scientific databases, online biomedical journals and Internet search engines. The ideal information source must be valid, relevant,

comprehensive and user-friendly (rapid and easy to access and use).

The most principal Internet sources are:

MEDLINE (through the PubMed search engine) The most used search engine in medicine is PubMed, the electronic version of MEDLINE, a database edited and maintained by the *US National Library of Medicine* (NLM) at the National Institutes of Health, that comprises more than 25 million citations, since 1879 to date, for biomedical literature from 5200 worldwide indexed journals. PubMed is a free tool that accesses primarily the MEDLINE database of references and abstract on life sciences and biomedical topics and may have links to full-text articles, some of which are freely available for any user. Furthermore, this free search engine allows for a number of options (e.g. filters and the combinations of keywords) to focusing and limiting the search. For example, one may limit to only specific study types like randomized clinical trials (RCTs) or systematic reviews, in order to better focus the research on topics of interest.

Embase It is a biomedical and pharmacological database created as Excerpta Medica (EM) Abstract Journals in 1946 and available online by subscription. Currently, it contains over 28 million records from over 8400 worldwide published journals.

Scopus It is an abstract and citation database of peer-reviewed literature for academic journal articles, available online by subscription. It offers a comprehensive overview of the world's research in the fields of science, technology, medicine, social sciences and arts and humanities. The journal coverage of Scopus is wider than MEDLINE and Embase. It allows for citation analysis of researchers or institutions.

Web of science Previously known as (ISI) Web of Knowledge, it is an online subscription-based scientific service that gives access to the most reliable, integrated, multidisciplinary research in the field of science, social science, art and humanities and that includes the Journal Citation Index.

Cochrane Library This is a subscription-based database provided by the Cochrane Collaboration and other organizations, specialized in the collection of systematic reviews, as well as randomized controlled trials, health economic and technology assessment. Cochrane reviews are considered to be the most rigorous and most reliable among systematic reviews because they are made through a very rigorous and extremely detailed process aimed at carefully evaluating and extracting information only from studies performed with the highest possible evidence level (RCTs).

- The Cochrane Library includes six databases:
  - Cochrane Database of Systematic Reviews
  - Cochrane Central Register of Controlled Trials
  - Cochrane Methodology Register
  - Database of Abstracts of Reviews of Effects
  - Health Technology Assessment Database
  - NHS Economic Evaluation Database

For the need of systematic review of clinical studies, the relevant database from the Cochrane Library is "Cochrane Central Register of Controlled Trials" or, in short, CENTRAL.

Google One of the most used generic search engines in the world is Google which presents also specialized sections as *Google Book Search* and *Google Scholar*. Google Book Search is qualified in book content: it is generally possible to view some pages of the selected books and to download those unsecured by copyright. Google Scholar was introduced in 2004, and it allows users to search for digital copies of articles from a variety of academic sources, such as full-text journal articles, technical reports, preprints, theses, books and other documents, including selected Web pages.

These Web-based search engines are very useful for the scientific information retrieval, especially regarding those sources not available with

other databases, but they present also some disadvantages, such as the absence of advanced searching functions, vocabulary, low reliability of the coverage (it is impossible to estimate how many of all scholarly documents on the Web they can find) and a lack of screening for quality.

Grey literature and unpublished studies are also important during the review process to minimize the risk of publication bias. Common grey literature includes reports (preprint, annual report, preliminary progress and advanced reports, research report, technical report, state-of-the art report, statistical report, etc.), working papers, government reports and documents, policy documents, fugitive literature, thesis, conference proceedings, bibliographies and many more. Many databases, libraries and websites are available for finding grey literature, but the cost, the nature and the difficulty of collecting and cataloguing it make it difficult to acquire and make grey literature accessible. Furthermore, for a number of reasons, it is also difficult to find relevant resources and assess the credibility and quality among the available grey literature.

Conclusion

Since the volume of published information is steadily increasing in the field of dentistry, as well as in many other fields of medical sciences, it is extremely important to know how to properly search the relevant information and to assess the level of evidence of the publications, in order to discern which information should be relied upon, with the ultimate aim to formulate an evidence-based treatment plan and provide the patients with the most accurate, up-to-date and predictable treatment.

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Links

Cochrane Library: http://www.cochranelibrary.com/.
Embase: https://www.elsevier.com/solutions/embase-biomedical-research.
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3 Evidence-Based Decision Making in Dentistry: The Endodontic Perspective

Eyal Rosen, Russell Paul, and Igor Tsesis

Abstract

Contemporary dentistry advocates that every reasonable effort should be made in order to preserve natural teeth. Implementation of principles of evidence-based dentistry in endodontics enables the practitioner to provide the patient with the best available treatment in each clinical scenario. Modern techniques and devices in contemporary endodontic practice allow for prevention and early identification and management of complications such as vertical root fractures, perforations, and root resorption. With a proper case selection, teeth that were traditionally planned for extraction can be successfully treated either nonsurgically or by endodontic surgery with a high success rate.

This chapter is aimed to present the endodontic perspective in the clinical decision-making process regarding the management and preservation of natural teeth. Endodontic case selection, treatment planning and long-term prognosis, contemporary endodontic technologies and treatment modalities, and decision-making considerations regarding the diagnosis and management of endodontic complications will be discussed.

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3.1 Introduction

The ultimate goal of endodontic treatment is to eliminate the bacterial infection inside the root canal system and to prevent the invasion of bacteria and their by-products from the root canal system into the periradicular tissues in order to preserve natural teeth [1–4]. However, many times the clinical situation may require a combination of endodontic, periodontal, and prosthetic intervention,

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thus complicating the decision-making process regarding the tooth's prognosis and the treatment alternatives [5] (Fig. 3.1).

Under certain circumstances practitioners may tend to derive their decision making mainly on their personal experience; however, personal experience can be misleading. Using the principles of evidence-based dentistry to support the practitioner's personal experience enables the clinician to provide the patient with the best available treatment possible under the circumstances [5, 6]. Evidence-based dentistry may be defined as an approach to oral healthcare that integrates the best available clinical evidence to support a practitioner's clinical expertise for each patient's treatment needs and preferences [7–9] and should be adopted by practitioners as a routine [5]. It is based on the process of systematically finding, apprising, and using research findings as the basis for clinical decision making and should result in a reduction of mistakes in the clinical decision-making process [5, 7–10].

A frequent dilemma is the decision whether to preserve the natural tooth by endodontic treatment or to extract the tooth and replace it with an alternative, such as a fixed partial denture or a dental implant [2, 11]. Contemporary dentistry advocates that every reasonable effort should be made in order to preserve natural teeth, while the goal of dental implants is to replace missing teeth and not present teeth [2, 11]. Thus, the long-term prognosis, the potential of modern endodontic treatment, the alternatives in case of treatment failure, posttreatment quality of life, and the patient's values should all be recognized and incorporated in the practitioner's decision making [2, 5, 11] (Fig. 3.2).

This chapter will focus on the endodontic perspective in the clinical decision-making process regarding the management and preservation of natural teeth. The chapter will discuss case selection, treatment planning and long-term prognosis as the basis for clinical decision making, contemporary endodontic technologies and treatment modalities, and decision making regarding the diagnosis and management of endodontic complications.

3.2 Case Selection, Treatment Planning, and Long-Term Prognosis as the Basis for Clinical Decision Making

The recent technological advances in endodontic technology together with increased scientific understanding of the endodontic disease have

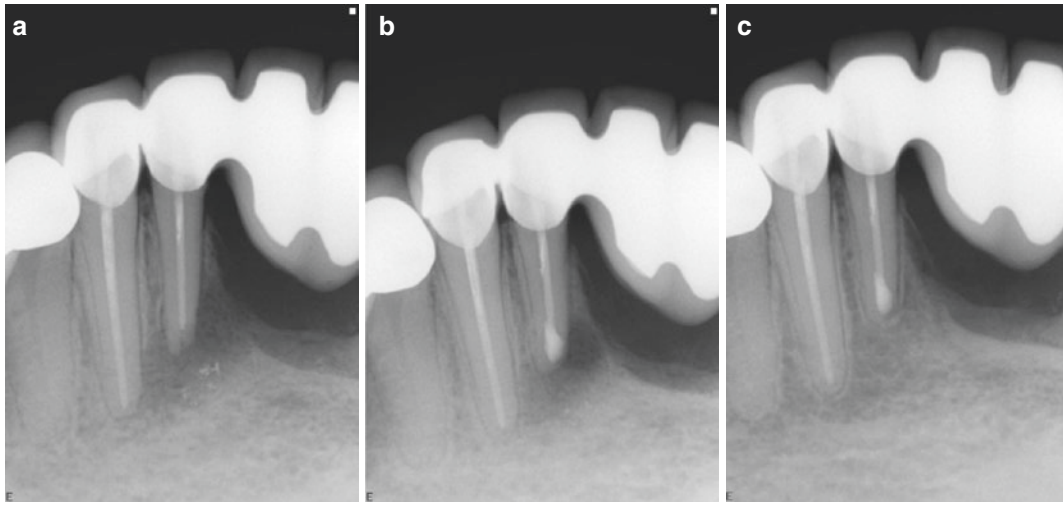

Fig. 3.1 A conservative treatment by endodontic surgery. (**a**) A 55-year-old female patient presented with discomfort in the area of mandibular incisors. The radiographic evaluation demonstrated a periapical lesion involving the mandibular right lateral incisor. Marginal alveolar bone loss involving the mesial aspect of the same tooth was also present. (**b**) Endodontic surgery was performed. (**c**) At 1-year follow-up, the patient was asymptomatic. Complete healing and regeneration of the alveolar bone evident

resulted in the ability to retain teeth that were previously deemed endodontically untreatable. However, technology cannot replace clinical judgment, but rather be an adjunct that practitioners can employ to reach their treatment goals. It is imperative that strict case selection and treatment planning be carried out based on a thorough clinical evaluation supported by the best available scientific evidence [12] (Fig. 3.3).

One of the key elements of case selection and treatment planning is the understanding of the long-term prognosis and the available treatment alternatives. The endodontic treatment outcome may be considered in terms of *treatment success* (defined as "absence of endodontic disease based on full clinical and radiographic evaluation") and by *tooth survival* (defined as "the retention of the tooth following the treatment").

About 90 % of teeth survive over 2–10 years following nonsurgical root canal treatment [13]. However, this general average of survival rates is impractical for treatment planning since many tooth- and patient-specific factors may alter these chances, for example, the presence, type, and quality of the coronal restoration; the presence and severity of a periodontal disease; and the presence of some predisposing systemic medical conditions. Thus, an adequate case selection and

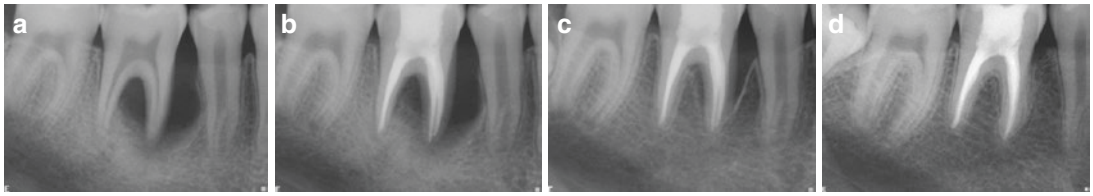

Fig. 3.2 A case of endodontic-periodontal considerations in the decision to preserve or extract a natural tooth. Treatment of a mandibular molar endo-perio lesion. (**a**) A 15-year-old patient presented with a combined endo-perio lesion involving a mandibular first molar. The tooth tested non-vital. (**b**) Endodontic treatment and primary periodontal treatment were performed. (**c**) One-year follow-up and (**d**) four-year follow-up at which time the tooth is asymptomatic and complete osseous healing is evident radiographically

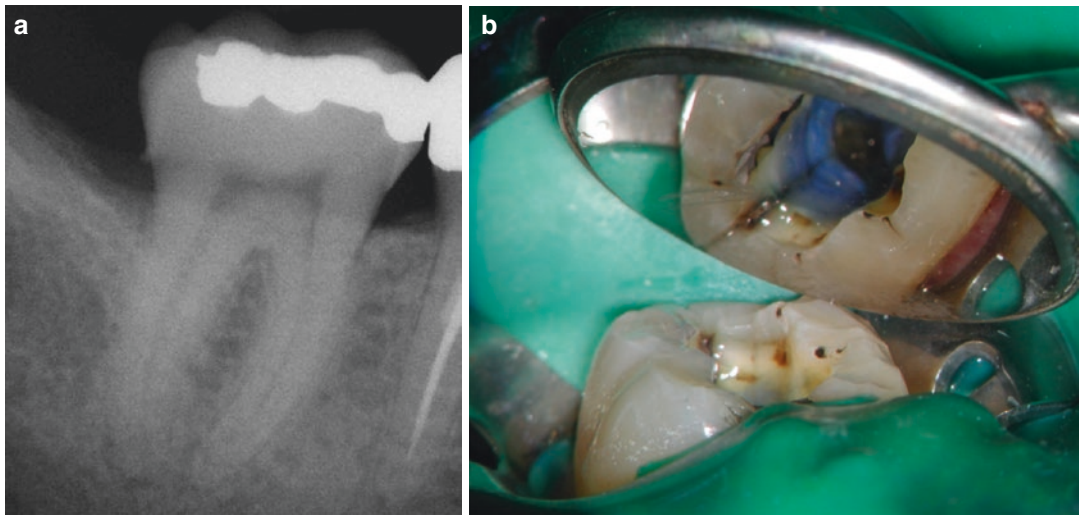

Fig. 3.3 A case of a cracked tooth diagnosed with irreversible pulpitis secondary to a coronal vertical crack. A 54-year-old male patient reported with a history of a lingering pain to cold in the lower right quadrant. (**a**) The clinical examination demonstrated a crack in the distal marginal ridge of the mandibular second molar. An MO amalgam restoration was present. (**b**) After the restoration was removed, the crack extended across the roof of the pulp chamber. Inside the pulp chamber, the crack entered the orifice of the distal canal and appeared to enter the canal to 2–3 mm depth

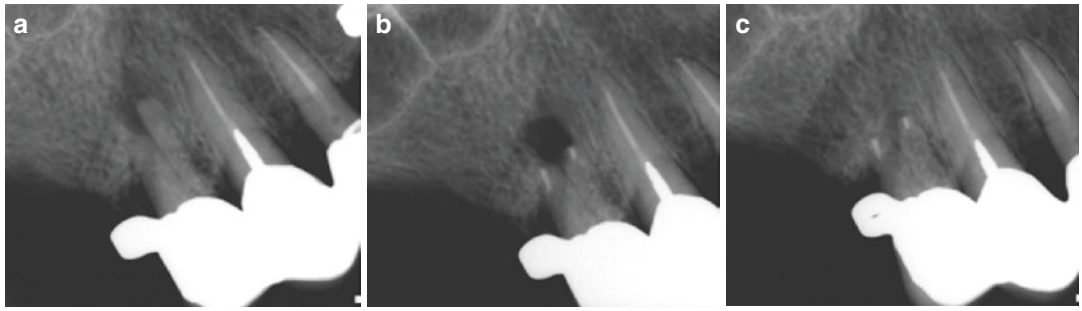

Fig. 3.4 A treatment choice dilemma: decision whether to endodontically treat or extract a compromised tooth based on prosthetic considerations and patient values. (**a**) A 75-year-old female presented with pain and a draining sinus tract in the area of the first maxillary premolar. The tooth serves as a distal abutment for an extensive prosthetic restoration. (**b**) The tooth was treated by endodontic surgery. (**c**) At a 1-year follow-up, the patient was asymptomatic and the tooth was functional

treatment planning process must be case specific, made so by evaluating all relevant endodontic and non-endodontic factors in order to perform rational decision making [2] (Fig. 3.4).

3.3 Contemporary Endodontic Technologies

Modern endodontic technologies such as the electronic apex locators, dental operation microscopes, ultrasonic instruments, and digital imaging systems led to a whole new paradigm in endodontic treatment. The next section will review contemporary endodontic technological developments and how these developments affect the modern endodontic practice.

3.3.1 Electronic Apex Locators

Root canal treatment procedures should be confined within the root canal system [14]. *Working length* is defined as the distance between a coronal reference point and the point at which canal preparation and obturation should terminate [15]. Maintaining a correct working length during root canal treatment is expected to positively influence the outcome of the treatment and to prevent postoperative symptoms [16–18]. However, variations in the apical root anatomy and other clinical limitations render the identification of the correct working length by radiography or other clinical means practically impossible [19]. Electronic root canal length measuring devices offer precise means of locating the working length during root canal treatment procedures [20, 21]. Modern electronic apex locators (EALs) use an alternating electric current with various frequencies in order to correctly estimate the most appropriate end point for root canal treatment [20, 21]. Early generation EALs were often inaccurate in the presence of conductive fluids or pulp tissue. Modern EALs are virtually free of these limitations; however, as with any electronic device, the proper use and understanding of the result is mandatory. EALs are virtually unable to miscalculate. The mistakes in electronic working length measurements with properly working device are always due to a faulty interpretation by the operator. The clinician should recognize the condition of the operating field and recognize when the EALs are not giving a reading of working length. In the presence of caries, metallic restorations, or marginal leakage, an ensuing electrical short circuit will prevent the operating of the device and result in false interpretation of the reading. On the other hand, completely dry canals or lack of apical patency may block the electrical current, thus preventing the working of the EAL [20, 21]. In such cases there is still a need for use of radiographs for working length estimation.

3.3.2 Magnification and Illumination Systems

Common magnification systems used in modern endodontics are the dental operating microscope and the surgical loupes [22, 23]. Loupes, the most common magnification system used in dentistry, use convergent lenses to form a magnified image and are available in many configurations [22, 24].

Dental operating microscopes were introduced to conventional endodontics during the 1970s [24]. Modern microscopes facilitate the variable magnification needed in endodontic practice ranging from X3 to X30 magnification. The microscope is superior to loupes when using higher magnifications, in its available depth of field, and its fiber-optic light source is far superior compared to the surgical headlamp that is sometimes attached to loupes [22, 24].

The benefits of using magnification devices for conventional endodontic treatment include the improved visualization of the treatment field, enhanced possibilities in locating canals, aid in the removal of separated instruments, diagnosis of root and tooth fractures, perforation repair, as well as case documentation [22] (Figs. 3.5 and 3.6).

Dental operating microscopes were introduced to endodontic surgery only in the early 1990s [25] and quickly became an integral part of modern endodontic surgical protocol [25, 26]. During endodontic surgery, locating, cleaning, and filling of the apical part of the root

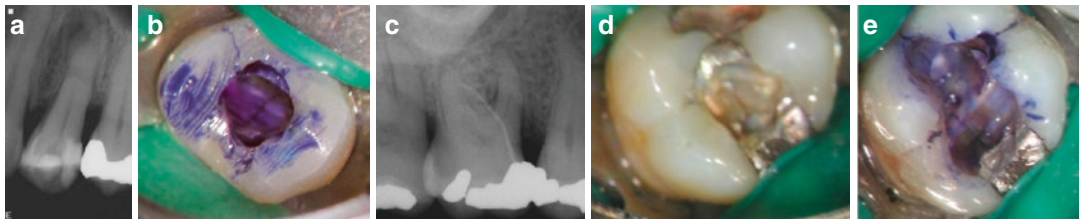

Fig. 3.5 Two cases of tooth fracture ("fracture necrosis") diagnosis using magnification. (**a**) A patient taking Tegretol due to trigeminal neuralgia presented after the referral source had already made coronal access to perform emergency treatment for a maxillary left second premolar. The initial diagnosis was "previously initiated therapy." (**b**) Under microscopic evaluation, a fracture under the distal composite not visible at the initial exam was observed. The prognosis is extremely poor. (**c**) A patient presented with a sinus tract leading to the distobuccal root apex of a maxillary right molar. Drainage from the sinus tract was present as well as limited vestibular swelling. (**d**) The restoration covered the fracture. (**e**) The amalgam restoration was removed, and the fracture was diagnosed with microscope

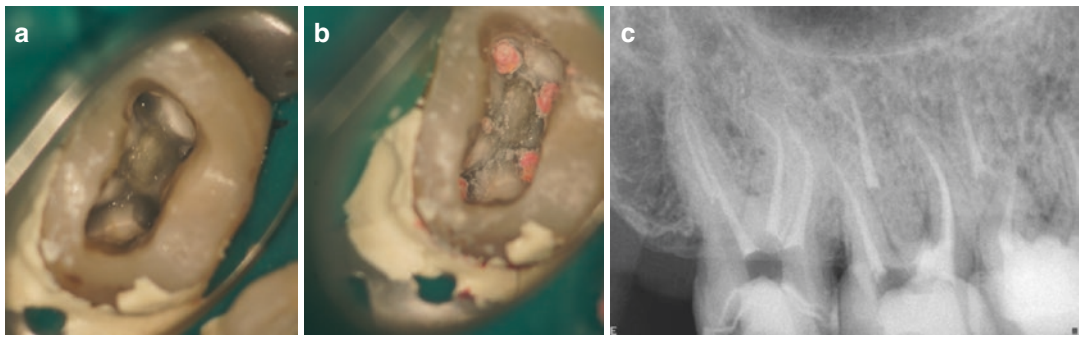

Fig. 3.6 A case of an upper 3rd molar referred to root canal treatment that was diagnosed with five root canals using a microscope. During endodontic treatment of an maxillary third molar,(**a**) a fifth canal was located in a distopalatal root, located with the aid of a surgical operating microscope. (**b**, **c**) All five canals were treated and filled

canal system are key elements to achieve predictable outcome results. These require the use of magnification and illumination systems [22, 25].

The basic principle of microsurgery is that the surgeon's hands can execute remarkable micromanipulations as long as the surgeon's eyes can see a magnified operation field [22, 24]. The traditional endodontic practice was restricted due to limited availability of visual enhancement accessories [24]. The inability to identify and adequately treat the entire root canal system was a major cause for treatment failure [16, 22, 27–29]. However, since the introduction of magnification devices to endodontics, modern endodontics is to a large extent perceived as a microsurgical procedure [22, 24, 30].

There are many advantages for microscopes in endodontic surgery, including good depth of field enhanced by a good illumination position closer to the lens, and it is possible to vary the power of magnification for either a surgical procedure or a diagnostic evaluation [22, 24, 30, 31]. In addition, the microscope self-illumination system permits a shadowless visualization of the surgical field. These properties and others allow surgeons to easily obtain a proper focus on the operation field [22, 24, 30, 31].

3.3.3 Digital Radiography

Direct digital radiographic modalities that were introduced into modern endodontic practice made a number of advantages over conventional radiographs, such as immediate availability of the image for evaluation, lower radiation dosage required for the image acquisition, superior archiving and sharing capabilities, and easier manipulation of several radiographic properties, such as image contrast, brightness, and sharpness [32, 33]. While it is still debatable whether digital radiography poses superior diagnostic efficacy over conventional radiography for endodontic diagnostic purposes [33–35], its simplicity and improved visibility on a large screen throughout the treatment significantly help the management of all endodontic cases.

3.3.4 Cone Beam Computed Tomography

The combination of clinical examination and diagnostic imaging is the basis for endodontic preoperative diagnosis and clinical decision making [36, 37]. The introduction of cone beam computed tomography (CBCT) to endodontics facilitated the visualization of the dentition and the surrounding anatomical structures in three dimensions [38, 39]. CBCT imaging has become a popular diagnostic modality in modern endodontic practice [38]. In a wide web-based survey of active members of the American Association of Endodontics (AAE) in the United States (USA) and in Canada, 34 % of the respondents reported that they were using CBCT for endodontic diagnosis and treatment planning purposes [36, 38, 40].

CBCT was suggested to be used for many complicated diagnostic demands in endodontics such as assessment of periapical periodontitis, assessment of the outcome of endodontic treatments, diagnosis of vertical root fractures, assessment of tooth and root canal anatomy, diagnosis of root resorption, and diagnosis and management of dentoalveolar traumatic injuries [41]. However, currently, the expected ultimate benefit of CBCT imaging to the endodontic patient and the efficacy of CBCT imaging to support the endodontic practitioner's decision making and, ultimately, to improve the treatment outcome are unknown [36]. At the same time, its relative high radiation dose to the patients and its long-term possible harmful effects must always be taken into consideration during case selection of patients to receive a CBCT evaluation [41]. Thus, a cautious and rational approach is advised when considering CBCT imaging for endodontic purposes [36].

3.4 Contemporary Endodontic Treatment Modalities

Modern endodontics provides a wide range of treatment alternatives for the management and preservation of compromised teeth. These strategies include nonsurgical endodontic treatment,

surgical endodontic treatment, and management of complications such as root perforations, separated instruments, and root fractures. These modern treatment alternatives may provide a predictable prognosis even for complicated cases. Currently, most of the teeth that undergo endodontic treatment survive for the long term, and those which are eventually extracted are usually lost because of non-endodontic-related factors, such as periodontal or prosthetic limitations [13, 42].

This section will review contemporary endodontic treatment modalities as well as modern approaches for the management of endodontic complications and how these strategies should be implemented in clinical decision making.

3.4.1 Nonsurgical Endodontic Treatments

Root canal treatment procedures are aimed to prevent or to eliminate bacterial biofilm colonization of the complex root canal system, by appropriate mechanical shaping, chemically active fluid irrigation, and subsequent three-dimensional filling. Contemporary endodontic instruments and techniques improved the clinical feasibility to effectively treat even teeth with complex root canal anatomy such as teeth with curved roots and calcified root canals [13].

However, a relatively high prevalence of persistent apical periodontitis in endodontically treated teeth, ranging 40–60 %, has been reported in the literature [43–46]. The main reason for the persistence of apical periodontitis following an endodontic treatment is remaining bacteria in the root canal system following the initial endodontic treatment or bacteria penetrating the root canal system as a result of continuing coronal leakage [47–52]. Coronal leakage is an important factor in the development of apical periodontitis in root canal treated teeth [50, 53, 54]. While it has been claimed that well-prepared and filled root canals can oppose bacterial penetration even without adequate coronal restoration, many studies stressed the significance of adequate coronal restoration for the long-term periapical healing [43, 53, 55, 56].

Additional possible etiologies include the presence of true cysts, extra radicular infections, and foreign body reactions [16, 43, 57–59]. The treatment alternatives for persistent apical periodontitis include nonsurgical endodontic re-treatment, surgical endodontic treatment, or in certain cases even tooth extraction [60, 61].

A decision to perform additional endodontic treatment for an endodontically treated tooth with apical periodontitis should be based on a combination of factors such as the technical feasibility of the treatment, systemic factors, and patient values and preferences [61–65] (Fig. 3.7).

The clinical decision regarding the treatment of asymptomatic teeth with a periapical radiolucency is even more complicated since the option of a follow-up may be sometimes considered and should be based on the evaluation of the restoration and root canal filling quality. It has been reported that teeth with unsatisfactory root canal fillings and/or restorations have a higher potential for continuous deterioration of their periapical condition [43].

The average success rates of nonsurgical endodontic re-treatments are around 70–80 %. However, these numbers are averages only and they are not necessarily relevant for the decision-making process regarding a specific tooth. Many case-specific factors may significantly affect the chances of success, and these factors should be evaluated and integrated into the decision-making process, including the presence of a preoperative periapical lesion and the presence of morphological changes or complications that happened during the former endodontic treatment that affect the ability to adequately re-treat the entire root canal system [32, 66, 67].

3.4.2 Surgical Endodontic Treatment

The main goal of a surgical endodontic treatment is to prevent the invasion of bacteria and their by-products from the root canal system into the periradicular tissues [68, 69]. Surgical endodontic treatment may be indicated for teeth with apical periodontitis, when a nonsurgical re-treatment is impractical [25, 26, 70] (Fig. 3.8).

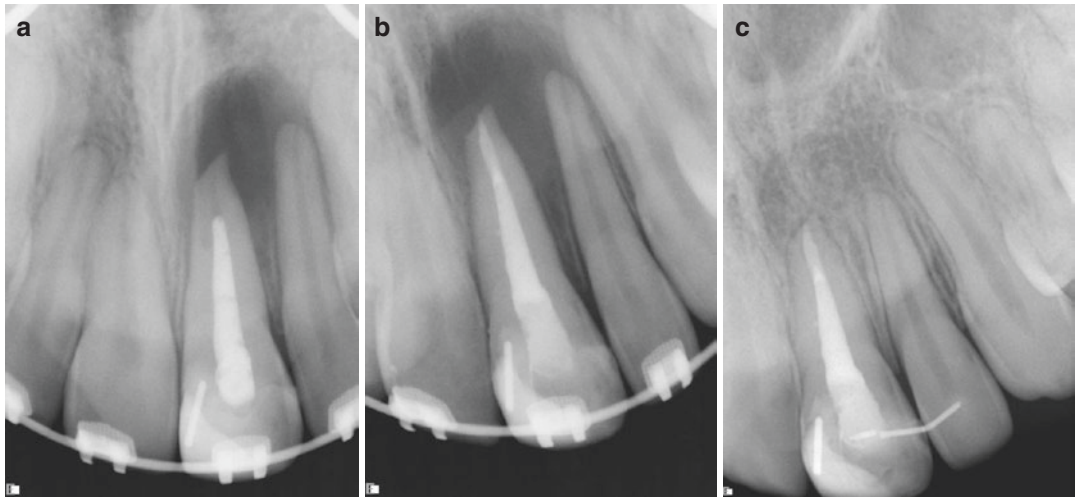

Fig. 3.7 Considerations regarding the re-treatment feasibility. (**a**) The patient presented with pain and swelling in the maxillary anterior area. (**b**) The maxillary left lateral incisor tested vital. (**c**) The maxillary left central incisor was re-treated nonsurgically and periapical healing was evident at the 1-year follow-up

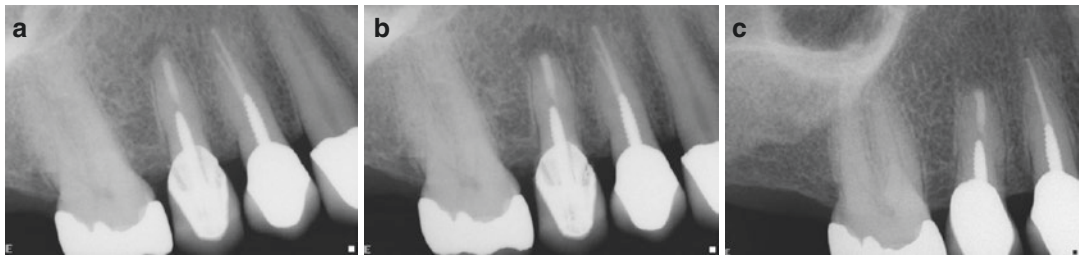

Fig. 3.8 A surgical endodontic treatment of a maxillary premolar. (**a**) A previously treated maxillary second premolar with a coronal restoration was diagnosed with symptomatic apical periodontitis. The options were [1] to extract the tooth, [2] to re-treat the tooth nonsurgically, or [3] to re-treat it surgically. The patient preferred to maintain the tooth if possible. A nonsurgical endodontic re-treatment in this case was impractical due to the poor prognosis following the removal of the crown and post. (**b**) A surgical endodontic treatment was performed with minimal root-end resection in order to prevent worsening of the crown-to-root ratio. (**c**) A 2-year follow-up radiograph. The tooth was periodontally stable, and the periapical pathosis healed

Traditional surgical endodontic treatment (traditional technique) was performed by a root-end resection with about a 45° bevel, a retrograde preparation of the canal with a bur, and the placement of a root-end filling [71]. A moderate success rate of approximately 50–60 % was reported with this technique [5, 72, 73]. This relatively unpredictable outcome was mainly related to the difficulties in locating, cleaning, and sealing the apical part of the root canal system [5, 68]. Today, traditional endodontic surgery is not a valid treatment for teeth with apical periodontitis and should NOT be performed in a modern dental practice.

The introduction of the dental operating microscope in the early 1990s together with additional technological and procedural developments led to a new era in surgical endodontics [25, 26, 74]. The modern surgical endodontic treatment (modern technique) uses magnification to enable a more accurate procedure with a minimal bevel of the root-end resection, a retrograde canal preparation with the aid of ultrasonic retro-tips to a depth of 3–4 mm, and a root-end filling [75].

The advantages of this modern technique include better identification of root apex anatomy and pathology, smaller osteotomies, and shallower resection angles that preserve the alveolar cortical bone and root length [68]. In addition, the resected root surface under high magnification and adequate illumination readily reveals isthmi, microfractures, lateral canals, and other important findings [68]. The modern technique has shown a much better long-term success rate (>90 %) compared to the traditional technique (<60 %) and is considered a predictable and efficient treatment modality [5, 25, 26, 69].

3.5 Decision Making Regarding the Diagnosis and Management of Endodontic Complications

Like any treatment modality, endodontic treatment is also exposed to the risks of complications [5]. These possible complications may include *patient-related complications* (i.e., undesirable, unintended, and direct results of treatment affecting the patient that are related to the patient-specific characteristics rather than to a practitioner's error) and *practitioner-related complications* (i.e., a practitioner's error that led to undesirable and unintended results affecting the patient) [5]. These complications may raise additional dilemmas during the decision-making process. This section will review major endodontic complications and how they may affect the clinical decision making regarding the preservation and management of such compromised teeth.

3.5.1 Vertical Root Fractures

Vertical root fracture (VRF) is a complication of root canal treatment, defined as "a complete or incomplete fracture initiated from the root at any level, usually directed buccolingually" [76]. VRFs are a relatively common complication in root canal treated teeth, with a reported prevalence of up to 20 % of extracted endodontically treated teeth [77–79].

A timely mannered diagnosis and an appropriate management are prudent to avoid extensive alveolar bone loss, which may impair the future reconstructive procedures, should implant therapy be the treatment of choice [79–81]. However, the clinical diagnosis of a VRF is challenging, and a definitive diagnosis of a VRF may be best attained by invasive diagnostic procedures like a direct observation of the suspected site during flap elevation [77, 79, 81–84].

Traditionally, attempts to treat a VRF, for example, by bonding of the fractured segments, were found to be unpredictable [79, 81, 85–88], and the prognosis of a VRF teeth was considered as hopeless [77, 79, 81, 88]. However, several recent reports suggested novel treatment alternatives aimed to preserve VRF teeth [30, 69, 77, 79, 81, 88, 89]. These novel treatment attempts are just in their initial stages of development and are based mainly on case reports [79, 81, 88]. Using magnification devices that improve the diagnostic and treatment capabilities [30, 90] and modern materials such as mineral trioxide aggregate (MTA) for the repair of VRF [79, 81, 88, 91] seems to offer promising treatment alternatives for certain VRF teeth [77].

When a VRF is diagnosed, the case selection process requires a combination of endodontic as well as prosthetic, periodontal, and esthetic considerations [2, 79]. The tooth type, the presence of a predisposing periodontal disease, the type of the coronal restoration, the alternatives offered by the modern endodontic treatment, the alternatives in the case of treatment failure, the post-treatment quality of life, and the patient's values should all be recognized and incorporated in the practitioner's decision making [2, 11, 77, 79, 92–96].

In multi-rooted teeth diagnosed with a VRF in one of the roots, there are potential alternatives to preserve the tooth, such as root amputation of the vertically fractured root [97]. However, for single-rooted teeth, the entire survival of the tooth relies on the ability to treat and maintain the fractured root [77, 81].

The periodontium serves as the supporting apparatus of the tooth, and periodontal diseases may lead to a destruction of the periodontium

[98, 99]. The periodontal status of the VRF tooth and especially the presence of a predisposing severe periodontal disease with deep periodontal probing depth, an associated bleeding and significant mobility, are important confounders for the ability to successfully treat and preserve the VRF tooth. Therefore, a meticulous periodontal evaluation is crucial as part of the clinical evaluation and decision making [77, 94, 100].

The clinical diagnosis of VRF is challenging and therefore it is frequently diagnosed only after all endodontic and prosthetic procedures have been completed [79, 83, 101–107]. The timing of the VRF diagnosis, either before or after the restorative procedures have been completed, and also the type of prosthetic restoration (e.g., a tooth that is a part of a bridge or a stand-alone restoration) may affect the decision whether to make additional efforts to treat and preserve the VRF tooth [77, 100]. Many prosthetic considerations affect the long-term prognosis of endodontically treated teeth, such as the post-endodontic treatment restoration, the amount of remaining tooth structure, the crown-to-root ratio, and the ferrule effect [77, 96, 108].

Therefore, the decision to perform additional treatment to preserve a VRF tooth should not be based only on the technical ability to endodontically treat the fracture line, but on a wider range of prosthetic, periodontal, and esthetic considerations that determine the long-term prognosis of the tooth and the risk of complications [77].

In certain cases of strategically important teeth diagnosed with VRF, modern endodontics provides new treatment alternatives to treat and maintain VRF teeth. These options should be considered based on the specific tooth type, the fracture type and location, and the prosthetic, periodontal, and esthetic condition of the tooth [77]. These treatment options include root amputation, apical surgery with root shaving coronally to the fracture line, sealing/cementation of the fracture following flap elevation approach, or extraction and replantation [77, 85, 88, 109–114]. Additional clinical studies are indicated to shed light on the prognosis of these new treatments [77].

3.5.2 Iatrogenic Root Perforations

Iatrogenic root perforations occur in up to 12 % of endodontically treated teeth [3, 69] and may be defined as "the mechanical or pathologic communication between the root canal system and the external tooth surface" [3, 115]. All endodontic procedures may lead to perforations including access cavity preparation and canal orifice search, root canal instrumentation, and post-space preparation [116–119].

Various risk factors for perforations have been identified, such as curved root canals, specific tooth locations, and the practitioner's skills and experience [69, 116, 120]. The prognosis of teeth with perforations depends on perforation location, perforation size, time from occurrence, and the presence of bacterial contamination [3, 121, 122].

Prevention is the most effective clinical approach to root perforations [69]. However, in case a perforation does occur, modern endodontic practice improves the ability to diagnose and successfully treat perforations [68, 69, 123–128]. Newly introduced endodontic materials for the treatment of root perforations [123, 125–127], the use of modern endodontic technology such as electronic apex locators [124], and [68, 128] are key elements in the modern management of root perforations [3].

The actual prevalence of perforations could possibly be higher than what has been reported in the literature [3] as it may be difficult to diagnose the presence of buccal or lingual perforations from radiographs due to the superimposition of the perforations on the root. Evaluating the radiographs at two different horizontal angles may improve the clinician's diagnostic accuracy in the identification of perforations [116], and new imaging modalities such as CBCT are also showing promising results [3, 129, 130].

The risk of a perforation may be related to an older age [131, 132]. This may be attributed to various anatomical, physiological, and pathological age-related factors such as apposition of secondary dentin and narrower root canals [133–136], morphological changes of the tooth crown that complicates the orientation during

endodontic procedures, and the increased number of teeth that undergo endodontic and restorative procedures with age [3, 119].

The prevalence of perforations is higher in mandibular molar teeth compared to other tooth locations [3]. The significant curvature and configuration of mandibular molar root canals may impose technical difficulties for the clinician during root canal preparation that may lead to perforations [137–139]. In addition, a concavity on the distal surface of the mesial roots of mandibular molars may also be related to an increased risk of perforations [3, 140].

The main complication following perforation is periodontal destruction due to bacterial infection and superimposition of irritating restorative materials on the perforation site [3, 69, 122, 141–143]. Specifically, *crestal perforations* and large perforations are usually associated with significant pathological changes in the adjacent periodontal tissues and with difficulty to provide an adequate seal, both reducing the chances for a desirable periodontal healing [3, 69, 122, 144, 145].

Modern endodontics offers new technologies, instruments, and materials that can assist in the prevention, identification, and management of perforations [146]. When a perforation occurs, the main treatment goal is to prevent additional long-lasting injury to the periodontium [3, 147, 148].

Modern nonsurgical and surgical endodontic techniques may allow efficient sealing of root perforations, thus preventing further damage to the adjacent periodontal tissues and improving the tooth prognosis [3, 127, 149]. In this context, modern materials, such as the use of MTA, a biocompatible material with good sealing ability, show promising results in the successful treatment of perforations, even for cases such as the repair of large furcation perforations that traditionally represented a significant clinical challenge [3, 123, 125–127, 149] (Fig. 3.9).

3.5.3 Separated Endodontic Instruments

All endodontic instruments, either manufactured from nickel-titanium or from stainless steel, might separate during root canal treatment [32, 150–152]. The retained instrument fragment may affect the endodontic treatment prognosis if it compromises the achievement of the treatment goals, by preventing adequate root canal preparation, disinfection, and obturation [32, 150]. A separated instrument retained in the canal at the initial root canal treatment also bares a medicolegal risk if not diagnosed preoperatively before a re-treatment procedure, since its presence within the canal might be later credited to the clinician performing the endodontic re-treatment procedure [32, 153].

The decision making on how to manage retained separated instruments may be crucial for the prognosis of the treatment and requires an

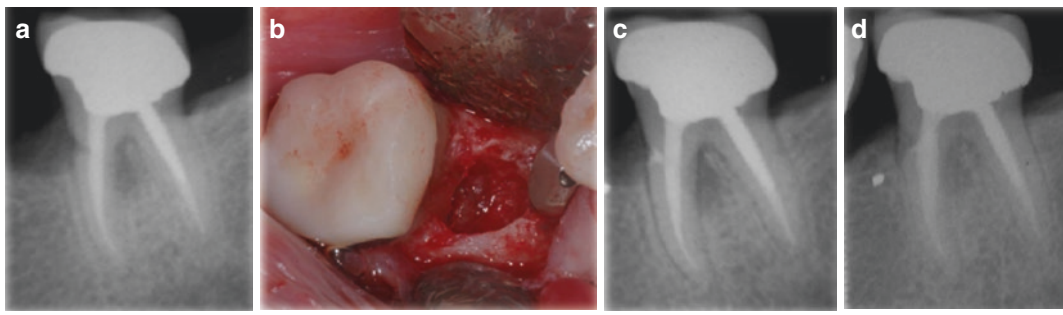

Fig. 3.9 Surgical treatment of a root perforation. A 35-year-old male patient presented with pain in the area of a mandibular left molar. (**a**) A periapical radiograph revealed an iatrogenic root perforation with associated periodontal damage in the mesial aspect of the mesial root that occurred during the extraction of the adjacent tooth. (**b**) Following flap elevation the perforation was sealed with MTA. (**c**) Postsurgical radiograph. (**d**) In a 20-month follow-up, the tooth was asymptomatic, with radiographic evidence of periodontal healing

integration of anatomical, technical, biological, and pathological considerations [32], including the root and the canal anatomy, the endodontic clinical diagnosis, the stage of the treatment, the location of the instrument within the root canal, and the size and type of the fragment [32, 150, 152–162].

The management alternatives for separated instruments include leaving the separated instrument in the canal while endodontically treating and sealing the more coronal parts of the canal, bypassing the instrument and incorporating it into the root canal filling, retrieving the instrument, a retrograde endodontic surgical approach to achieve the endodontic treatment goals, or in certain cases consideration of tooth extraction [25, 26, 32, 150]. It is prudent to consider the expected benefits versus the possible risks of each treatment option [150, 152–162] (Fig. 3.10).

A separated instrument located in the apical third of a filled root canal faces the clinician with even more intense diagnostic challenges and clinical dilemmas. The continuous radiopaque appearance of the instrument and the filling material within the canal [163–166] may lead to inability to radiographically detect the instrument [32].

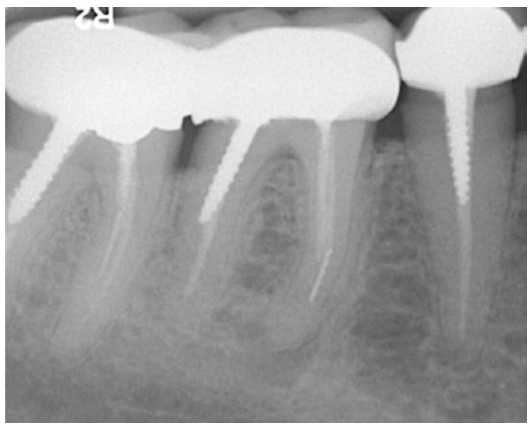

Fig. 3.10 Considerations regarding the re-treatment feasibility of a tooth with a separated endodontic instrument. A previously treated mandibular first molar was diagnosed with asymptomatic apical periodontitis and was scheduled for endodontic re-treatment. In this case the presence of a retained separated instrument in the apical third of the mesial root significantly reduces the feasibility to efficiently re-treat the entire root canal space. Therefore, the tooth was scheduled for endodontic surgery

Therefore, the possibility of an undetected separated instrument should always be considered during the decision-making process even when all radiographic methods failed to demonstrate such instrument. In addition, in such cases when the fragment is located in the apical third of the canal, there might be a limited expected success and an increased risk of root perforation and reduced root strength during fragment removal or bypass attempts [32, 150, 152, 154, 155, 157–159]. Endodontic surgery or even tooth extraction may be the only options in such cases [25, 26, 32].

3.5.4 Root Resorption

Root resorption is a pathological process that can occur inside the root canal (internal resorption) or on the outer surface of the tooth (external root resorption) and can ultimately lead to tooth loss. External root resorption occurs when the outer tissue on the root surface is damaged as a result of operative, traumatic, pathological, or procedural *injury* and is usually associated with a *continues stimulation* such as pulp infection. Root resorption may also rarely occur as a result of systemic diseases such as hyperparathyroidism and may sometimes continue without further stimulation such as in the case of cervical root resorption or replacement resorption [167–170] (Fig. 3.11).

The diagnosis of root resorption is based on radiographic and clinical examination. Intraoral radiographs obtained at different angles may be useful to determine which surface of the root is involved and the extent of the resorption. Recent studies have indicated that CBCT may be a useful adjunct diagnostic tool [167, 171, 172].

When root resorption is diagnosed, the treatment goal is to stop the ongoing resorption stimulation (i.e., the pulp infection, the pressure from the unerupted tooth, or the forces applied as a result of orthodontic tooth movement), remove the affected tissue, and restore the tooth to allow its function and esthetics. If there is pulpal involvement, root canal treatment may be required. If the root resorption is extensive, the treatment is more complicated, and extraction may be indicated. However, modern endodontics

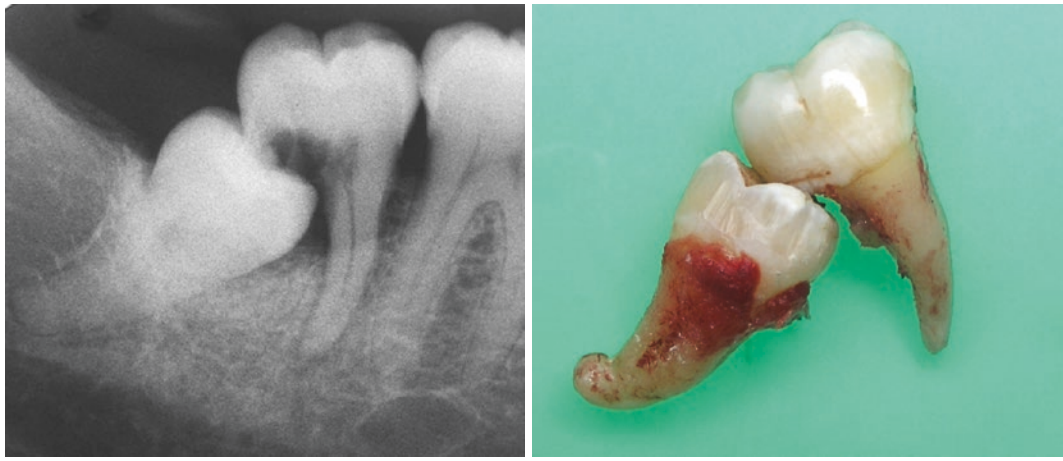

Fig. 3.11 A case of impacted tooth-related root resorption. Resorption of the root of a second mandibular molar associated with an impacted third molar. The extensive destruction of the tooth structure is seen after the involved teeth were extracted

allows the treatment and preservation of teeth with root resorption that were previously extracted [167, 168, 170–172].

3.6 Conclusions and Key Learning Point

- The long-term prognosis, the potential of modern endodontic treatment, the alternatives in case of treatment failure, posttreatment quality of life, and the patient's values should all be recognized and incorporated in the practitioner's decision making regarding the management and preservation of natural teeth.
- Modern endodontic technologies such as the electronic apex locators, surgical operation microscopes, and modern instruments and imaging systems may improve the ability to treat and retain teeth. However, technology cannot replace clinical judgment, but rather be an adjunct that practitioners can use to reach their treatment goals.
- Modern surgical endodontic treatment may be indicated for teeth with apical periodontitis, when a nonsurgical re-treatment is impractical. Magnification is used to enable a more accurate procedure. Root-end resection with a minimal bevel, a retrograde root canal preparation with the aid of ultrasonic retro-tips, and a root-end filling are performed. This technique is considered a predictable and efficient treatment modality.
- Traditional endodontic surgery is not a valid treatment for teeth with apical periodontitis and should NOT be performed in modern dental practice.
- Like any treatment modality, endodontic treatments are exposed to the risks of complications that may raise additional dilemmas during the decision-making process.
- The treatment should focus on the patient interests and values, and the treatment plan should apply the principles of evidence-based medicine.
- Modern endodontic treatments result in a predictably favorable long-term outcome and allow retention of the natural dentition.
- Using modern treatment techniques and adequate case selection, cases that were traditionally planned for extraction can be successfully treated endodontically.

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4 Evidence-Based Decision Making in Periodontal Tooth Prognosis and Maintenance of the Natural Dentition

Carlos E. Nemcovsky and Anton Sculean

Abstract

The main objective of periodontal therapy is long-term preservation of the periodontium. Before a treatment plan is established, diagnosis and etiological factors of the disease as well as the prognosis of the remaining teeth should be determined, while predicting the final functional and esthetic result. An accurate prognosis is most critical when periodontal therapy is combined with large oral prosthetic rehabilitation or with dental implants; in these complex cases, an accurate long-term prognosis of the involved teeth must be established at the time of treatment planning. According to several patient- and tooth-related factors, tooth prognosis can artificially be classified into good, fair, poor, questionable, hopeless, and indicated for extraction; however, borders are not always evident. Among the factors affecting tooth prognosis related to the patient, age, systemic condition, remaining teeth in the arch or mouth, personal and family history of periodontal disease, oral hygiene, compliance with recall visits, smoking, parafunctional oral habits, and willingness to preserve tooth or teeth can be enumerated. Among the tooth-related factors, the number of teeth involved, clinical attachment loss, loss of bone support, remaining supporting area, architecture of bone defects, furcation involvement, mobility, crown/root ratio, caries and/or endodontic involvement, root defects, tooth position, root proximity, rehabilitation involving the tooth, type of periodontal treatment performed, therapist knowledge and skill, strategic value of the tooth, and treatment alternatives can be enumerated. Evidence-based dentistry requires application of current evi-

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dence in making decisions about the care of individual patients, actually closing the gap between clinical research and real clinical practice. Evidently, evidence-based dentistry requires integration of the best evidence from literature with clinical expertise as well as patient preferences and therefore informs, but never replaces, clinical judgment. The present chapter will review all prognosis-related factors while at the same time trying to suggest a chart that might help in determining tooth prognosis for every single case. The alternatives for each case must be considered; in most cases where teeth are extracted for periodontal reasons, implant therapy will demand large bone augmentation procedures, and therefore, morbidity, duration, and success of these must be carefully evaluated before periodontal therapy is discarded. Furthermore, periodontal patients seem to be more prone to peri-implant diseases and implant loss.

4.1 Introduction

The main objective of periodontal therapy is long-term preservation of the periodontium [1, 2]. Therefore, periodontal treatment should be directed to maintaining the natural dentition of the individual. Most patients with periodontal diseases will attain periodontal health after therapy at the vast majority of sites [3]. Treatment of severe periodontal disease may result in clinically healthy periodontal conditions, a state that can be maintained in most patients and sites for very long periods of time [4]. Surgical and nonsurgical periodontal treatment alternatives are available. The goals of periodontal surgery can be defined as access to contaminated root surfaces for proper debridement of the lesion, establishing a gingival morphology conductive to plaque control, and, whenever possible, regeneration of the lost periodontal attachment. The available treatment options are defect elimination by resection, maintenance of the area without or with minimal bone resection, regenerative procedures, and tooth extraction.

Before a treatment plan is established, diagnosis and etiological factors of the disease as well as the prognosis of the remaining teeth should be determined, while predicting the final functional and esthetic result. According to several patient- and tooth-related factors, tooth prognosis can artificially be classified into good, fair, poor, questionable, hopeless, and indicated for extraction; however, borders are not always evident.

In most periodontally involved dentitions, several difficult decisions must be made regarding the survival of a variable number of teeth. In cases with severe periodontal breakdown, it seems, however, difficult to establish a definite line and clearly decide which teeth will not respond to periodontal treatment and are, therefore, indicated for extraction [5, 6]. An accurate prognosis is most critical when periodontal therapy is combined with large oral prosthetic rehabilitation or with dental implants; in these complex cases, an accurate long-term prognosis of the involved teeth must be established at the time of treatment planning. Although one or several teeth might be lost, this does not detract from the possible relative success of the treatment, provided the dentition can be restored to good function with good chances of long-term survival. An ideal treatment plan should address the main complaints of the patient; provide the longest-lasting, most cost-effective treatment; and meet or exceed the patient's expectations whenever possible [7].

Evidence shows that the definition of good has much higher predictability than the one for a worse prognosis [8].

Periodontitis is an infectious disease with varying severity degrees [9]; therefore, both patient- and tooth-related factors, as well as the therapist knowledge and skills, must be taken in consideration when evaluating prognosis. Until reliable predictors of periodontal disease

progression at each site and accurate tooth prognosis are available, the use of surrogate clinical variables to reflect long-term tooth survivability must be used [10].

Prognostic factors may be categorized according to: (1) Those that can be controlled by the patient (daily plaque removal, smoking cessation, compliance with wearing occlusal guards, compliance with the recommended preventive maintenance schedule); (2) Those that may be affected by treatment (probing depth, mobility, furcation involvement, trauma from occlusion, bruxism, other parafunctional habits); (3) Those associated with systemic diseases (diabetes mellitus, immunologic disorders); (4) Those that are uncontrollable (poor root form, poor crown/root ratio, tooth type, age, genetics) [11].

A simpler classification of those factors suggests (1) patient related and (2) tooth related. Among the factors affecting tooth prognosis related to the patient, age, systemic condition, remaining teeth in the arch or mouth, personal and family history of periodontal disease, oral hygiene, compliance with recall visits, smoking, parafunctional oral habits, and willingness to preserve tooth or teeth can be enumerated.

Among the tooth-related factors, the number of teeth involved, clinical attachment loss, loss of bone support, remaining supporting area, architecture of bone defects, furcation involvement, mobility, crown/root ratio, caries and/or endodontic involvement, root defects, tooth position, root proximity, rehabilitation involving the tooth, type of periodontal treatment performed, therapist knowledge and skill, strategic value of the tooth, and treatment alternatives can be enumerated.

Evidence-based dentistry requires application of current evidence in making decisions about the care of individual patients, actually closing the gap between clinical research and real clinical practice. Evidently, evidence-based dentistry requires integration of the best evidence from literature with clinical expertise as well as patient preferences and therefore informs, but never replaces, clinical judgment. In a recent study, it was found that on average, 37 % of experts (range: 15–50 %) changed their opinion on the topic after review of meta-analytic evidence compared to their uninformed decisions prior to confrontation with scientific literature [12].

The present chapter will review all prognosis-related factors while at the same time trying to suggest a chart that might help in determining tooth prognosis for every single case.

4.2 Patient-Related Factors

Age Generally, it could be established that the older the patient, the better the long-term prognosis. Comparing two subjects of different ages, with similar loss of periodontal support, susceptibility to periodontal breakdown is clearly higher in the younger individual. The older the patient, the fewer the years remaining for the dentition to serve; therefore, a better prognosis may be granted. If progress of periodontal destruction has been very slow over the last years, then prognosis is better than in cases where the downhill situation is of recent origin. In a prospective study of over 20 years, age has been found negatively correlated to the number of lost teeth [13]; however, another report found that age had little effect upon tooth survival [14] and on bone level variation [15], and the other one found a positive correlation between age and tooth loss due to periodontal breakdown [16–18]. Treatments of periodontal disease and maintenance programs have been found equally effective in young and older individuals [4].

Systemic conditions Several systemic patient conditions may contraindicate certain periodontal treatment procedures. Certain drugs are associated with gingival hyperplasia, complicating plaque control during maintenance. Diabetes is one of the most frequently systemic conditions that have been related to periodontal deterioration and poor response to treatment [19–23]. Diabetes patients are at greater risk of developing periodontitis, may not respond as well to periodontal therapy as nondiabetic patients, and may require more aggressive treatment to manage periodontitis [24].

Number of remaining teeth The greater the number of teeth present, the fewer the demands on the remaining teeth in the dentition. Certain individual teeth are critical, tooth position in the arch is important, and the presence of certain teeth in strategic locations is important for a more favorable prognosis. Although general dentition prognosis must be considered, survival often depends on the retention in health of certain strategic teeth that make future restoration feasible [25].

Family history of periodontal disease The influence of family history of periodontal disease on tooth prognosis is not completely clear, while certain reports have found a minor effect of it upon tooth survival [14, 22]; others support a stronger genetic influence [26].

Quality of oral hygiene and compliance with supportive periodontal therapy After treatment, periodontal patients should perform meticulous oral hygiene; adequate bacterial plaque removal is a key factor for prevention of recurrent periodontal diseases. Periodontal treatment should carefully be reevaluated for patients not presenting adequate oral hygiene in view that recurrence of disease together with worsening of prognosis of involved teeth is extremely likely, providing disappointing long-term results. Periodontal maintenance is intended to minimize the recurrence of periodontal disease in treated patient and to reduce the incidence of tooth loss [27]; however, compliance may not assure a lower rate of tooth loss over long periods of time [28]. Patients fully complying with supportive periodontal maintenance tend to show a reduction in plaque and bleeding on probing over time [28]. Bad oral hygiene and lack of compliance with recall visits have been largely associated with recurrent periodontal disease and tooth loss [13] following treatment; patients that did not comply with supportive periodontal therapy showed a 5.6 times greater risk for tooth loss following active therapy than those patients regularly complying [29]. Compliance with maintenance following periodontal treatment was associated with very low levels of tooth loss over long-term follow-up [17, 30]. Noncomplying individuals have the highest risk of recurrent periodontitis. even if they had completed thorough treatment [31]. Good oral hygiene is associated with an improved periodontal status following treatment [14, 22]. Plaque control has an important role on long-term stability of results following regenerative periodontal surgery [32]. In a periodontal specialist practice in Norway, patients who left the maintenance program had a higher rate of tooth loss than patients who were compliant [33].

Smoking Smoking has been related with poor immediate- and long-term response to periodontal treatment [13, 31, 34–37] and positively associated with total tooth loss due to periodontal reasons and tooth loss after active periodontal treatment [5, 16–18, 38, 39], and it was found to be a significant long-term risk factor in marginal bone loss [13]. Smoking decreases the likelihood of improvement in tooth prognosis due to periodontal treatment by 60 % and doubles the likelihood of worsening the prognosis at 5 years [22]. Tooth loss because of periodontal reasons in smokers is 2.5 times higher than in nonsmokers [18]. Heavy smoking increased the risk for tooth loss by almost three times, while the combined effect of IL-1 genotype positive and heavy smoking increased that risk by 7.7 times [40]. Smoking was found to have the most negative impact (246 % greater chance of losing their teeth), far exceeding the impact of PD, mobility, or furcation involvement [41]. However, in a small number of patients treated for advanced periodontal disease and well maintained over 5–8 years, no statistically significant differences were found between smokers and nonsmokers in clinical probing depth and radiographic bone loss measurements [42].

Parafunction The effect of occlusal overload on periodontal disease is still not completely elucidated; few studies have evaluated the effect of parafunction and other oral habits on tooth prognosis [43]; in one report on tooth loss in 100 treated periodontal patients, parafunctional oral habits appeared to decrease tooth survival, while not wearing a bite guard seemed to worsen this effect [14].

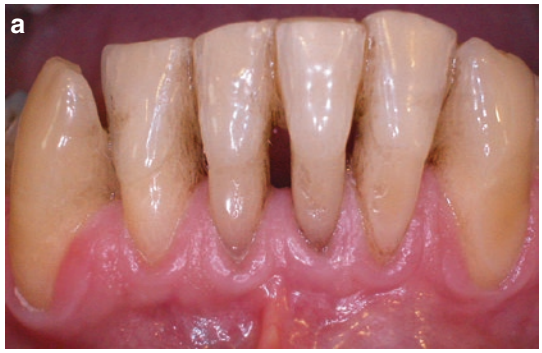
Willingness of the patient to preserve tooth or teeth Willingness of the patient to preserve tooth or teeth can be critical, especially when planning treatment of teeth with poor prognosis; in these cases, treatment outcome is not clear and may not be able to prolong the life and function of the tooth in the patient's mouth. In certain occasions periodontal regenerative treatment may be performed on teeth with a poor prognosis, provided the patient is willing to "try" treatment as an alternative to immediate extraction. Tooth extraction is sometimes mandatory during the maintenance phase, after active treatment has been completed [5, 6, 13, 14, 16–18, 22, 29, 37–39]. Propensity to choose extraction over other treatment alternatives, as reported by the patient before treatment, is strongly predictive of tooth loss [44].

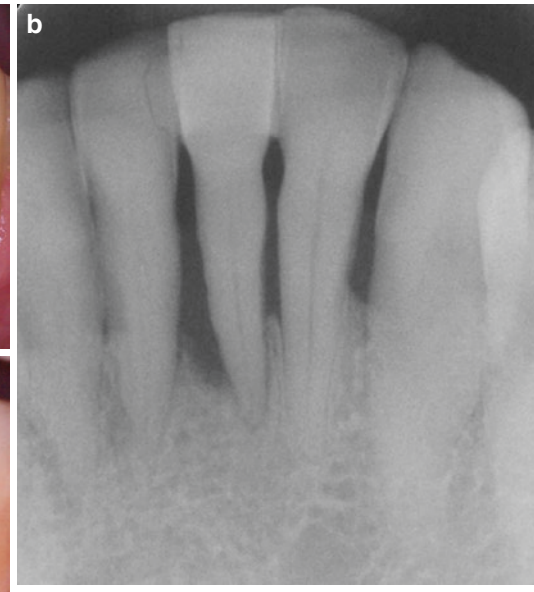
4.3 Tooth-Related Factors

Number of teeth involved The treatment alternative will largely depend on the number and distribution of periodontally involved teeth to be treated, while periodontally regenerative surgery with the use of barrier membranes is suitable for single-tooth defects; the use of enamel matrix protein derivative allows for treatment of numerous proximal teeth. Certain teeth with poor prognosis and minimal chances for success might be treated together with proximal teeth presenting with a better prognosis, thus preventing extractions at an early phase of periodontal treatment. Extractions might be decided after treatment, if teeth show clinical and/or radiographic signs of deterioration. When only a few teeth are affected, in patients suffering from chronic periodontal disease, secondary etiological local factors should be carefully evaluated.

Clinical attachment loss Teeth with advanced loss of attachment and deep probing depths will have a decreased survival compared to those presenting with shallow probing pocket depths [14, 22]. Sites with deeper pretreatment pocket probing show a poorer prognosis compared to those with initial shallow pockets; deeper pretreatment pockets are associated with larger bone loss following treatment and a 10-year maintenance period [15]. Attachment level up to 2 years before tooth loss is strongly predictive of incident tooth loss, with increases in risk for each millimeter in attachment loss [44]. Gingival recession, grades III and IV [45] involving also the interproximal areas, may largely be a difficult periodontal regenerative treatment; buccal and mesial attachment losses ≥2 mm are significantly related to higher tooth mortality risk [43]; the increase risk for tooth mortality associated with a clinical attachment loss of ≥3 mm during a 10-year period is 2.3 % [43] (Figs. 4.1 and 4.2). Teeth with severe periodontal breakdown and clinical attachment loss of ≥7 mm are most likely to lose further attachment in a 48-month follow-up; furthermore, tooth-specific baseline attachment level is strongly predictive of subsequent tooth loss [44]. High residual probing depths following active periodontal treatment are predictive of further disease progression and tooth loss [46]. In subjects without periodontal care, increasing attachment loss is a significant predictor of tooth loss over time [47].

Loss of bone support and remaining supporting area Bone support remaining to the tooth is a critical factor; however, its anatomy and position in the dental arch should be carefully considered. Radiographic evaluation of the remaining bone support is an important tool for evaluating tooth prognosis, although, definitely, not the only one. Increased percent of bone loss before periodontal treatment is associated with increased risk of tooth loss [14, 22]; mean percentage of almost 50 % bone loss was found among teeth that were lost during a mean of 10-year maintenance period, compared to almost 35 % found among those that survived [14]. However, it should be noted that the average time of survival for teeth that were lost was almost 6 years [14]. Loss of bone support in a site over time is related to the initial bone loss at that site [48]. Insufficient bone support may prevent normal function of the tooth and healing after periodontal therapy. Cells responsible for periodontal regeneration have their origin from





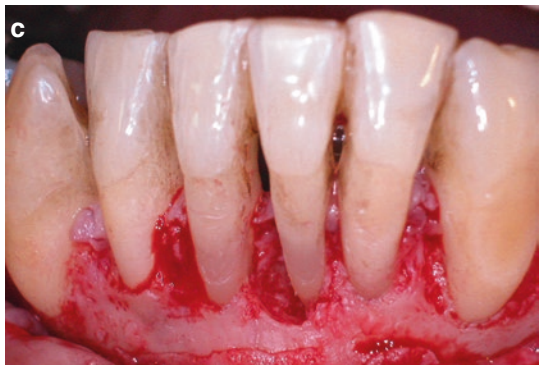


Fig. 4.1 (**a**). Gingival recession involving 360° around the lower anterior teeth (class IV) is evident. (**b**) Periapical radiograph shows large loss of periodontal support around lower incisors. (**c**) Intraoperative aspect of lower anterior teeth, extreme loss of periodontal support is evident

the remaining supporting apparatus [49–51]. Sites with higher baseline loss of bone support may have the possibility to relatively gain more bone after treatment [15]; therefore, the amount of bone loss, rather than the residual supporting bone, may have a prognostic value for future bone loss at a specific site [15].

Architecture of bone defects The healing potential of the infrabony lesions is primarily dependent on the defect morphology and, specifically, the number of associated bone walls [52]. Multiple bony walls in a periodontal defect will increase progenitor repairing cell and nourishment resources from the periodontal ligament; for the same reason, the healing capacity of intrabony defects is higher than the horizontal, suprabony ones [53]. The increasing number of bony walls enhances stability during early wound healing, allowing for adequate tissue maturation [52] (Fig. 4.3). Histological analysis following preparation of experimental defects in the dog and flap repositioning, without any further treatment, shows that the number of bony walls determines the regenerative capacity of the defect, a longer junctional epithelium, a shorter extension of new cementum, and diminished bone regeneration where appreciated in one-wall compared to two- and three-wall defects [52]. Periodontal regenerative surgery with and without the use of bone grafts has shown a statistically significant greater gain in hard tissue probing at surgical reentry than open flap debridement [54]. Narrow and deep infrabony defects radiographically and clinically respond more favorably to regenerative periodontal surgery than wide and shallow defects [55–57]. Single and multiple teeth with horizontal bone loss may be more difficult to treat than those with angular bony defects (Figs. 4.4 and 4.5). The intrabony component of bony defects, as determined by the projection of the most coronal extension of the lateral bony wall on the root surface, seems to be a good predictor of bone fill following GTR pro-

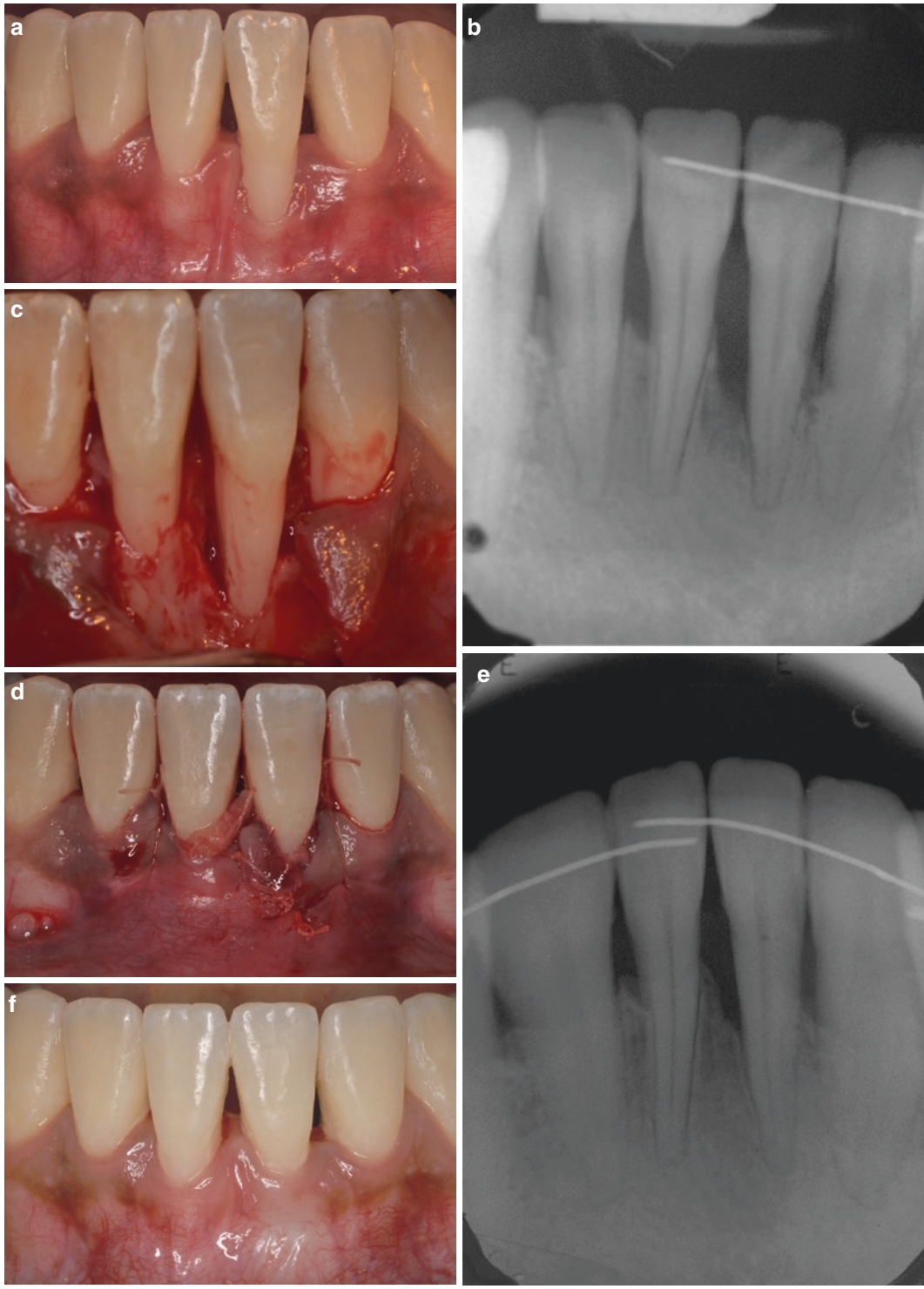


Fig. 4.2 (**a**). Gingival recession together with interdental loss of periodontal support on central lower incisors, especially on the left, and lack of attached keratinizing gingiva is evident. (**b**) Periapical radiograph shows large periodontal destruction around central lower incisors. (**c**) Intraoperative aspect shows large loss of periodontal support around lower left central incisor. (**d**) Immediate postoperative aspect of central lower incisors. Regenerative periodontal therapy combined with a free soft tissue graft was performed. (**e**) 1-year postoperative aspect of lower anterior segment. (**f**) 1-year postoperative periapical radiograph shows periodontal support gain on lower incisors

cedures [55, 56]. Teeth with deeper intrabony components of the defects at baseline will respond to therapy with larger bone gains [15]. Non-contained (one- to two-wall) defects show greater recession and lower bone defect fill and periodontal regeneration extent than contained (three-wall) defects after regenerative periodontal surgery [58]. Bone grafting in combination with regenerative periodontal surgery is advised in the treatment of non-contained bony defects [58]. Large clinical attachment level gains (5.4–6.8 mm) and resolution of the initial intrabony component of the defect (88.2–94.7 %) can be achieved 1 year after regenerative periodontal surgery of deep (9-mm baseline probing pocket depth) contained and non-contained intrabony defects [59]. Regenerative periodontal treatment presents a valuable treatment alternative for the management of severely compromised teeth with intrabony defects; tooth retention and clinical improvements can be maintained for long periods of time in the vast majority of cases. Tooth survival, more than 10 years after regenerative treatment of deep intrabony defects (average depth 6.6 mm), was greater than 96 %; in those cases, clinical attachment level was equal or coronal than pretreatment in 92 % of cases followed for 15 years [38]. However, the type of bone loss appears to have little impact on tooth survival [14] (Fig. 4.6).

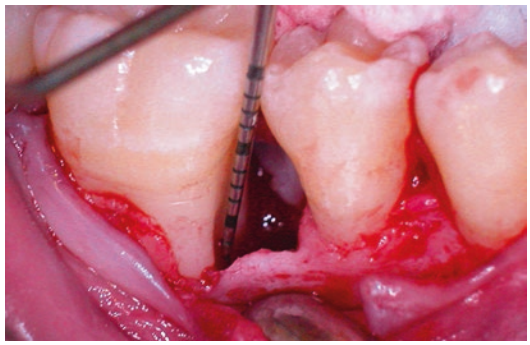


Fig. 4.3 Vertical bone defect on mesial aspect of lower molar. In the most coronal aspect, a one-wall defect, while in the apical area, a two–three-wall defect, may be appreciated

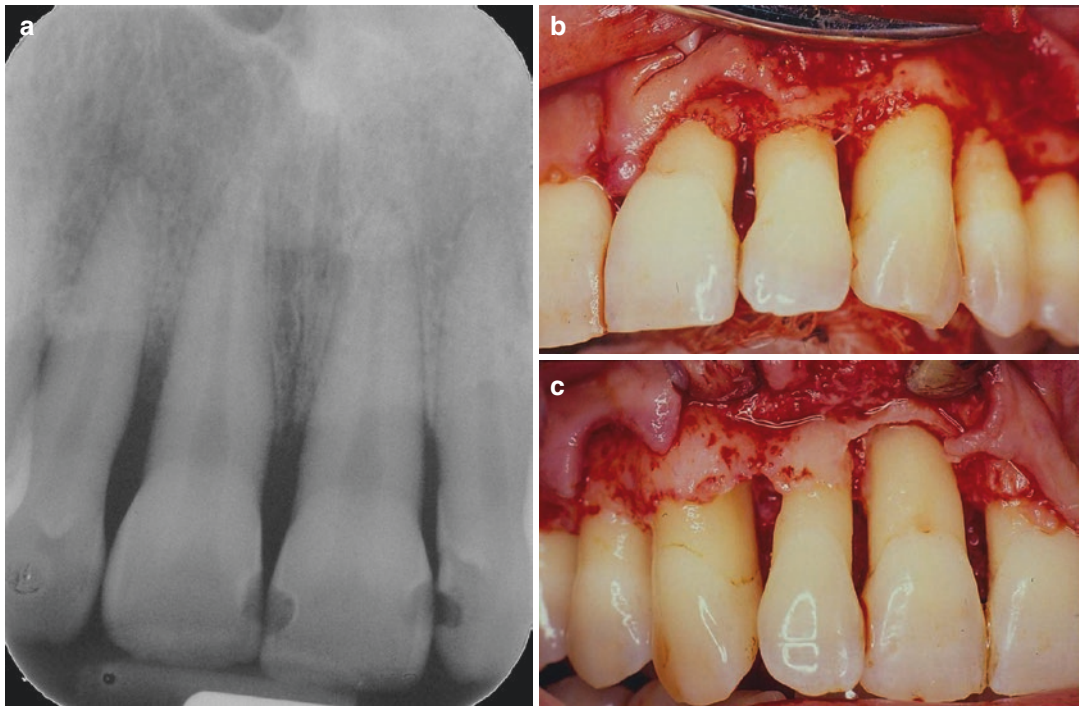


Fig. 4.4 (**a**). Periapical radiograph of upper incisors shows horizontal bone loss. (**b**) Intraoperative aspect shows horizontal bone loss on *left side*. (**c**) Intraoperative aspect shows horizontal bone loss on *right side*

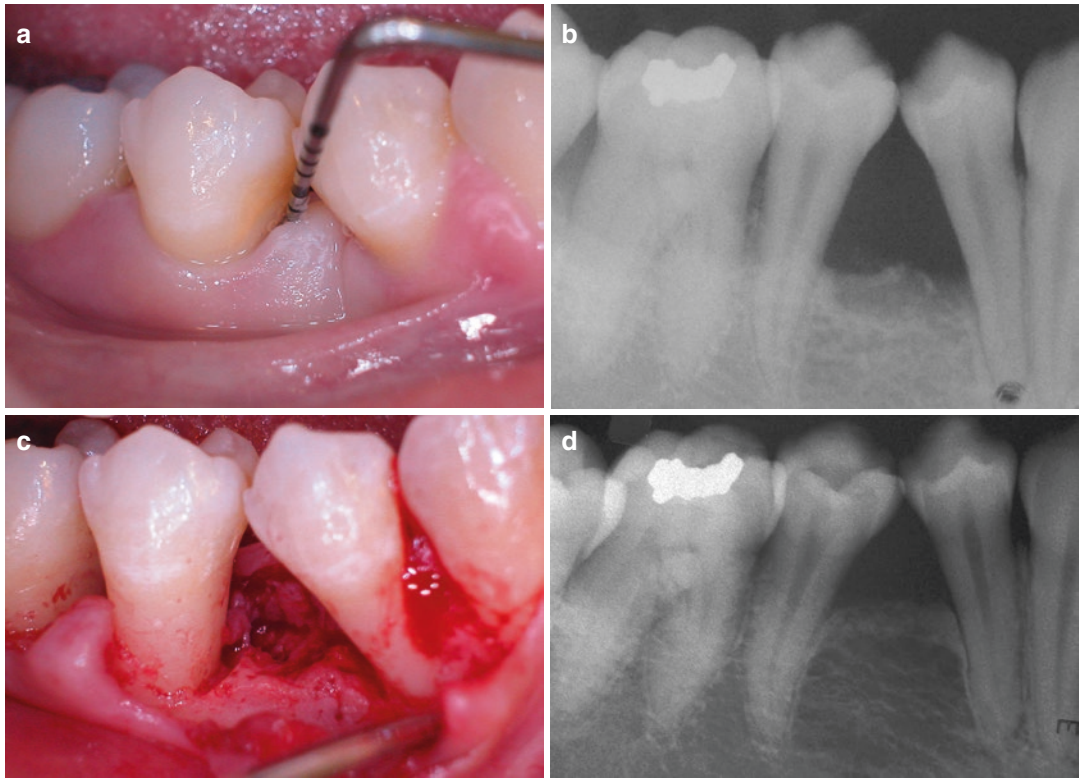


Fig. 4.5 (**a**). Deep periodontal pocket on mesial aspect of lower second premolar is evident. (**b**) Periapical radiograph of lower premolars shows mostly horizontal bone loss. (**c**) Intraoperative aspect shows mostly horizontal bone loss between both lower premolars. (**d**) Seven-year post-periodontal regenerative surgical treatment, enhanced bone support between both premolars compared to Fig. 14 is evident

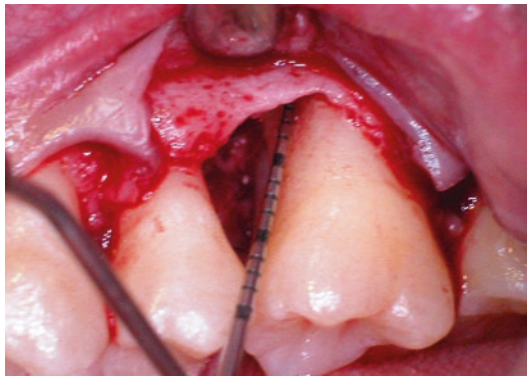


Fig. 4.6 Intrabony defect on mesial aspect of upper molar reveals furcation entrance apical to the bone crest level

Furcation involvement Furcation involved molars that respond less favorably to periodontal therapy than those without furcation involvement or single rooted teeth and are at greater risk for further attachment loss and tooth loss compared with other teeth with lower degrees of involvement [14, 22, 39, 60]. Over a 22-year mean period of maintenance in 600 patients, 7.1 % of all teeth were extracted due to periodontal reasons, but 31 % among the teeth with furcation involvement [61]. Molars with furcation involvement of degrees I and II had a comparable prognosis to teeth without furcation involvement after active periodontal therapy; class III furcation involvement (through and through) is more frequent in the maxilla and negatively influences the survival time of molars with a hazard ratio of 3.25 [39]. The location of the bone crest relative to the furcation, meaning the vertical component of the furcation involvement, seems to have great importance for successful periodontal regenerative treatment [62]; horizontal bone loss to a level apical to a degree III

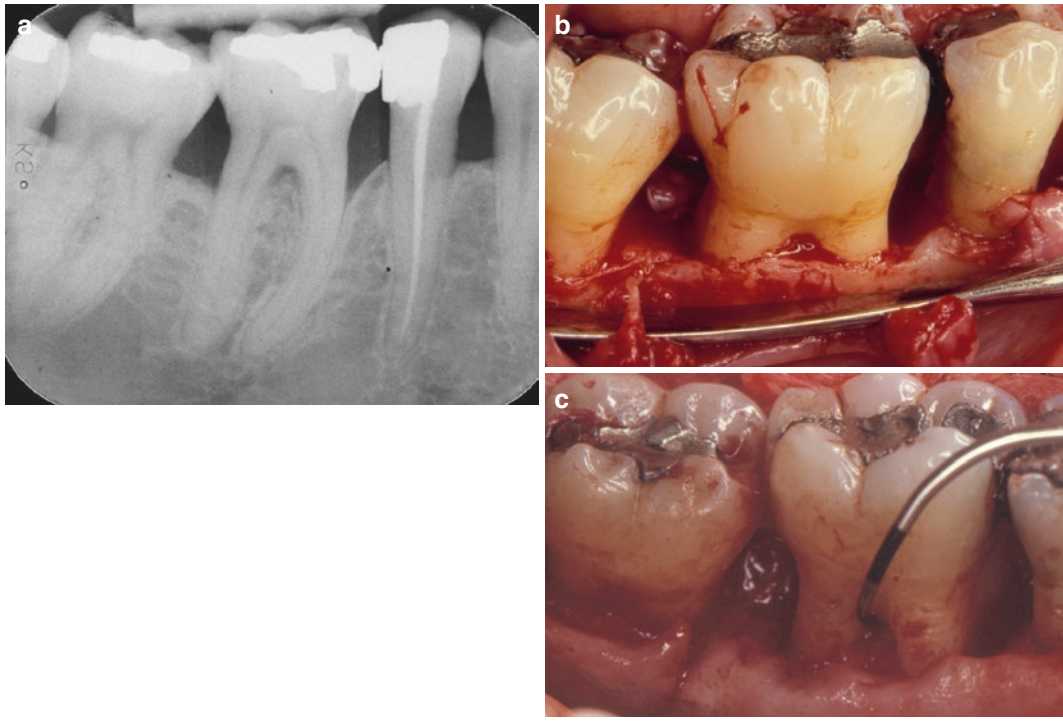


Fig. 4.7 (**a**). Periapical radiograph shows loss of periodontal support around posterior lower teeth; furcation involvement in the first molar is also evident. (**b**) Intraoperative aspect shows one-wall intrabony defects at mesial and distal of the first molar; buccal furcation is only minimally involved (class I). (**c**) Lingual aspect reveals extensive furcation involvement at a level apical to the bone crest

furcation involvement does not seem to be amenable to treatment (Figs. 4.7 and 4.8). Tunnel preparation in maxillary molars may have a large degree of tooth failure, apparently due to the difficulty in plaque removal, therefore not significantly improving the long-term prognosis of those teeth [39]. Although the survival rate of molars (85.9 %) was found to be inferior to non-molar teeth (97.2 %), almost half of all extracted molars were lost in a small number of patients, indicating a patient-dependent influence to periodontal treatment outcome [39].

In a long-term retrospective study (15–40 years with an average of 24), 79.4 % of surviving molars had an initial PD ≤ 5 mm, while 92 % of those survived in periodontal health.

Resection of the distal root of a mandibular molar and root-resected molars that are lone standing terminal abutments and/or associated with untreated parafunction show a high incidence of failure [63].

Periodontal regeneration has been established as a viable therapeutic option for the treatment of class I and II furcation defects; however, class III furcation involvement does not seem to be amenable to treatment. Therefore, regenerative periodontal therapy should be considered before resective therapy or extraction. The application of combined therapeutic approaches (i.e., barrier, bone replacement graft with or without biologics) appears to offer advantages over monotherapeutic alternatives. Adverse systemic and local factors should be evaluated, and controlled and stringent postoperative care and subsequent supportive periodontal therapy are essential to achieve sustainable long-term regenerative outcomes [64].

Various regenerative procedures have been proposed and applied with the aim of eliminat-

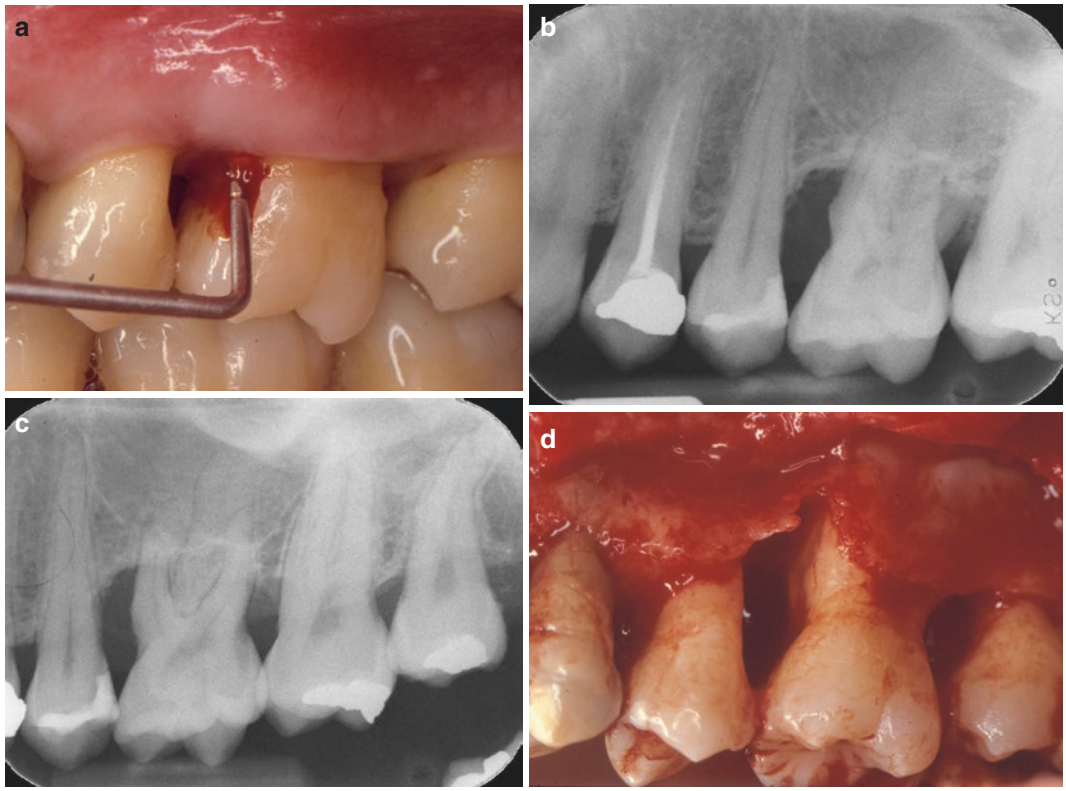


Fig. 4.8 (**a**). Deep periodontal pocket together with clinical signs of inflammation on mesial aspect of the first molar. (**b**, **c**) Periapical radiographs show loss of periodontal support around first molar; large intrabony defect and mesial furcation involvement are evident. (**d**) Intraoperative aspect shows large periodontal destruction mainly on mesial aspect of first molar; however, partially, bone crest is slightly coronal to furcation entrance

ing the furcation defect or reducing the furcation depth. The effectiveness of membrane therapy (guided tissue regeneration) for buccal class II furcation involvement of mandibular and maxillary molars compared with open flap surgery has been largely established. Bone grafts/substitutes may enhance the results of guided tissue regeneration; however, complete furcation closure is not a predictable outcome. Although enamel matrix protein therapies have demonstrated clinical improvements in the treatment of buccal class II furcation defects in mandibular molars, complete closure of the furcation lesion is achieved only in a minority of cases. Neither guided tissue regeneration nor enamel matrix protein therapy has demonstrated predictable results for approximal class II and for class III furcations [60].

Mobility Initial preoperative tooth mobility has been associated with lower tooth survival following periodontal treatment, during the maintenance period [14, 22, 37, 44]. Deeper probing depths at a site and tooth mobility at baseline are associated with a bad long-term tooth prognosis [15]. Teeth with increased mobility should be evaluated for occlusal overload and accordingly treated before any intent of surgical periodontal therapy. Increased tooth movement is associated with a widened PDL space [65]; at the time of periodontal surgery, it may be difficult to distinguish the nature of the soft tissue near the defect, and part of the supporting PDL may also be eliminated with the granulation tissue of the lesion. Although interproximal, intraosseous defects around teeth with limited presurgical mobility (Miller's classes 1 and 2) favorably respond to

regenerative periodontal surgery [66], teeth with advanced mobility should be stabilized through provisional splinting previous to treatment, to avoid spontaneous exfoliation during or shortly after therapy. Teeth with vertical mobility (Miller's class 3) should be carefully considered for treatment; the lack of possibility to stabilize these teeth before treatment might prevent success.

Crown-to-root ratio Poor crown-to-root ratio has been associated with tooth loss; in a 10-year follow-up study, 63.4 % of teeth that were lost had unsatisfactory crown-to-root ratio before treatment, while only 17.7 % of teeth that survived presented that feature [14, 22]. In another 14-year follow-up study, it was found that the mean crown-to-root ratio among the teeth that were lost was 49 % compared with a crown-to-root ratio of 17 % among the teeth that survived the whole period and that teeth with unfavorable crown-to-root ratio have a lower chance of survival, with 3.59 risk ratio [40].

Caries and/or endodontic involvement Interproximal and cervical carious defects can be secondary etiological factors for periodontal disease. Largely decayed teeth may be untreatable, therefore, affecting tooth prognosis. Teeth with more carious and restored surfaces are more likely to be lost during follow-up [44].

Several studies have reported varying incidences of tooth extractions associated with caries and/or endodontic involvement after periodontal treatment. In a retrospective study of 5 years or more after periodontal treatment, endodontic lesions or combined periodontal-endodontic lesions were responsible for the extraction of 43 % and caries for 5.2 % of all extracted molars [39]. In a 5-year follow-up, endodontic pathology and other problems in the absence of periodontitis were the reason for extraction in 29 % of the lost teeth [6]. During a10-year maintenance period, 30 % of the teeth that were extracted were lost due to endodontic reasons [37]. However, in another study, with a similar follow-up period, only 10 % of lost teeth were extracted due to caries and endodontic reasons [16].

Even in the absence of periodontitis, inflammation and drainage from an endodontic abscess can cause a sinus tract along the periodontal ligament developing a deep isolated probing depth that may arrive to the tooth apex or the furcation area in molars, performing periodontal surgery in these cases will cause serious damage, and sound periodontal tissues with repairing potential might be erroneously debrided and eliminated. Infection within the radicular canals will prevent any possible periodontal healing, the actual prognosis of a tooth with combined endodontic and periodontal involvement might be established only after successful endodontic treatment, and its failure will command tooth extraction, preventing any further treatment. Teeth after endodontic treatment can be functionally maintained for long periods of time; long-term success rate of endodontically treated teeth is very high; among teeth endodontically treated by unskilled dental practitioners, the percentage of roots with periapical radiolucencies was reduced from almost 50 % at the time of root filling to 16.6 % observed 10–17 years later; and further 6.4 % 10 years later, the percentage of cases with normal periapical findings 20–27 years after treatment was 86.4 % [67]. Based on survival rates, 95 % of teeth that have undergone endodontic treatment remain functional over time [7]. Treatment of perio-endo lesions according to GTR principles, rather than open flap debridement, may result in large healing of the defects with increased amounts of bone, periodontal ligament, and new cementum [68].

Root defects While the etiology of periodontal disease is bacterial, factors that may enhance bacterial plaque accumulation should be taken in consideration in treatment of periodontal disease and prognosis of those teeth. Enamel pearls and other projections, root grooves, root resorption, fractures, and fissures should be evaluated [69]. Enamel pearls and projections are most likely to

be found on buccal surfaces of second molars in both arches; different studies have found this aberration with varying frequency in 9–25 % of molars [69]. They are strongly associated with the presence of furcation involvement and may present a real inconvenience in treatment. Prevalence of root grooves is highest among the maxillary incisors; they appear in 8.5 % of individuals and almost 5 % of maxillary incisors [70]. A groove from the crown extending apically, subgingivally, may prevent plaque removal and become an easy gate for microorganisms to access this area. Periodontal attachment and bone loss can occur; they are associated with poorer periodontal health and may present a serious therapeutic problem. External root resorption located in the coronal third of the root has the potential for periodontal destruction; it is extremely difficult to achieve stable long-term results, therefore, largely worsening the tooth prognosis.

Root fractures can be caused by mechanical stress due to occlusal forces; restorative procedures with the use of intraradicular posts or endodontic procedures are usually associated with periodontal lesions as a result of growth of oral bacteria. Vertical root cracks and fissures, although sometimes difficult to clearly diagnose, will make the tooth unsuitable for treatment. Root fragments may initially be glued and the fissure sealed; however, biomechanical failure is likely. Vertical root cracks, fissures, or fractures are an obvious reason for early tooth extraction; in a 30-year maintenance, the main reason for tooth loss was root fracture [71]; however, in a retrospective study of 5 years or more after periodontal treatment, root fracture was responsible for the extraction of only 7.9 % of all extracted molars [39].

Tooth position The effect of tooth malposition on tooth loss after periodontal treatment has not been completely elucidated. Faulty and tilted tooth position can be enhancing factors for plaque accumulation, rendering oral hygiene and maintenance more difficult. Tooth malposition is associated with more unfavorable prognosis and lower survival rate [14, 22]. Orthodontic treatment, where possible, after active periodontal treatment, may be considered for these teeth.

Root proximity The minimal inter-root distance, at the site of the closest proximity of roots in an interproximal space, ranges between 0.1 and 4 mm; cancellous bone and lamina dura can be appreciated where this distance exceeds 0.5 mm; at sites with less than that, cancellous bone that is not present and the cortical alveolar bone from the proximal teeth are fused together; and roots are connected only by PDL, with no bone present where the distance is less than 0.3 mm [72].

A thin interdental septum consisting only of cortical bone has a low regenerative capacity due to reduced blood supply, especially since the direction of blood vessels is from the apical to the coronal aspect of alveolar bone.

Root proximity can be accepted if the distance between adjacent roots does not exceed 0.8 mm [96]. Root proximity in the maxilla is most prevalent between the first and second molar and between the central and lateral incisors [73] and in the mandible the incisor area; almost 70 % of all root proximities can be found in these areas. The actual role of root proximity in the etiology of periodontal disease is not clear; in untreated periodontal patients, it has no influence on the loss of bone support [73]; however, it should definitely be taken into consideration in choosing treatment options; splinted crowns in areas of root proximity will not allow for proper maintenance, orthodontic treatment, root amputation, or even tooth extraction which might be indicated in these cases.

Rehabilitation involving the tooth The evaluation of an abutment for a future rehabilitation demands the consideration of periodontal prosthetic and endodontic factors, as well as the

esthetic expectations of the patient. There is a close relationship between restorative dentistry and periodontal prognosis. Prosthetic restorations in both younger and middle-aged patients with severe periodontitis showed high survival, if pre-prosthetic active periodontal therapy and regular supportive periodontal therapy had been performed [74]. When there is a need for extensive rehabilitation involving a tooth with poor periodontal prognosis, the cost effect of the whole treatment should be evaluated. The survival of certain teeth might be critical to the treatment plan; sometimes the fate of other teeth depends on the survival of a key tooth. Tooth or teeth that will be part of an extensive rehabilitation must be considered differently from those that need no reconstruction; the weakest tooth will dictate the prognosis of the whole rehabilitation. Strategic extractions might be indicated where they significantly may improve the prognosis of the adjacent teeth or even the overall prognosis of the rehabilitation. Where extensive implant-supported rehabilitation is planned, certain sparse remaining teeth, although with fair prognosis, might have to be extracted to allow for better planning and construction of the rehabilitation. Fixed abutments appear to have increased survival, whereas removable abutments have decreased survival rates [14]. Mean survival time of teeth in young patients was 15.2 for fixed partial dentures and 11.6 years for removable [74]. Wearing of removable partial dentures is positively correlated with total tooth loss in the upper and lower arches [18]. Poorly fitted removable partial dentures, especially with no distal abutments, may cause enhanced plaque accumulation and overloading on the abutment teeth; whenever periodontal support of the retaining teeth is largely reduced due to periodontitis, removable partial dentures might be an important risk factor for tooth loss.

Periodontal treatment performed Periodontal treatment may be effective in stopping the progression of periodontal disease over time; several studies have shown that surgical and nonsurgical periodontal treatment might be equally effective; however, when determining tooth prognosis, the individual tooth and not the patient should be used as the primary unit of evaluation [75]. When individual teeth are used as the basis for analysis, teeth that receive no treatment or nonsurgical treatment show a significant worsening of probing depths, furcations, mobility, and prognosis when compared to teeth that received surgical periodontal treatment, while surgically treated teeth show significant improvement in probing depths [75]. Surgical therapy is more effective than nonsurgical scaling and root planning in reducing the overall mean probing pocket depth and in eliminating deep pockets; more nonsurgically treated patients exhibit signs of advanced disease progression in the 1–3-year period following active therapy than those surgically treated [76]. In subjects with severe periodontal disease, surgical therapy provides better short- and long-term periodontal pocket reduction and may lead to fewer patients requiring additional adjunctive therapy [76]. Regenerative periodontal treatment presents a valuable alternative for the management of severely compromised teeth, large amounts of regenerated periodontal support can be achieved, and the main role of regenerative periodontal therapy is to achieve more support for the tooth; however, the stability against further progression of periodontal disease is not increased [77]. Regenerated attachment seems to be as susceptible to periodontal breakdown as healing obtained by procedures intended to heal by repair rather than regeneration [77].

Therapist knowledge and skill Unfortunately, treatment plans are frequently influenced by the therapist preferences and skills and not necessarily based on all the alternatives available for a certain case. It seems difficult to have expertise in all dental disciplines; certain treatments are technique sensitive, and, therefore, the therapist's experience, skill, and knowledge will have a critical influence on their outcome. Periodontal

regenerative therapy is an extremely valuable tool when properly performed. Tooth extractions might sometimes be avoided using the right therapeutic periodontal procedures. It may seem sometimes easier to extract compromised teeth; however, the short- and long-term functional and esthetic results of an alternative treatment plan are not always evident.

Strategic value of the tooth and treatment alternatives The different therapeutic options should be fully evaluated before a final decision regarding the best treatment alternative is taken. Treatment of teeth with a doubtful long-term prognosis in need of extensive rehabilitation, and/or endodontic treatment should be considered regarding the cost-effectiveness of tooth preservation compared to other treatment alternatives. Periodontal treatment seems to lead to long-term survival of the vast majority of involved teeth. However, not all patients respond similarly to treatment [4, 5]. In the presence of clinical and radiographic signs of continuing periodontal destruction, even after therapy, tooth preservation should be carefully considered; in these cases, tooth maintenance will be accompanied with large alveolar bone loss, which will be difficult for other treatment alternatives, especially with the use of dental implants. Long-term results, extending beyond 10 years after periodontal therapy, have proven high survival rates of over 85 % of treated teeth during maintenance [78]. Hirschfeld and Wasserman retrospectively studied the outcome of periodontal treatment and maintenance of 600 patients that were followed for 15–55 years; findings reveal that tooth survival was of approximately 93 %; a similar molar survival after periodontal therapy and maintenance of 5 years or more was reported [39], where the mean loss of molars per patient during the maintenance period was only 0.06 teeth/year. The average time of survival for teeth that were loss during supportive periodontal therapy was almost 6 years [14, 22]. The survival rate of implants placed in combination with bone augmentation procedures is approximately 87 % [79]. Implants placed in sites where teeth were removed for periodontal reasons are 2.3 times more likely to fail than implants placed in other sites [80]. Although implant survival seems to be similar in periodontal and non-periodontal patients, peri-implantitis, with loss of bone support around implants, is more frequent among patients with previous history of periodontal disease [81, 82]. Periodontal disease itself is associated with a success rate significantly below the overall average [83]). Following ligature-induced periodontitis and peri-implantitis in study animals, a significant loss of supporting bone was found to be limited to implants and did not occur in relation to normal control teeth. The presence of marginal inflammation around implants clearly showed more serious implications than around teeth with a periodontal ligament [84–87].

Miller at al. [41] selected six prognostic factors that could be quantitatively evaluated to be scored: (1) age, (2) PD, (3) furcation involvement, (4) mobility, (5) molar type, and (6) smoking. A statistically derived score was determined for each factor. The sum of these scores became the score for that tooth. Of all these prognostic factors, smoking had the most negative impact, far exceeding the impact of PD, mobility, or furcation involvement. Molar type had a lesser impact, and age had the least impact.

When considering the replacement of teeth by implants, several well-established facts must be taken into consideration:

1. Short roots (less than 7 mm) are acceptable, while short implants (less than 7 mm) are not predictable [88].
2. Teeth with loss of periodontal support (root exposure) can be maintained for long time, while implants with loss of support (implant surface exposure) are difficult to maintain.
3. Root proximity is not necessarily detrimental, while implant proximity is highly problematic.

4. Gingiva is highly vascularized and responds well to aggression, while implant mucosa is poorly vascularized and does not respond well to aggression [89, 90].
5. Esthetic outcome of rehabilitation involving proximal teeth is highly predictable, while esthetic outcome of implant-supported rehabilitation on proximal implants is unpredictable.
6. Infection around teeth is limited to the gingival component, while infection around implants is not limited and extends to the supporting bone.
7. PDL connects the root and bone and prevents bone resorption, while implant has no PDL and does not prevent bone resorption after tooth extraction [91, 92].
8. Long-term (over 50 years) survival of teeth is evident, while long-term (over 50 years) survival of implants is yet to be proven.
9. Periodontal treatment is highly predictable, while treatment of peri-implantitis is unpredictable.
10. Periodontal regeneration is achievable, while regeneration of lost supporting bone and reintegration to implants are rare.
11. Root coverage is predictable, while coverage of exposed implant surface is extremely difficult.
12. Malposed teeth may be restored and maintained, while misplaced implants are difficult to restore and maintain.

The alternatives for each case must be considered; in most cases where teeth are extracted for periodontal reasons, implant therapy will demand large bone augmentation procedures, and therefore, morbidity, duration, and success [93] of these must be carefully evaluated before periodontal therapy is discarded. The success rate of bone augmentation surgical procedures according to guided bone regeneration principles seems to be extremely variable ranging from 60 to 100 %, while survival rates of implants combined with these bone reconstructive procedures are around 90 % [80, 94].

Increased susceptibility for periodontitis may also translate to an increased susceptibility for implant loss, loss of supporting bone, and postoperative infection. Implants inserted in patients that had previously suffered from periodontitis, even if properly treated, are prone to experience more implant loss and complications including higher bone loss and peri-implantitis than non-periodontitis patients [82, 95, 96].

Peri-implantitis therapy effectiveness is impaired in patients with poor compliance which was significantly lower for smokers and a nonacceptable oral hygiene level, as well as by severe periodontitis, severe mean marginal bone loss around the implants, poor oral hygiene, and low compliance [97].

A retrospective study carried out encompassing all patients who had initial periodontal treatment followed by implant placement and maintenance therapy found that peri-implantitis prevalence was 53.5 % at the patient level and 31.1 % at the implant level. Further findings showed that although the mean number of disease-free years was statistically significantly similar for implants and teeth, the extra cost of maintaining the implants was about five times higher than for teeth [98].

The following criteria could be used for establishing prognosis in periodontally affected teeth:

Diabetes	Worsens prognosis
Small number of remaining teeth	--
Large number of remaining teeth	+
Family history of periodontal disease	-
Faulty oral hygiene	Worsens prognosis
Compliance with SPT	+
Smoking	Worsens prognosis
Parafunction	Worsens prognosis
Willingness to preserve the teeth	+
Large number of teeth involved	--
Small number of teeth involved	+
>7-mm clinical attachment loss	--
100–75 % remaining bone support	-
75–50 % remaining bone support	--

Diabetes	Worsens prognosis
50–25 % remaining bone support	---
≤25 % remaining bone support	----
Horizontal bone defect	-
Vertical bone defect	+
No furcation involvement	+
Class I furcation involvement	-
Class II furcation involvement with vertical component	-
Class II furcation involvement without vertical component	---
Class III furcation involvement	----
Degrees 1–2 mobility	-
Degree 3 mobility that may be provisionally stabilized	---
Degree 3 mobility that cannot be provisionally stabilized	-----
Favorable crown-to-root ratio	+
Unfavorable crown-to-root ratio	--
Large carious lesion that may not be treated	-----
Endodontic involvement that may not be successfully treated	-----
Root resorption	----
Vertical root fracture	-----
Unfavorable tooth position	---
Root proximity	--
Tooth is abutment of a fixed partial denture	+
Tooth is free standing abutment of removable partial denture	Worsens prognosis
Surgical regenerative periodontal treatment can be performed	+
Surgical periodontal treatment cannot be performed	-
Good therapist knowledge and skill	+
Root grooves	--
Clinical signs of active infection that may not be controlled	-----

Prognosis: one or more of the following (prognosis determined by worst criteria) for each tooth. Certain factors marked as "worsen prognosis" may decrease prognosis. Addition of several negative factors may worsen prognosis +, good; -, fair; --, poor; ---, questionable; ----, hopeless, -----, indicated for extraction

Good: control of etiological factors and adequate periodontal support as evaluated clinically and radiographically assure that tooth is relatively easy to maintain

Fair: most of periodontal support remains. Adequate treatment will allow long-term tooth survival provided good patient compliance

Poor: large loss of periodontal support, provided good patient compliance, treatment will lead to prognosis improvement and maintenance but with certain difficulty

Questionable: most of the periodontal support around the tooth has been lost. Tooth not easily amenable to maintenance care. Treatment outcome is not fully predictable

Hopeless: possibilities for successful treatment and long-term tooth preservation are extremely limited. Preoperative attachment could be insufficient to maintain the tooth. Extraction may be suggested

Indicated for extraction: no possibility for treatment exists, tooth preservation in the arch may cause irreversible damage, and tooth should be promptly extracted

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5 Evidence-Based Decision-Making in Restoration of the Natural Dentition

Nissan Joseph and Barbu Horia

Abstract

The restoration of pulpless teeth is a topic that yet remains controversial. This chapter emphasizes the uniqueness of restoring endodontically treated teeth and some important principles to be observed. It has been proven that diminishing the amount of remaining tooth structure and interfering with the apical seal of the endodontic filling are detrimental for a long-term successful restoration, indicating the core material to be used, restoration type and timing, related or not to posts, ferrule importance, etc.

5.1 Introduction

Endodontically treated teeth can serve as abutments for fixed or removable partial dentures [1, 2]. The most common approach to restore endodontically treated teeth is based on a combination of post, core, and crown, which should be able to withstand mechanical and biological challenges, such as tooth fracture, secondary caries, and coronal leakage that could ultimately lead to periapical pathosis [3]. Remaining coronal tooth structure and functional requirement are important factors for long-term survival.

While endodontically treated teeth have been widely studied, the treatment planning, restorative materials, and some other clinical features are still controversial.

Although modern endodontic, prosthodontic, and periodontal therapies have allowed patients to retain severely compromised teeth for longer periods of time, the restoration of endodontically treated teeth remains a challenge. Despite a number of innovations and decades of research, failures still can occur when endodontically treated teeth are restored [4].

5.2 Restoration Type and Timing

Clinicians often debate whether it is preferable to place a permanent restoration immediately after completion of the endodontic treatment or

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to await the resolution of the rarefying osteitis. Safavi et al. [5] examined the influence of delayed coronal permanent restoration placement on the prognosis of endodontically treated teeth. A total of 464 endodontically treated teeth were evaluated with the use of follow-up radiographs. A higher success rate was found in teeth with permanent restorations than in teeth with provisional restorations; they suggested that an appropriate and prompt permanent restoration after completion of endodontic treatment should be performed [5].

In another study that compared restoration type in 166 patients, the survival of 176 endodontically treated teeth was significantly more likely where restored with cast restorations (91.7%) than teeth restored with temporary restorations (34.5%). Mean follow-up time is 38 months; range is 12–60 months. Loss of endodontically treated teeth occurred more often with those restored with temporary restorations (34.5%) than other restoration types ($p<0.05$) [6].

Sorensen & Martinoff [7] classic study contained records of 1273 endodontically treated teeth for a period of up to 25 years. Conclusions were the following: The rate of clinical success was significantly improved with coronal coverage of maxillary and mandibular premolars and molars. Coronal coverage did not significantly improve the rate of clinical success for maxillary and mandibular anterior teeth. There was no significant increase in resistance to fracture or dislodgment gained with intracoronal post for all groups of teeth [7].

Thus, the decision on whether to use a crown depends on functional requirements (posterior or anterior teeth), and the most important factor is the remaining tooth structure to support the restoration.

Coronal leakage is considered as one of the important factors that influence tooth survival during and after canal treatment. Salivary microleakage is considered a major cause of endodontic failure due to bacteria and endotoxin penetration along the root canal filling [8–11].

Periapical lesions around endodontically treated teeth are caused by bacterial infection or endotoxins inside the root canal. It has been shown that endotoxins from mixed bacterial communities can penetrate the root canal system easily and more quickly than bacteria [12, 13].

Sundqvist et al. [14] have shown bacterial presence in all teeth where periapical pathoses occurred. It is important to prevent bacterial contamination through the tooth crown after completing root canal treatment and the restoration [15, 16]. Bacterial penetration through the crown could lead to recolonization of the root canal, inflicting periapical inflammatory pathoses and restoration failure with the underlying root canal treatment [17–19].

Ray and Trope [20] study was based on 1010 endodontically treated teeth restored with a permanent restoration and evaluated the relationship between the quality of coronal restorations and coronal leakage by examining periapical status radiographs. They observed that a combination of good coronal restorations and endodontic treatment resulted in fewer periradicular inflammatory lesions (8.6%), whereas poor coronal restorations and good endodontic treatment resulted in periradicular inflammation in 48.6% of the teeth examined. Furthermore, when poor endodontic treatments were followed by good permanent restorations, the resultant in 32.4% is periradicular inflammation. The authors concluded that apical periodontal health depends significantly more on the coronal restoration than on the technical quality of the endodontic treatment [20].

Based on the literature, it can be concluded that a high standard of treatment with regard to root canal treatment and crowns contributes to long-term survival of the restored tooth, making it more resistant to coronal leakage [21]. Cementing agents may play a role as a defense line against coronal leakage at the post-core level and/or at the crown level. The following clinical recommendations are to be had: Permanent restoration should be placed as soon as possible after the completion of root canal therapy. Post space preparation and cementation should be performed with rubber dam isolation. The post space should be prepared with a heated plugger. Endodontic retreatment should be considered for teeth with a coronal seal compromised for longer than 3 months [21].

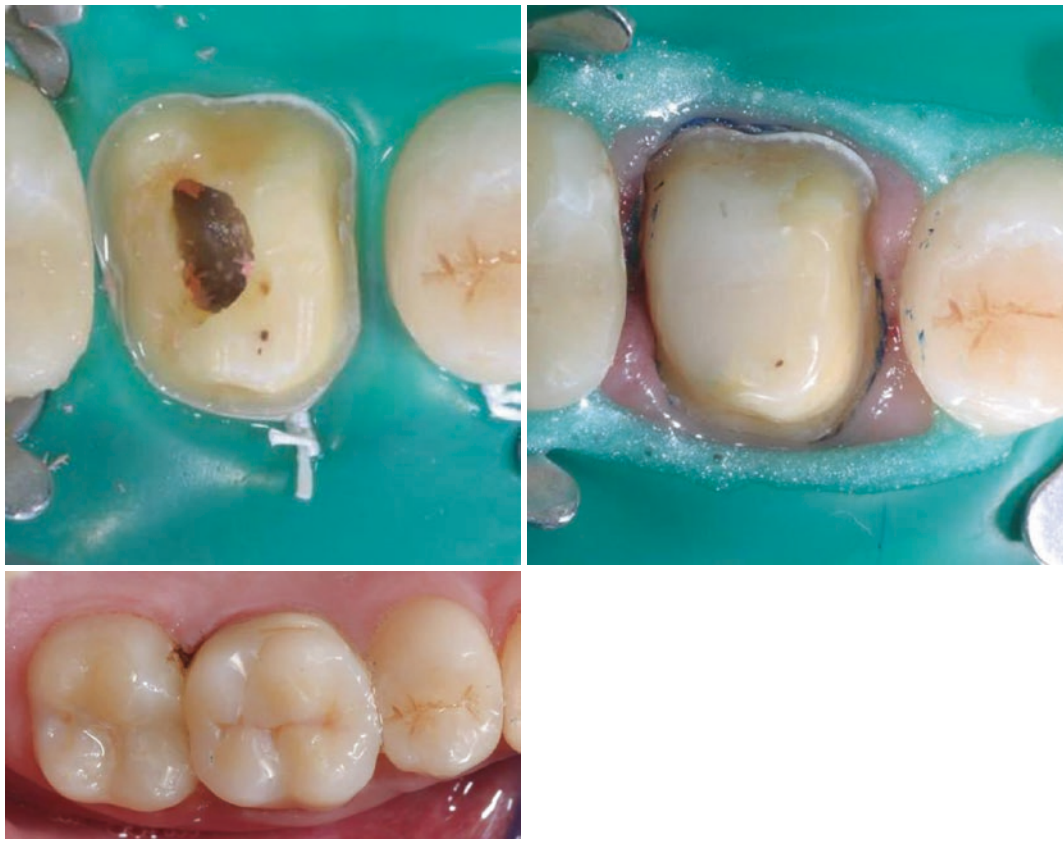
5.3 Post Type, Size, and Cementation

Posts are advocated in teeth with extensive coronal destruction to retain the core that replaces lost coronal structure, but not to reinforce the endodontically treated tooth [22]. Loss of post retention and root fractures is common and can affect tooth survival [23–28]. Therefore, the use of a post that minimizes these risks is of utmost importance. The preservation of sound root structure while using posts increases fracture resistance and decreases occurrence of periapical lesions of the restored endodontically treated teeth [19, 29–36]. Sound root structure and the apical seal of the endodontic filling are preserved by using posts with a reduced length in combination with composite resin cement in order to improve tooth survival [37].

In the past, some researchers believed that posts could improve the fracture resistance in endodontically treated tooth; nowadays, it is known that preparation of a post space may increase the chances of root fracture [38]; for that reason, posts should only be used when other options to retain a core are not available [22]. The decision to use root posts depends on the amount of remaining coronal tooth structure and the functional requirements [39, 40]. Depending on the remaining tooth structure, different treatment plans can be suggested. Loss of tooth structure greater than 50 % would determine the use of root posts to retain a core.

Posts should be used only for retention of a core within remaining tooth structure when there are no other alternatives and not to strengthen endodontically treated teeth.

Based on the evidence from laboratory studies, root-filled premolars and molars with limited tissue loss, where 50 % or more coronal structure is preserved, can be restored without intraradicular retention, particularly when total coverage are planned [41, 42] (Figs. 5.1, 5.2, and 5.3).

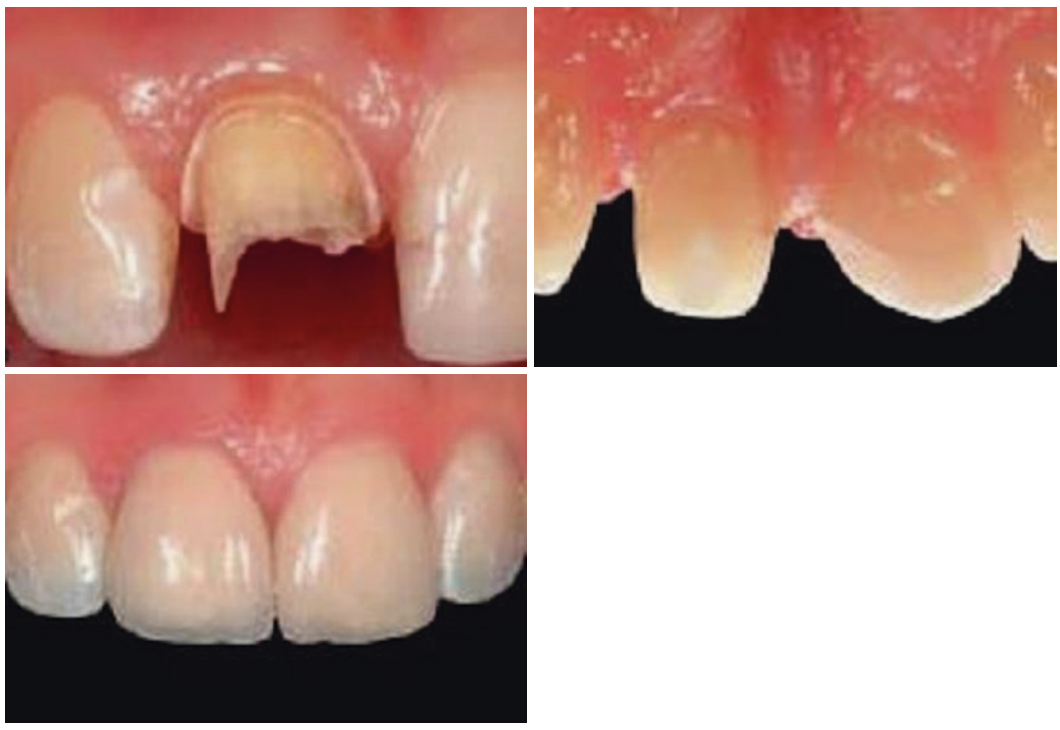


Figs. 5.1, 5.2, and 5.3 The molar with limited tissue loss restored with crown without intraradicular retention

The center of root or canal is neutral area with regard to occlusal force concentration, and in its given position, post receives minimal stresses under occlusal load and consequently does little to reinforce root under such a load [22]. Many studies [22, 23, 32, 33] support the assumption that the resistance to fracture of endodontically treated teeth covered by a complete cast crown with a 2-mm margin on healthy tooth structure is not affected by the post. The crown becomes the equalizer because it changes the force distribution to the root and the post and core complex, rendering the post characteristics insignificant [22].

Fiber posts have been indicated with loss of root structure since its modulus of elasticity is close to the dentin; however, some coronal remaining structure is necessary to retain the core using adhesive systems. Fiber post failures are more associated to displacement or detachment of the post and crown or prosthesis decementation than root fractures, a common failure related to conventional metal cast posts. Because metal cast posts present high rigidity, they appear to vibrate at high frequencies when loaded with lateral forces, which achieving critical points, may determine longitudinal fractures of the root [43] (Figs. 5.4, 5.5 and 5.6).

The choice of a root post should follow some principles like preservation of tooth structure, retention and resistance, retrievability, ferrule effect, and failure mode [44]. Preparation for a post space should, whenever possible, preserve coronal and radicular tooth structure (removing only root canal filling and not radicular dentin). Retention form is associated to the cement used, usually composite resin cement (allowing use of reduced post length and avoiding coronal microleakage), in correlation to post length. Post must be placed in a passive mode into the root canal. Post length does not influence the fracture resistance of endodontically treated teeth restored with a complete cast crown with a 2-mm ferrule on healthy tooth structure. The selection of a dowel should be based on a system that preserves maximal sound tooth structure and apical seal (reduced post length, no more than 5 mm) and possesses suitable retention (composite resin cement) of the core for the restoration [37, 45, 46] (Fig. 5.7).



Figs. 5.4, 5.5 and 5.6 Fiber post with composite resin as core material in the aesthetic zone

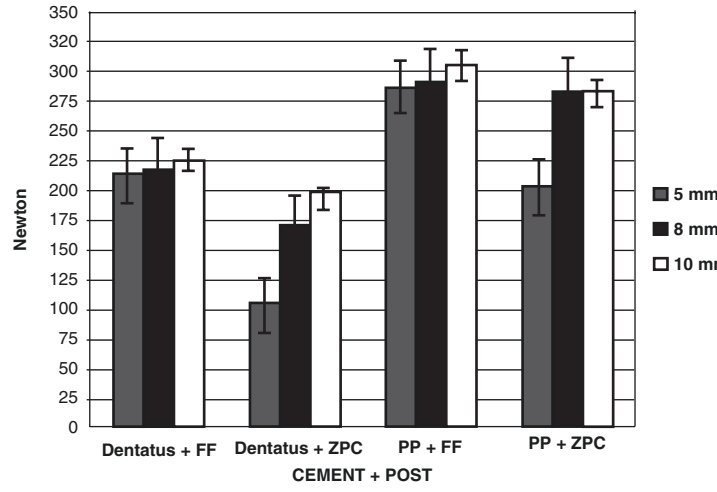


Fig. 5.7 No statistical significance difference between mean failure forces for all post length groups (5, 8, 10 mm), post cemented with resin (*FF*) superior to post cementation with *ZPC*

In most cases, passive, tapered posts offer the least retention of the prefabricated since their tapered shape resembles the overall canal morphology. If adequate canal length is available, they are a good choice, particularly in thin roots such as maxillary premolars [47]. Adequate length is considered to be 5 mm into the root canal; additional retention can be gained by the use of resin cement.

The resistance is affected by the remaining tooth structure and the ferrule area of the restoration that contributes for the ability of the tooth to withstand lateral and rotational forces and transmitting occlusal loads. Retrievability should also be considered in a choice of a post, so as the failure mode observed when different posts are used.

5.4 Core Materials

The purpose of the post is to retain the core, which in sequence helps retain the crown.

With cast post and cores, the core is formed on the post directly on the tooth or indirectly on a cast. The shape and orientation of the core is developed during fabrication. Its advantage is strength and durability, but on the other hand, it demands extensive removal of tooth structure in order to achieve path of insertion for both post and core; it is very difficult to retrieve for performing retreatment and expansive due to lab preparation. The incidence of complications, such as core loosening and tooth extraction, was significantly higher in cast metal cores; it also was associated with a significantly lower core survival rates [40, 48] (Fig. 5.8).

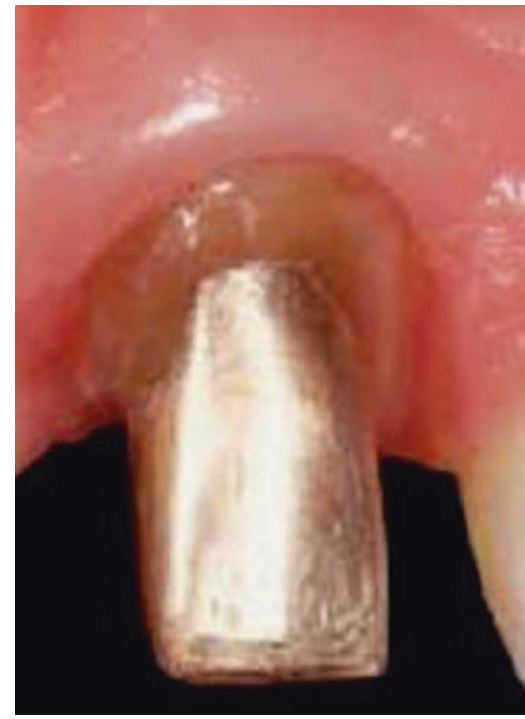


Fig. 5.8 Cast post and core for extensive tooth structure loss

On the other hand, prefabricated posts are used in combination with a restorative buildup

material which is formed after cementation of the post. The choices are amalgam, composite resin, or glass-ionomer materials.

The glass-ionomer materials, including resin-modified glass ionomer, lack adequate strength as a buildup material and should not be used in teeth with extensive loss of tooth structure. When there is minimal loss of tooth structure and a post is not needed, glass-ionomer materials work well for blockout, such as after removal of an MOD restoration [40].

Amalgam has been used as a buildup material, with well-recognized strengths and limitations. It has good physical and mechanical properties and works well in high-stress areas. In cases with minimal coronal tooth structure, placement can be problematic, and the crown preparation must be delayed to permit the material enough time for setting. Amalgam can cause esthetic problems since it may render the gingiva a dark appearance; there is also a risk for tattooing the cervical gingiva with amalgam particles during the crown preparation [40].

For these reasons, and potential concern about mercury, it is no longer widely used as a buildup material. Amalgam has no natural adhesive properties and should be used with an adhesive system for buildup. Dental amalgam undergoes dimensional changes within the first 24 h; amalgam creep is about 5 % due to corrosion products that have the potential to "seal" the restoration, the end result of which is expansion that exert pressure on the walls of the cavity. A non-vital tooth is more vulnerable than a vital tooth to the influence of the expanding amalgam confined within its walls. If amalgam is to be used as a core material, it should be remembered that the base for the final cast restoration is already under a permanent static load before the final restoration is put into place [49, 50].

Currently, composite resin is the most popular core material due to some characteristics of an ideal buildup material. It can be bonded to many of the current posts and to the remaining tooth structure to increase retention. It has high tensile strength, and the tooth can be prepared for a crown immediately after polymerization. Pilo et al. [51] showed that composite cores have fracture resistance comparable to amalgam and cast post and cores, with more favorable fracture patterns when they fail [51]. It is tooth colored and can be used under translucent restorations without affecting the esthetic result. On the negative side, composite shrinks during polymerization, causing gap formation in the areas in which adhesion is weakest. Strict isolation is an absolute requirement. If the dentin surface is contaminated with blood or saliva during bonding procedures, the adhesion is greatly reduced. Although composite resin is far from ideal, it is currently the most widely used buildup material. Composite is not a good choice, particularly if isolation is a problem. Stiffness of the core material did not affect the fracture resistance or failure mode of teeth restored with cast crowns with margins 2 mm apical to the core.

The dominant pattern of failure is usually unrepairable root fractures. Only the composite cores exhibited repairable fractures [40].

5.5 Ferrule Effect and Cementation

Preserving intact coronal and radicular tooth structure and maintaining cervical tissue to create a ferrule effect are considered crucial to optimize the biomechanical behavior of the restored tooth. A ferrule effect is defined as a 360° collar of the crown surrounding the parallel walls of the dentine extending coronal to the shoulder of the preparation. The result is an elevation in resistance form of the crown from the extension of dentinal tooth structure. More precisely, parallel walls of dentin extending coronally from the crown margin provide a "ferrule," which after being encircled by a crown provides a protective effect by reducing stresses within a tooth called the "ferrule effect." The "ferrule effect" is important to the long-term restoration success. A ferrule is defined as a vertical band of tooth structure at the gingival aspect of a crown preparation. It

adds some retention, but primarily provides resistance form and enhances longevity. A ferrule with 1 mm of vertical height has been shown to double the resistance to fracture versus teeth restored without a ferrule [52]. Other studies have shown maximum beneficial effects from a minimum of 2 mm of vertical height and 1 mm of dentin thickness. The presence of a 1.5- to 2-mm ferrule has a positive effect on fracture resistance of endodontically treated teeth. Including a ferrule in preparation design could lead to more favorable fracture patterns. Providing an adequate ferrule lowers the impact of the post and core system, luting agents, and the final restoration on tooth performance. In teeth with no coronal structure, in order to provide a ferrule, crown-lengthening procedures combined or not with orthodontic extrusion should be considered. If neither of the alternative methods for providing a ferrule can be performed, available evidence suggests that a poor clinical outcome is very likely [53].

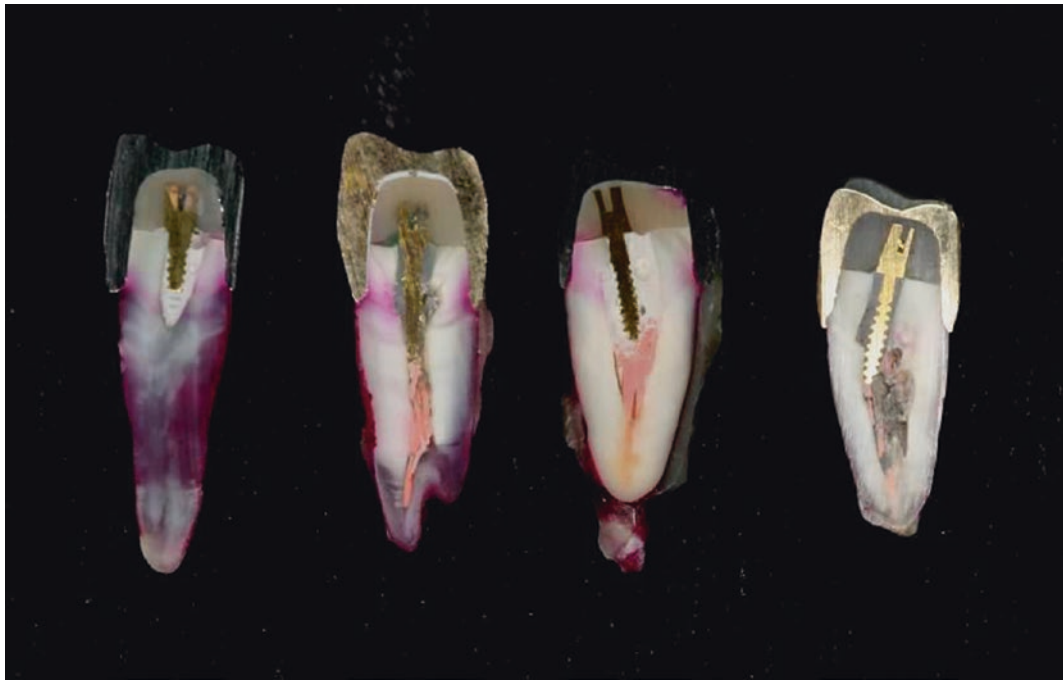
Any of the current luting cements can be used successfully to restore endodontically treated teeth. The most common luting agents are zinc phosphate, resin, glass ionomer, and resin-modified glass-ionomer cements.

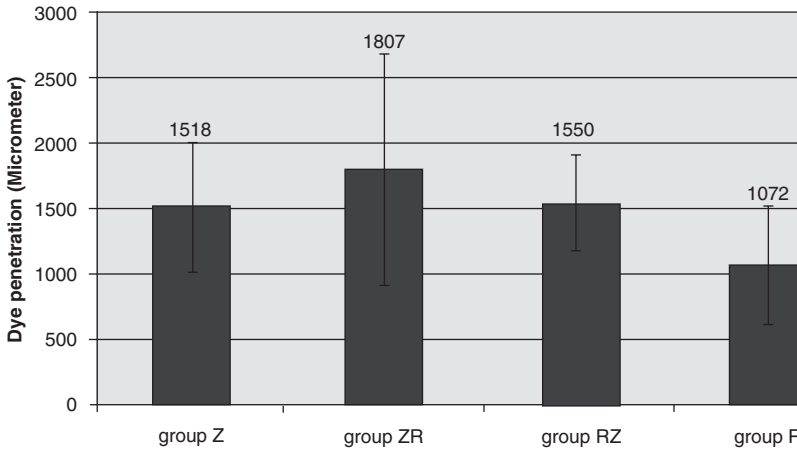
The recent trend has been toward resin cements, because they increase retention, tend to leak less than other cements, and provide at least short-term strengthening of the root. A study by Bachicha et al. [54] reported less leakage when resin cement was used with stainless steel and fiber posts compared with zinc phosphate or glass-ionomer cements.

Similar results were reported by Reid et al. [55]; Junge et al. [56] reported that posts cemented with resin cements were more resistant to cyclic loading than those cemented with zinc phosphate or resin-modified glass-ionomer cement. Bonded resin cements have been recommended for their strengthening effect in roots with thin walls [57, 58]. Resin may be bonded to some types of posts, so theoretically, the dentin/resin/post can be joined via resin adhesion into one unit. Unfortunately, resin cements have some disadvantages. Resin cements are more "technique sensitive." They require extra steps such as preparing the canal walls with acid or EDTA and placing a dentin-bonding agent. Contamination of the dentin or post should be avoided. Self-cure or dual-cure cements should be used because of limited light penetration into the root, even with translucent posts.

A high standard of treatment with regard to root canal treatment and crowns contributes to long-term survival of the restored tooth, making it more resistant to coronal leakage [59]. Cementing agents may play a role as a defense line against coronal leakage at the post-core level and/or at the crown level. Zinc phosphate cement (ZPC) is one of the most frequently used cements and is considered as the gold standard to which all cements are compared. In a marginal leakage study of extracted teeth covered by cast crowns with clinical service of at least20 years, zinc phosphate cement was an effective luting agent [60]. In the last 15 years, resin cements have gained in popularity because of their improved physical properties and ability to adhere to enamel, dentin, composite, and porcelain [61]. Radiographs show that the quality of the coronal restoration is more dominant in determining periapical health than biomechanical post space preparation and root canal obturation [20, 62].

Resin cements can serve as efficient coronal sealers, preventing dye material from penetrating the root canal system, and therefore, minimizing potential microleakage. The use of resin cements for both posts and crowns proved superior in preventing coronal leakage coopering to ZPC. These materials with their accompanying bonding systems create adhesion to the tooth substance. In contrast, zinc phosphate cement relies on micromechanical retentive features only [63, 64]. This difference may explain the superiority of combined composite cement for luting the crowns and the posts to create a tight coronal seal compared to the other combinations that included zinc phosphate cement. The cement combination offering the best coronal sealing is the resin cement for both posts and crown [65] (Figs. 5.9 and 5.10).





Figs. 5.9 and 5.10 Mean and SD of penetration scores for all cementation combination groups. (Specimens from *left to right* represent groups: Z–ZPC for both post and crown cementations, ZR–ZPC for post cementation and resin cement for crown, RZ–resin cement for post and ZPC for crown cementation, R–resin cement for both post and crown cementation) Specimen on the right shows a tight coronal seal compared to the other experimental groups

5.6 Conclusion and Clinical Recommendations

In order to achieve high levels of clinical success in restoration of endodontically treated teeth, these principles should be followed:

- Coronal leakage is considered as one of the important factors that influence tooth survival during and after canal treatment.
- Apical health depends significantly more on the coronal restoration than on the technical quality of the endodontic treatment.

- Permanent restoration should be placed as soon as possible after the completion of root canal therapy.
- Preservation of coronal and radicular tooth structure is desirable in order to get restoration longevity.
- The purpose of a post is to retain core buildup.
- Use posts with thin diameters, passive insertion, retrievability, and reduced length (5 mm into the root canal); additional retention can be gained by the use of resin cement.
- Loss of tooth structure greater than 50% would determine the use of root posts to retain a core. Posts should be used only for retention of a core within remaining tooth structure when there are no other alternatives and not for strengthening endodontically treated teeth.
- Core stiffness material did not affect the fracture resistance or failure mode of teeth restored with cast crowns with margins 2 mm apical to the core.
- Composite resin is the most popular core material due to some characteristics of an ideal buildup material.
- The cement combination offering the best coronal sealing is the resin cement for both posts and crown.
- A ferrule is highly desirable when restoration is performed. An adequate ferrule is considered a minimum of 2 mm of vertical height and 1 mm of dentin thickness.
- A crown with a 2-mm margin on healthy tooth structure is not affected by the post. The crown becomes the equalizer because it changes the force distribution to the root and the post and core complex, rendering the post shape, type, and characteristics insignificant.
- Endodontic retreatment should be considered for teeth with a coronal seal compromised for longer than 3 months.
- Posterior teeth with root canal treatment should receive cuspal coverage restorations.
- Anterior teeth with minimal loss of tooth structure can be restored conservatively with bonded restorations.

5.6.1 Vital Teeth Full Crown Coverage Restoration

- In most circumstances, it is required to perform root canal treatment in vital teeth before a crown preparation in order to prevent pulpal complications such as pulp inflammation, necrosis, and infection. However, in certain clinical scenarios, root canal treatment may not be required prior to crown placement. The decision whether to perform a root canal treatment involves both endodontic and prosthetic considerations [66].

Endodontic Considerations A vital dental pulp that has been subjected to repeated injury, such as from previous operative procedures or caries, may be at risk for deterioration from a healthy or an asymptomatic condition to a diseased condition. These pulpal complications can be caused by additional operative trauma or as a result of exacerbation of a predisposing undiagnosed pulpal disease. Therefore prior to any extensive restorative procedure such as crown preparation, the tooth pathological and operative history as well as the extent of the planned operative procedure should be considered in order to assess the pulp condition and capability to withstand the additional operative trauma [67]. *Prosthetic considerations*: Extensive tooth wear seems to be major factor that require vital teeth restoration.

It is mainly attributed to factors related to the diet such as a result of dental erosion. For the elderly, the longer times for which they remain dentate as well as their increasing life span imply a risk of advanced tooth wear and need for rehabilitation. Also, lifestyle changes and chronic diseases that are controlled with medications that may, in turn, result in regurgitation and/or dry mouth are possible reasons for the extensive clinical impression of an increasing prevalence of tooth wear. The etiology of tooth wear is multifactorial and the role of bruxism is not known [68].

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6 Preserving the Natural Tooth Versus Extraction and Implant Placement: An Evidence-Based Approach

Frank Setzer and Syngcuk Kim

Abstract

Both dental implants and endodontically treated teeth have demonstrated favorable outcome rates. However, there is still controversy regarding when to extract in favor of an implant and when to keep a natural tooth. Much of this controversy stems from the way the outcome of dental implants is defined. A majority of implant studies have used the measure of "survival" instead of "success." Survival rates up to 95.5 % after 1 year of follow-up have been reported. By contrast, most endodontic studies have applied strict success criteria, in particular requiring the resolution of apical periodontitis and the absence of symptoms. This renders a direct comparison to implant survival studies obsolete. If survival studies are compared, there is no significant difference in outcome between restored single-unit implants (95 %) and endodontically treated teeth (94 %) over 6 years.

When it comes to tooth preservation, there are several factors to consider beyond the endodontic aspects. A favorable periodontal status and sufficient remaining internal and external tooth structure are needed to allow for tooth preservation. Key to restorability are an acceptable crown-to-root ratio and sufficient supra-osseous tooth structure with adequate biological width and ferrule. Crown lengthening and orthodontic extrusion are adjunctive procedures that may provide for additional supra-crestal hard tissue structure if necessary. When all these factors are properly addressed, restorations on teeth have a good long-term prognosis. However, keeping a natural tooth must fit in the overall treatment plan for the patient. Restorations on implant

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fixtures, on the other hand, have lower life expectancies over 5–10 years than the implant itself, and biological, technical, or esthetic complications have frequently been reported. At 10 years and in long-term studies >15 years, natural teeth were shown to exceed the life expectancy of implants, including endodontically treated or periodontally compromised teeth. However, keeping a natural tooth must fit in the overall treatment plan for the patient.

Recently, attention in implant dentistry has been drawn to marginal gingivitis, periimplantitis, and long-term esthetic problems. Thus, the focus has shifted away from prematurely extracting teeth, knowing that reimplantations in previous implant locations are more demanding if an implant is failing or has been lost. Priority should be aimed at preserving the natural dentition, and implants should replace only missing or non-restorable teeth but not teeth per se.

6.1 Introduction

Dentists are healthcare professionals that strive to provide patients with a healthy dentition, either by maintenance or by repair of the oral soft and hard tissues. It has been a dilemma for the treating clinician where to draw the line when it comes to preserving a natural tooth versus extracting it and even more so since dental implants have become a widely available substitute or alternative to the natural tooth. This issue has been hotly debated over the past 15 years and involved almost all dental specialties [1–3]. The assessment of when to extract or when to retain has never been easy, and the approach to this question has now shifted back and forth several times.

When looking back over 30 years of dental history, available treatment options were tooth preservation by restoration, extraction, and replacement using fixed partial dentures and partial or complete dentures, all depending on the extent and condition of the remaining dentition. The introduction of implantology into modern dentistry promised to be a great benefit for patients and allowed for restoring patients with conditionally or fully fixed dentures without the inclusion of natural teeth. The earliest commonly used implant designs included various now obsolete concepts, such as fibro-osseous integration [4, 5] or blade-shape implants [6, 7]. Most modern implant systems are screw-type root-form titanium fixtures that heal by osseointegration. Osseointegration is the direct apposition of vital bone on a titanium implant surface [8]. This direct bone apposition allows for an immobile anchorage of restorative abutments and closely resembles ankylosis due to the lack of a surrounding ligament structure. The earliest dental applications were restorations of fully [9, 10] or partially [11] edentulous patients. Single-unit implants help to avoid fixed partial dentures, thus helping to save healthy tooth structure on abutment teeth. Single-unit implants demonstrated superior survival rates in comparison to fixed partial dentures [12], particularly when abutment teeth were endodontically treated [13, 14]. Thus, the proper use of dental implants provides benefits that could not be achieved in the past.

The prognoses of dental implants and restored teeth have been studied extensively over the past decades. While it is per se difficult to compare the outcome of two vastly different dental procedures, the multifactorial nature of both treatment modalities, short-term versus long-term outcome, as well as the differences in outcome assessment and advances in techniques have made this comparison even more challenging.

6.2 Outcome Assessment of Implants and Teeth

The outcome of implants or natural teeth can be assessed in many different ways. This may include considering the overall longevity of the unit with or without the permanent restoration, addressing biological and technical complications, as well as

taking into account the patients' acceptance of or satisfaction with the restoration. All these factors can be evaluated with a variety of study designs, ranging from randomized clinical trials to cross-sectional studies. Furthermore, outcome evaluation may refer to the determination of success or survival, depending on how strict the evaluation criteria were chosen.

6.2.1 Outcome Assessment of Dental Implants

No ubiquitously accepted outcome criteria are commonly applied to dental implants. Thus, the implant field lacks a singular definition of success. The most recent guidelines of the Academy of Osseointegration describe "the desired outcome of successful implant therapy" as "not only the achievement of the therapeutic goal but the maintenance of a stable, functional and esthetically acceptable tooth replacement for the patient" [15] and refers to "variations from the desired outcome of implant placement" as a substitute of defined outcome criteria. Historically, a great variety of success criteria had been proposed [16–26]. Variations in different criteria may include implant loss or mobility, inability to adequately restore the implant fixture, persistent symptoms such as pain or general discomfort, neuropathy and/or loss of function, persistent peri-implant radiolucencies, progressive bone loss, increased probing depths, persistent uncontrolled inflammation and/or infection, instability of the prosthodontic reconstruction, fractured or loosened occlusal materials or prosthetic components, and fractures of the implant fixture. Implant criteria may range from very loose (e.g., Buser et al., 1991) [21], where success does not differ much from survival, to very strict (e.g., Albrektsson et al., 1986) [19], with clearly defined requirements for an implant to be considered successful.

According to Albrektsson, success was defined as the absence of mobility, no evidence of peri-implant radiolucency, less than 0.2 mm of bone loss annually after the first year of service, and the absence of persistent and/or irreversible signs and symptoms such as pain, infection, neuropathies, paresthesia, or any violation of the mandibular canal. Buser's criteria include the absence of mobility and no persistent subjective complaints (including pain, foreign body sensations, and/or dysesthesia). In contrast to Albrektsson's criteria, however, the presence of a radiolucency around the implant is still accepted as a positive outcome. While the bony attachment of the implant should be maximal according to Albrektsson, it may be almost entirely lost according to Buser's criteria and still be considered successful, thus making this marginally different from survival. Initially, strict outcome criteria were used in implant research, but these were modified early on and became more lenient. Per Smith and Zarb [20], "sleeping implants" – implants that had been placed, but were not restorable for a variety of issues – were now preferably not included in the outcome evaluation. In contrast, Albrektsson's original criteria required implants to be restorable satisfyingly for the patient and dentist. According to Smith and Zarb, implant-specific mishaps such as anesthesia, paresthesia, or perforation of sinus and nasal cavity do also not result in a classification as implant failure. Furthermore, it was suggested that implant units should only be included in outcome calculations if they already had osseointegrated and also already survived a functional loading phase. However, early failures have not only been reported prior to osseointegration [27] but also throughout a loading phase. Morris and Ochi [28] demonstrated the impact of failures during functional loading in a study investigating different ways to assess implant outcome. Over 36 months of follow-up, implants were either evaluated beginning at placement or only after successful loading as proposed by Smith and Zarb [20]. The study evaluated 2900 implants of six different designs in 829 patients at 32 study centers. For upper completely edentulous applications, 85.3 % of all implants placed had remained including all failures since implant placement and 95.6 % using the post-loading method for evaluation. In the lower posterior, for partially edentulous applications, this difference was still 5.8 %.

It was recognized by several authors that the outcome of implant studies might be inflated [29, 30]. Listgarten et al. mentioned that implant studies were mostly longitudinal and descriptive in nature, obtaining survival rates, often under ideal clinical conditions, with strict inclusion and exclusion criteria. It has been repeatedly addressed that the literature often reports on the survival of implants rather than an outcome based on well-defined success criteria [30, 31]. As a result, for meta-analyses of implant outcome, studies may mix criteria. An example is Lindh et al. [32] where Albrektsson's or Smith and Zarb's criteria were mentioned "as a useful yardstick," but lastly any publications that "sufficiently described criteria for failure or survival" were included.

It is important to understand that evaluation based on either success or survival will lead to significantly different outcomes. A study by Brocard [33] investigated these differences in over 1000 implant units over a period of 7 years. While the cumulative survival was 92.2 %, the cumulative success was only 83.4 %. In 2004 a similar study by Romeo et al. found cumulative implant survival/success rates of 95.6 % [survival]/75.6 % [success] for single-unit implants, 94.4 %/76.3 % for cantilever fixed partial prostheses, 96.1 %/73.8 % for fixed partial prostheses, 100 %/63.8 % for fixed complete prostheses, 90.6 %/70.6 % for implant-/tooth-supported prostheses, and 95.7 %/78.6 % for overdentures [34]. In general, outcome rates exceeding 95 % were frequently reported, in particular after short-time follow-up. An overall survival rate of 95.5 % after 1 year was reported by den Hartog et al. [35] or 96.7–97.5 % for single-unit implant and 92.5–93.6 % for fixed partial restorations according to two meta-analyses [32, 36]. Over longer periods of time, lower survival rates were demonstrated with 93 % for two-stage implants over 15 years and 85 % for one-stage implants over 10 years, with the inclusion of early failures [37]. Changes in implant surface treatments, such as acid-etching or sandblasting, resulted in survival rates of 97–98 % [38, 39].

According to a systematic review and qualitative verification of investigations over a term of 20 years, even the arguably most well-researched implant systems by Nobel Biocare, Straumann, 3i, and Dentsply had used survival rather than true success criteria for the majority of studies [40]. This confirmed an earlier statement by Morris and Ochi, who criticized the quantity of survival versus success reports and the lack of use of cumulative percentages of success in consecutive patients in favor of reporting absolute percentages, which results in much too optimistic outcomes [41].

The long-term implant outcome was assessed in a systematic review comparing tooth preservation with implant placement by evaluating survival rates after a minimum investigation time of 15 years [42]. The authors' initial search resulted in 2700 studies investigating teeth and 2243 assessing implants, of which nine studies for teeth and ten studies for implants, respectively, were included in the final analysis. The study investigated restorative, periodontal, as well as endodontic aspects. Follow-up periods for tooth-related studies ranged from 16 to 30 years and 15–23 years for implant studies. While a meta-analysis was not performed due to the heterogeneity of the data, results indicated a generally higher loss rate for implants (0–33 %) than for teeth (3.6–13.4 %). The increasing rate of mean implant loss was a particularly interesting finding when the authors compared it to a previous study that evaluated shorter follow-up periods of up to 10 years with implant loss ranging from 1 to 18 % [43]. Another long-term study by Holm-Pedersen et al. also demonstrated that implants do not exceed the life expectancy of natural teeth at 10 years, including endodontically treated or periodontally compromised teeth [44]. A further co-finding of Levin and Halperin-Sternfeld's systematic review was the fact that the ten implant studies selected for data comparison did not sufficiently address a variety of important aspects, such as different implant types, variations in implant surfaces, implant placement in augmented bone, the incidence of peri-implant disease, as well as other biological and mechanical complications, and patient-related factors such as smoking, diabetes mellitus, or history of periodontal disease. Comorbidity and combined risk

factors, however, were shown to enhance the risk of experiencing implant failure or associated diseases, such as periimplantitis. As an example, a higher risk would be expected in a patient who is a current smoker with a history of periodontal disease who might be in need of an augmentation procedure before undergoing implant placement.

Increased risks of implant failure were found in smokers, with up to 31 % of implant failures [45, 46], in patients were implants were placed in areas with inferior bone quality with 16–35 % implant loss in type IV bone [47], patients with unsatisfactory oral hygiene [48, 49], or exhibiting parafunctional habits and occlusal overload [50, 51]. In addition, patients with a history of alcohol abuse have been shown to demonstrate greater implant bone loss than smokers [52]. Morris and Ochi [53] had remarked that authors should declare which patients had undergone implant placement as part of a study population and that implant systems should label which patient subpopulations, e.g., smokers or patients with limited bone volume, had not been part of the clinical trial. Moreover, they also pointed out the necessity for long-term clinical trials that evaluate implant fixtures and their ability to support a dental prosthesis over periods of one or more decades, since the large number of recently inserted implants diluted the small fraction that already went through a maximum observation period. In summary, promoting to the general population success or survival rates of >95 % for implants is based on erroneous information, because these values stem from ideal situations only. The outcome in the general population would be significantly lower [3].

6.2.2 Periodontal Factors Related to the Outcome of Teeth

To date, no general overall outcome criteria for teeth exist, and teeth are assessed by individual periodontal, endodontic, restorative, and esthetic prognoses. Extraction and implant placement were recommended for periodontally compromised teeth, particularly in esthetically challenging situations, if there was a presence of apical periodontitis or when surgical or nonsurgical retreatment was needed [54]. However, periodontal therapy has historically proven to be highly favorable, so this should be considered prior to choosing to extract a periodontally compromised tooth. Success rates for periodontal therapy were reported to range between 88.6 and 97.1 % [55–60]. Nevertheless, successful periodontal treatment depends on a careful assessment of the status quo and changes over an initial pretreatment phase with the subsequent reassessment of the patient's compliance as well as reevaluation of critical sites.

Nyman and Lindhe [61] demonstrated that teeth with reduced periodontal attachment could be effectively used for single crown restorations or as abutment teeth for fixed partial dentures if the periodontal therapy was successful. McGuire and Nunn [62, 63] established criteria for a periodontal classification, characterizing teeth suffering from periodontal disease as either "good," "fair," "poor," "questionable," or "hopeless," based on the severity of attachment loss, the mobility, and the degree of furcation involvement. The authors found that after an observation period of 8 years, the fate of single-rooted teeth was more predictable than that of multi-rooted teeth and that the prognosis of "fair," "poor," "questionable," or retained "hopeless" teeth was often better than projected at the onset of the study. Hence, periodontal prognosis projections were often inaccurate other than for the category "good."

In fact, teeth with moderate vertical bone loss, even if the furcation is affected, have a good prognosis if proper periodontal treatment is rendered and clearly hopeless teeth are removed from the dentition [64]. The aforementioned study investigated 1313 molars with furcation involvement and decided on the onset of the investigation between maintenance of the tooth with periodontal treatment only (68 %), root resection (4 %), or extraction (28 %). After 8–12 years of follow-up, 96 % of all retained molars were still in function, including 89 % of the teeth that had undergone root resection. Mobility, tooth position, and lack of occlusal antagonism were identified as influencing factors. The authors con-

cluded that a conservative approach to molars with even deep furcation invasions might show a high long-term success rate with appropriate maintenance care. This possibility of maintaining teeth with furcation involvement is in agreement with several other studies on periodontal therapy and maintenance [55, 56, 65–68].

6.2.3 Endodontic Prognosis

Successful endodontic therapy calls for prevention or elimination of apical periodontitis. Apical periodontitis is mostly linked to teeth suffering from intracanal infection. In comparison to teeth with irreversible pulpitis, the treatment of teeth with pulp necrosis, infected root canal system, and apical periodontitis has been historically associated with lower outcome rates. The arguably most commonly used outcome criteria used in endodontics are Strindberg's criteria [69] and the PAI [70]. These criteria are more strict than those for implants [3, 31]. Success according to Strindberg requires the patient to be free of clinical signs and symptoms, an intact lamina dura, and a reconstitution of the periodontal ligament, only with the exception of a widened periodontal ligament space around excess filling materials. The PAI has similarly strict criteria for positive outcome but, moreover, requires the examiner to undergo case calibration with a standard set of 100 radiographs depicting disease and healing stages according to Ørstavik's criteria [70].

A systematic review and meta-analysis of primary endodontic treatment described cumulative success rates of 68–85 % for the decades between 1950 and 2000, with success ranging between 69.6 and 81.4 % for teeth with apical radiolucency and 82.1–90.1 % without [71]. The included studies exhibited a great variety regarding treatment techniques, practitioners, and follow-up periods. Many university-based studies included treatments rendered by predoctoral students without significant experience and follow-ups as short as 6 months, although endodontic healing, particularly of larger lesions, may take up to 4 years [70] or even longer [72].

Intracanal infection is considered the primary reason for endodontic failure. Infection may be recurrent or primary if microorganisms enter the root canal system during or after the endodontic therapy of vital cases. Nonsurgical endodontic re-treatment is the first treatment choice for most failed endodontic cases. A systematic review and meta-analysis of endodontic re-treatment reported an overall weighted pooled success rate of 77.2 % based on data from 17 studies from 1961 to 2005 [73]. Cases with apical periodontitis demonstrated an overall outcome of 65 %, of those, lesions larger than 5 mm in diameter were reported to heal in 41 % of the cases. However, the authors mentioned that the follow-up periods for larger lesions might not have been long enough to demonstrate complete healing.

As nonsurgical re-treatment primarily addresses intracanal infection, it might be unsuccessful in the presence of extraradicular pathology, including true cysts, foreign body reactions, or extracanal infections such as actinomycosis or *Arachnia propionica* [74]. Moreover, the technical quality of the initial endodontic treatment, as well as the nature of intracanal infections, such as biofilms, as well as physiologic changes in root canal anatomy cannot be overcome by endodontic treatment, and the overall success rate of nonsurgical re-treatment will be affected. Gorni and Gagliani described the outcome of 454 nonsurgical re-treatment cases depending on the presence or absence of apical periodontitis as well as the accessibility of the root canal system for complete reinstrumentation and disinfection during re-treatment [75]. While cases where previous complications could be overcome and the root canal system was completely accessible to treatment demonstrated an overall healing of apical periodontitis in 83.8 %, re-treatment of teeth with apical periodontitis and inaccessibility of the root canal system in situations such as internal or external transportation, apical or strip perforations, as well as internal resorption were only successful in 40 % of the cases [75]. For a situation with a non-favorable nonsurgical re-treatment prognosis, particularly when disassembly of the existing restoration may lead to a situation where the tooth becomes non-

restorable, as well as failed previous nonsurgical re-treatments, surgical re-treatment may be the better and less invasive option [74].

The outcome of endodontic surgery is commonly assessed by surgical criteria such as Rud et al.'s [76] or Molven et al.'s [77]. While a systematic review of studies of surgical endodontics found success rates ranging from 37 to 91 %, this included historical data with traditional techniques as well as modern studies [78]. Now obsolete, traditional root-end surgery (apicoectomy) is commonly defined by the use of a straight surgical handpiece, root resection at a bevel, as well as a retrograde preparation at inadequate angles with a variety of handpieces and often a retrograde filling with amalgam. The success rate of this approach was reported to be 59.0 % [79]. Modern endodontic microsurgery utilizes ultrasonic instruments for root-end preparation along the long axis of the root, the operating microscope to identify the complexity of the canal anatomy on the resected root surface at high magnification (12–24×), and biocompatible root-end filling materials [80]. The biocompatible root-end filling materials such as mineral trioxide aggregates (MTA) have demonstrated favorable healing [81]. However, MTA is difficult to manipulate, thus the latest bioceramic root-end filling materials come with the consistency of a putty and are much more user friendly in terms of application during surgery, while providing excellent healing of the periradicular tissues [82]. Two meta-analyses on the outcome of root-end surgery on teeth with true endodontic lesions and favorable periodontal support demonstrated cumulative success rates for contemporary microsurgical techniques after at least 1 year of follow-up of 93.5 % [83] and 91.4 % [84], respectively. Last but not the least, it has to be pointed out that endodontic surgery is the one field in endodontics that best demonstrates the impact of modern advancements with the utilization of modern techniques and advanced armamentarium. To date, no higher-level evidence study for primary endodontic treatment nor nonsurgical re-treatment exists that evaluates the outcome of therapy when standard modern treatment techniques, such as nickel-titanium instrumentation and dental operating microscope, or modern diagnostic tools such as CBCT imaging were applied (Fig. 6.1).

6.2.4 Restorative Aspects

Restorative issues, such as mobility, crown-to-root ratio, crown/root fractures, and remaining tooth structure, are often listed as critical factors whether a tooth can and/or should be preserved.

The crown-to-root ratio describes a restorative aspect addressing the prosthodontic value of a tooth. The ratio of anatomic crown versus the anatomic root is defined as the ratio of the vertical dimensions of tooth structure coronal versus apical of the cementoenamel junction. In a healthy situation, this commonly correlates with the hard tissue structure supragingivally versus subgingivally. On the other hand, the ratio of clinical crown versus clinical root describes the ratio of the vertical dimensions of supra-osseous versus subosseous tooth structure, radiographically determined by the portion of the tooth within the alveolar bone compared to the portion not within the alveolar bone. Penny and Kraal described a clinical crown-to-root ratio of 1:2 as ideal, 1:1.5 as acceptable, 1:1 as minimal, and 1:<1 as poor or questionable [85]. However, a description of this relationship based on two-dimensional radiographs is problematic.

In reality, besides the radiographic clinical crown-to-root ratio, the root surface area, root morphology, and root diversions all influence the mobility of a tooth [86]. Different root forms exist in different periodontal biotypes. Patients with a thin-scalloped periodontal biotype often demonstrate triangle crown shapes and tapered roots, whereas individuals with a thick/flat periodontal biotype often demonstrate triangle crown shapes are known to exhibit rather square crown shapes with a tendency to more parallel root forms. As a clinical consequence, due to the tapered roots and thus a larger root surface area lost, a similar clinical crown-to-root ratio in a patient with a thin-scalloped periodontal biotype is very likely to be less favorable when compared to a parallel root form in a person with a thick/flat

periodontal biotype [87]. In addition, a long root trunk may provide additional support, as well as reduce the risk of any future furcation involvement [88]. Root diversions also enhance the long-term stability of a natural tooth. Depending on the scale of the treatment plan, an unfavorable crown-to-root ratio can be overcome by choosing different restorative designs. Instead of a single crown restoration, splinted designs combining several teeth can add additional strength to the restoration. In these situations, even a tooth with a limited crown-to-root ratio will provide additional overall root surface to the combined restoration. Also, the more teeth are added to a splinted restoration, the more retention is gained from overall root diversions.

The most critical restorative aspect is the remaining external and internal tooth structure. After removal of old restorations and caries, the remaining tooth structure is evaluated to assess structural integrity and the margins of a future permanent restoration. Preparation of defined

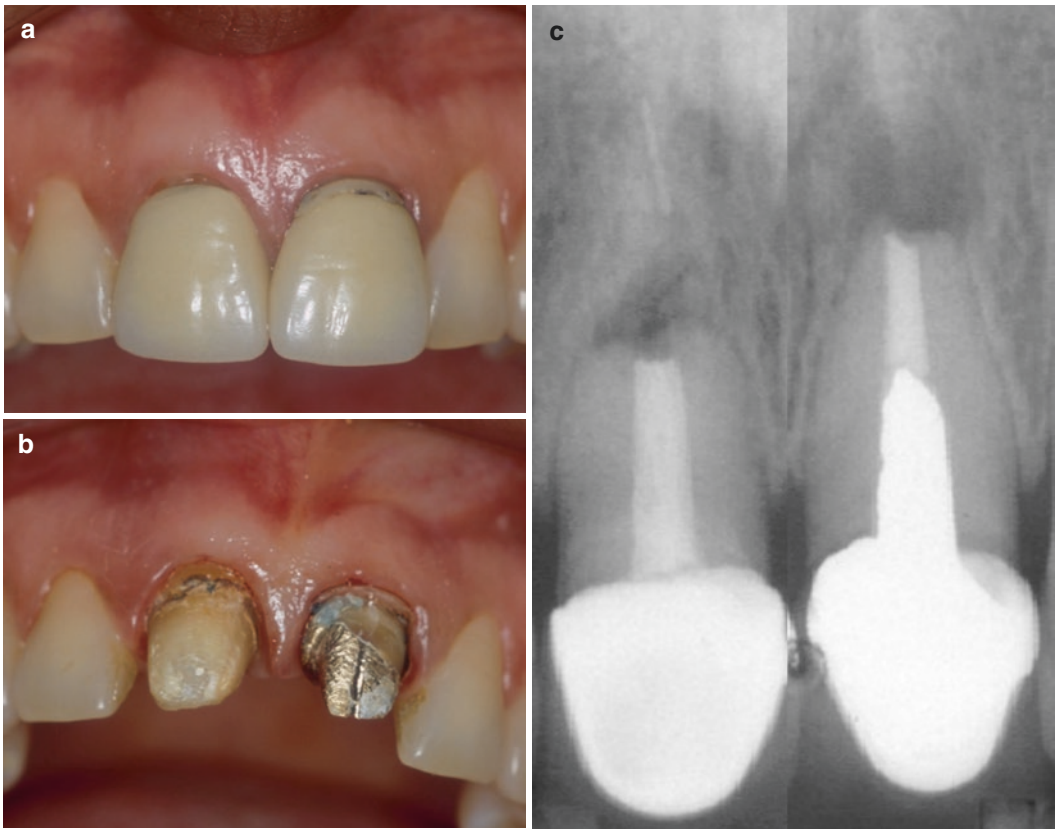


Fig. 6.1 A 49-year-old female patient, presenting to prosthodontist, discolored and exposed crown margins of both central maxillary incisors. Case demonstrates that although the patient's primary concern was a simple esthetic issue, the decision-making for a new permanent restoration had to include endodontic, periodontal, restorative, and esthetic aspects, as well as weigh the prognosis of teeth with endodontic re-treatment and permanent restoration versus the prognosis of an implant-supported restoration. (**a**) Preoperative clinical situation; (**b**) situation after crown removal, exposing calculus, buildup, and amount of remaining tooth structure; (**c**) radiograph revealing the complexity of the situation with history of incomplete root-end surgeries on both incisors (missing root-end fillings), apical periodontitis, and compromised crown-to-root-ratios; (**d**) the decision was made to retain the teeth, postoperative radiograph after nonsurgical re-treatment of right and surgical re-treatment of left central maxillary incisor; (**e**) 10-month follow-up radiograph demonstrating periapical healing; (**f**) clinical situation at follow-up with esthetically pleasing new permanent restorations, patients being free of pain and symptoms (Courtesy Dr. Howard Fraiman, Philadelphia, PA, USA, and Dr. Samuel Kratchman, Exton, PA, USA)

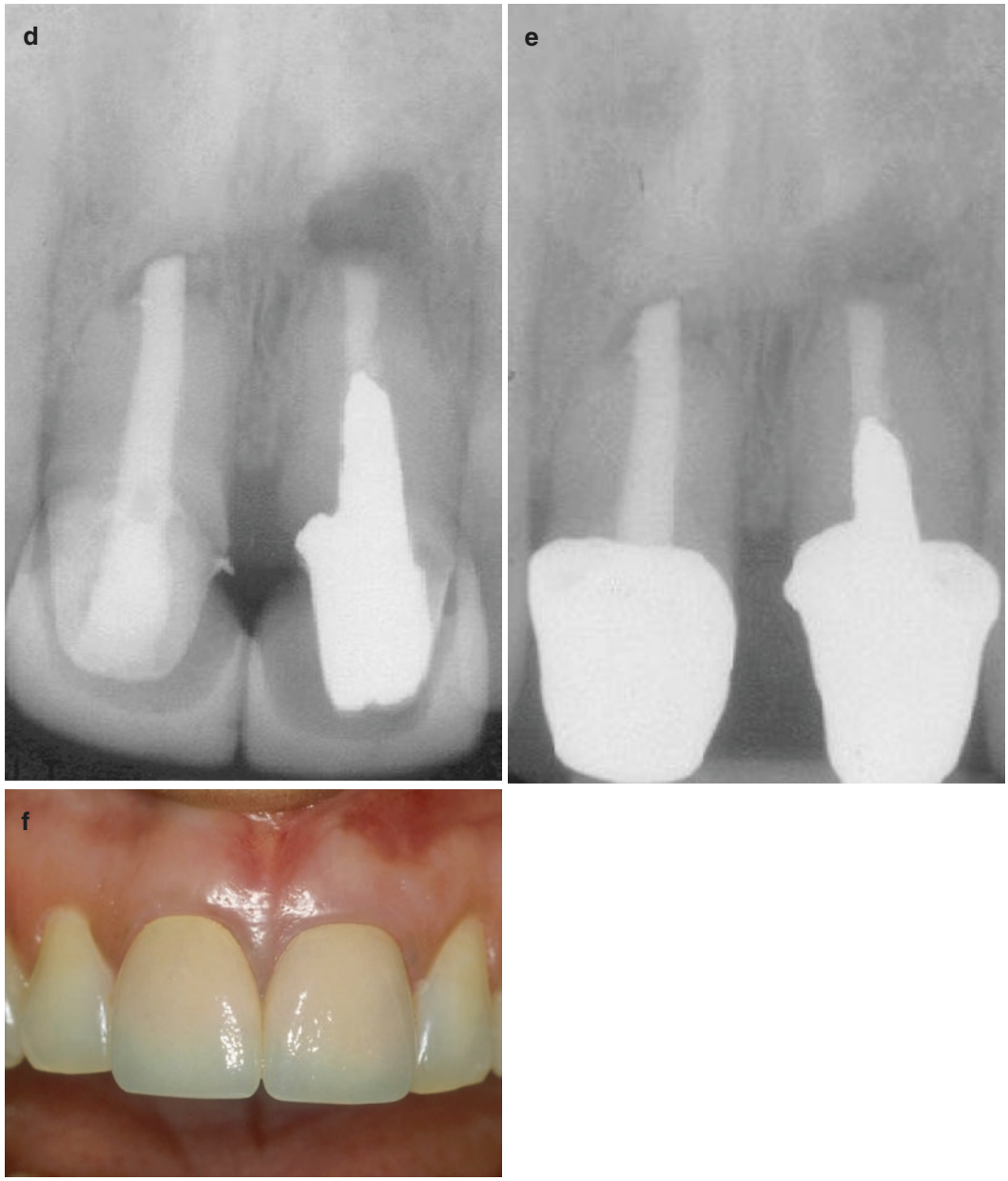


Fig. 6.1 (continued)

margins may be more difficult with the presence of root caries. With an increasing population of elder people, there will be higher incidences following gingival recession, since cementum is more vulnerable to mechanical and chemical destruction due to its lower mineral content and smaller hydroxyapatite crystals than enamel. The amount of supra-bony tooth structure has a positive influence on protection from root fracture, recurrent caries, or dislodgment of the permanent restoration and can prevent disturbances of the biological width. The term "biological width" was first described by Ingber et al. [89]. Subgingival restorations may have damaging

effects on the neighboring hard and soft tissues, especially when they encroach on the junctional epithelium and the supra-crestal connective tissues. To preserve periodontal health and to remove irritation that might damage the periodontal attachment apparatus, a safe distance from prosthetic restorations is warranted. Gargulio measured the mean biological width as 2.04 mm, adding the values found for the junctional epithelium to those for the supra-crestal connective tissue [90]. However, this value may vary depending on the individual tooth and its location. In addition to the biological width, 1.0–2.0 mm of restorative finish line is necessary [91], resulting in a minimum of 3.0 mm of supra-crestal tooth structure needed between the preparation margin and the alveolar bone to maintain healthy periodontal tissues for 4–6 months [92].

Lastly, it is important that the ferrule effect is respected. Studies suggested that for teeth with full coronal cast restorations, an encircling band of 1.5–2.0 mm of metal around the coronal tooth structure was necessary to withstand significantly higher occlusal forces before fracture, counteracting functional lever forces and wedging effects of tapered posts [93–95]. Hence, the summation of all values for biological width, restorative finish line, and ferrule results in a total required supra-crestal tooth structure of 5.0–6.0 mm for ideal conditions. Not all teeth fulfill this requirement after caries excavation. Adjunctive procedures such as crown lengthening or orthodontic extrusion may be utilized to regain the necessary supra-crestal tooth structure. Crown lengthening is the surgical removal of hard and soft periodontal tissues to regain supra-crestal tooth length, allowing for longer clinical crowns and reestablishment of the biological width. It is indicated if decay is at or below the gingival margin, the presence of crown fractures, inadequate interocclusal space, or for esthetic reasons. Crown lengthening involves the reflection of a partial-thickness mucogingival flap, osseous resection with rotary and hand instruments, odontoplasty to control the embrasure space and the emergence profile, and the fixation of the soft tissues on the periosteum in a more apical position [96]. A clinical study over 5 years by Dibart et al. demonstrated that after crown lengthening procedures, at least 4.0 mm of sound tooth structure from the restorative margin to furcation should be retained to have no risk of furcation involvement [97]. On the other hand, if the initial distance was less than 4.0 mm, furcation involvements were inevitable [97]. Orthodontic extrusion or forced eruption was described by Heithersay [98]. Indications include teeth with long roots and little remaining tooth structure or, particularly in esthetic areas, when a crown lengthening procedure alone may compromise the esthetic outcome. Common examples are maxillary incisors after trauma with complicated, subgingival crown/root fractures or subgingival perforations after endodontic therapy or misaligned attempts of post placement. As bone and soft tissues will extrude vertically with the root, forced eruption has to be combined with hard and soft tissue recontouring in most of the incidences.

It is recommended to restore endodontically treated teeth permanently as soon as possible to reduce the risk of caries reoccurrence around disintegrated temporary fillings with subsequent risk of coronal leakage. In a comparison of 464 endodontically treated teeth with temporary versus permanent restoration, better success rates were demonstrated for definitive restorations [99]. Cast restorations were shown to improve axial contours, restore proper contacts and optimal occlusion, as well as to protect a weakened tooth from horizontal and vertical forces. Aquilino and Caplan [100] investigated the clinical results of 203 teeth in a retrospective study. In their study, endodontically treated teeth without crown coverage were lost at six times the greater rate. The authors suggested initiating the permanent restoration within 7 days after endodontic treatment with at least the definite buildup placed to achieve a significantly higher success rate. Sorensen and Martinoff [101] investigated 1273 endodontically treated teeth from multiple treatment centers retrospectively over a term of 1–25 years and determined the clinical significance of post reinforcement and coronal coverage. Recorded failures included tooth or root fractures and iatrogenic perforations. No significant differences were found for the placement of posts in

the overall population; however, the location of the tooth within arch and whether coronal coverage had been in place was significant for all premolars and molars. In a follow-up study of the identical patient population, the same authors looked at the influence of post placements on the failure rate depending on the type of abutment [102]. The highest failure rate of 24.2% was associated with teeth that had not received full coronal coverage, followed by 22.8% for teeth being abutments in removable partial dentures, and 10.8% in fixed partial dentures. Teeth restored with single crown restorations failed in 5.2%. These differences were statistically significant. The placement of posts was associated with a significantly decreased success rate in single crowns.

While most studies investigated traditional cast restorations, modern adhesive dentistry provides alternative techniques. A long-term investigation of IPS Empress ceramic in and onlays over a period of 8 years demonstrated successful outcomes even with a significant loss of tooth structure [103]. No differences between endodontically treated and vital teeth could be identified. Modern adhesive technologies also allow for buildups and posts bonded to dentin. Composite buildups show high tensile strength, demonstrate fracture resistance comparable to amalgam, allow for immediate placement, and are suitable to be placed under esthetic reconstructions. However, composites may shrink during polymerization, absorb water, undergo plastic deformation under repeated occlusal loads, and are technique sensitive by requiring strict isolation.

Similarly, modern post systems also make use of adhesive systems. In general, it has been recognized that posts do not strengthen the tooth, but classic post preparations weaken the tooth. As the conservation of tooth structure is critical, posts are not necessarily still recommended if sufficient tooth structure remains. The placement of a post is applicable in a situation where less than half of coronal tooth structure is left and two or more walls missing. In these instances, the primary function of a post is the retention of the core buildup. General risks of post placement include iatrogenic errors, such as root perforations or canal over instrumentation regarding length or width. Classic post preparation techniques require a good clinical understanding of anatomy, canal angulation, and root curvatures. Overly long posts, as well as screw posts, are considered obsolete due to the concentration of internal stresses that may weaken the tooth. The placement of one or several bonded glass fiber-reinforced posts in the unaltered shape of the root canal preparation has been advocated instead of prefabricated metal or ceramic posts. Metal posts may result in an increase of root fractures, while ceramic posts may become unremovable in retreatment situations due to the hardness of the ceramic. Fiber-based posts – composite materials of glass fibers or quartz fibers surrounded by a matrix of polymer resin – were shown to be favorable due to the high tensile strength and an elasticity modulus similar to dentin. This is seen as a significant advantage as fiber posts flex under load and distribute stress between post and dentin [104]. Fiber-based posts were effective in reducing the incidence of vertical root fracture although failure thresholds were significantly lower than for conventional cast and posts [105, 106]. Clinical success rated for fiber-based composite posts was shown to be 95% versus 84% with conventional prefabricated core and post systems after 4 years [107].

In the situation of a single compromised tooth that can be kept as a single free-standing unit in an otherwise intact arch, the treatment options are greater than in a complex situation with a comprehensive overall prosthodontic treatment plan, in which extraction of the compromised tooth may be the preferred option to prevent long-term complications [108]. Zitzmann et al. laid out several common clinical scenarios with suggested treatment proceedings. In the esthetic zone with potential for gingival recession or interproximal tissue loss, preservation of the natural tooth is preferred to implant placement. However, if the adjacent teeth are in need of full crown restorations, a conventional fixed partial denture may be favorable to avoid long-term complications with the compromised tooth. If implant placement is required in one or both of

the proximal locations to the compromised tooth, a two- or three-unit implant-supported fixed partial denture on two implants might be a preferred option compared to retaining a questionable tooth next to one or between two implants. Posterior teeth with no or less expectation of esthetic complications may be replaced with less restraint. Questionable teeth should not be included in long-span fixed partial dentures. To avoid long-term complications with the overall reconstruction, root canal-treated teeth require a good prognosis if they are intended to serve in a strategic position within a long-span tooth-supported fixed partial denture [109, 110]. Dental implants can be used to avoid long-span tooth-supported fixed partial dentures by placing additional implants that support single crowns or short-span implant-supported fixed partial dentures. Walton et al. demonstrated a reduction of the overall failure rate of tooth-supported fixed partial dentures from 4 to 2 % after 5–10 years of follow-up after the introduction of implant-supported restorations resulting in less long-span tooth-supported fixed partial dentures [111]. Non-restorable end-standing posterior teeth should preferably be replaced by a dental implant to reduce the increased risk of failure of fixed partial dentures with distal cantilevers [112, 113]. Combined fixed tooth and implant-supported restorations show unfavorable outcome rates and should be avoided [112, 113].

6.3 Comparison of Endodontically Treated Teeth and Dental Implants

A direct comparison of endodontically treated teeth and dental implants is a difficult endeavor. As described above, most endodontic studies used strict success criteria, whereas the majority of implant studies used survival as a basis of evaluation. If tooth retention without symptoms, regardless of the periapical status, is defined as a positive outcome, the survival of endodontically treated teeth is comparable to dental implants. A systematic review and meta-analysis by Iqbal and Kim [31] compared restored endodontically treated teeth with restored single-unit implant restorations. This provided for a unit-to-unit comparison, rather than a flawed comparison of a restored dental implant as a functional unit with the status of the inflammatory disease apical periodontitis. Their meta-analysis included 55 studies investigating dental implants and 13 studies investigating endodontically treated teeth with various follow-up periods. At the earliest point of comparison at 1 year, implant survival was higher at 97.5 % (CI 96.5–9.85 %) compared to tooth survival of 96.9 % (CI 90.5–100 %). This trend showed reversal at long term after 6 years when implant survival had declined to 94.2 % (CI 92.0–96.4 %) and endodontically treated teeth were retained at 97.2 % (CI 94.8–99.6 %). Over all time periods, 95.0 % of implants and 94.0 % of endodontically treated teeth survived.

Another systematic review of the survival of endodontically treated teeth by Ng et al. [114] found pooled proportions of tooth survival over 2–10 years ranging between 86 and 93 %. This systematic review included 14 studies published between 1993 and 2007 that investigated permanently restored as well as unrestored teeth. The authors listed four conditions that had been identified to improve tooth survival significantly. From most to least important, these included crown restoration after endodontic therapy was completed, existing mesial and distal proximal contacts, the tooth not functioning as an abutment for removable or fixed partial dentures, as well as the tooth type regarding anteriors and premolars versus molars. Several other individual studies on tooth survival after endodontic treatment investigated data from health insurance carriers. A total of 1,462,936 teeth with primary endodontic treatment were followed over 8 years by Salehrabi and Rotstein [115]. Of these teeth, 97.0 % survived with the primary endodontic treatment still in place. The remaining 3.0 % were either extracted or received surgical or non-surgical re-treatment. A similar study from Taiwan followed 1,557,547 endodontically treated teeth over a period of 5 years, with a 92.9 % survival rate [116].

A comparison of restored single-unit implants and restored single-unit endodontically treated

teeth from the same study population was published by Doyle et al. [117]. The authors matched 196 single implants with 196 endodontically treated teeth and recalled up to 10 years. Teeth were selected by randomly choosing three potential matches from the university database according to ADA codes of a tooth at the same site as the matching implant. Subsequently, these three endodontic charts were evaluated until a subject met inclusion criteria, such as at a minimum one adjacent tooth or at least 1 year of follow-up. Implants had been placed by oral surgeons, periodontists, or periodontic residents, and the root canal treatments had been performed by endodontists, endodontic residents, or dental students. Success for implants was defined as the implant being functional and present in the mouth at the time of recall without definite signs of absolute failure, such as peri-implant radiolucency or implant mobility. Implant survival was defined as presence in the mouth with either subsequent posttreatment intervention or adjunctive procedures. Implant failure was considered when the implant had been lost or was scheduled for removal. Success, survival, and failure for endodontically treated teeth were based on the PAI [70]. Endodontically treated teeth were labeled success if radiographic and recorded clinical data demonstrated that the tooth was present without clinical symptoms and either no signs or a minimal presence of apical periodontitis (PAI scores 1 and 2). Tooth survival with or without intervention was based on a PAI score ≥ 3. If the tooth had been extracted or was planned for removal, it was recorded as failure. Results demonstrated that the failure rates for dental implants as well as for endodontically treated teeth were identical at 6.1 %. Tooth success was reported at 82.1 %, survival without intervention at 8.2 %, and survival with intervention at 3.6 %. For dental implants, the success rate was 73.5 %, survival without intervention 2.6 %, and survival with intervention 17.9 %. The authors also noted that implant restorations required a longer time to function and to get positive feedback from the patients, as well as presented with a much higher incidence of complications.

6.4 Dental Implant Complications

While both teeth as well as dental implants are good clinical options for patients, it has become evident that implants and in particular implant restorations are more prone to biological and technical complications than teeth. Various large-scale trials and meta-analyses have suggested that there are more complications with implants compared to conventional restorations. Implant prostheses were reported to have a higher complication rate compared to restorations on natural teeth [118]. Berglundh et al. suggested an underestimated incidence of biological and technical complications with dental implants [119]. Pjetursson et al. reported that almost 40 % of patients experienced any complication, including biological, technical, or esthetic [120]. The same authors also demonstrated a declining survival rate of restorations on dental implants in comparison to the actual implant fixtures. They reported that after 5 years 95.4 % and after 10 years 92.8 % of implant fixtures were in function, whereas after 5 years 95.0 %, but after 10 years only 86.7 % of the prosthodontic abutments were still in place. Although implant designs, surfaces, techniques, and restoration types have changed in the past decade, these complication rates have not significantly changed. Recently, Zembic et al. reported incidence rates for technical complications of 11.8 % (95 % CI 8.5–16.3 %) and biologic complications of 6.4 % (95 % CI 3.3–12.0 %) [121]. The authors did not address esthetic complications in their study. Pjetursson et al. stated that although higher survival rates and lower complication rates were reported in more recent clinical studies, the actual incidence rate of esthetic, biologic, and technical complications remained still high [122] (Fig. 6.2).

Mounting evidence also exists for the widespread occurrence of periimplantitis [123–125]. Investigating a random sample of 588 patients out of several thousand implants placed by their study group 9 years earlier, Derks et al. demonstrated the presence of periimplantitis in 45 % of all patients [126]. In a meta-analysis on prevalence, extent, and severity of peri-implant

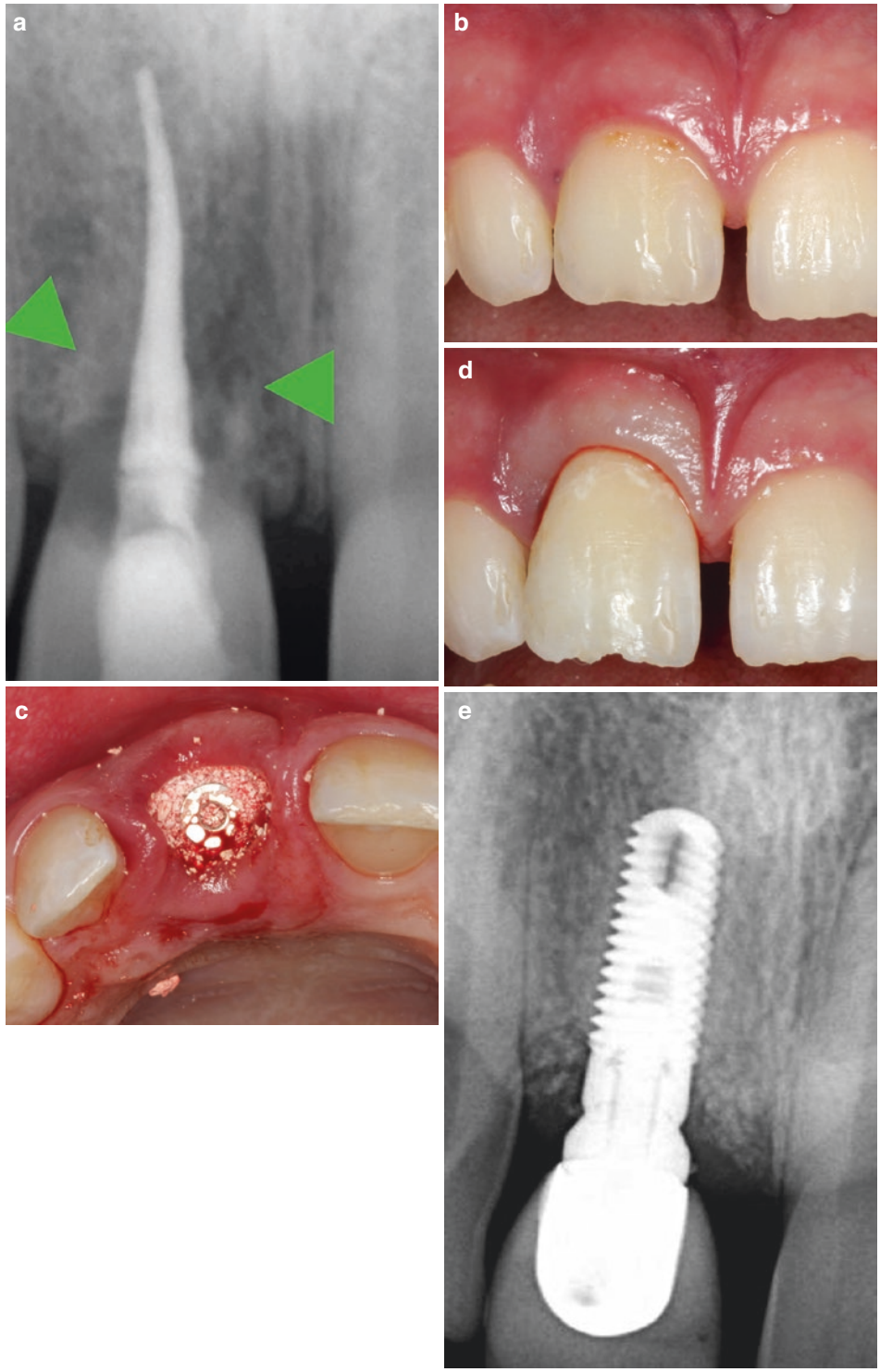
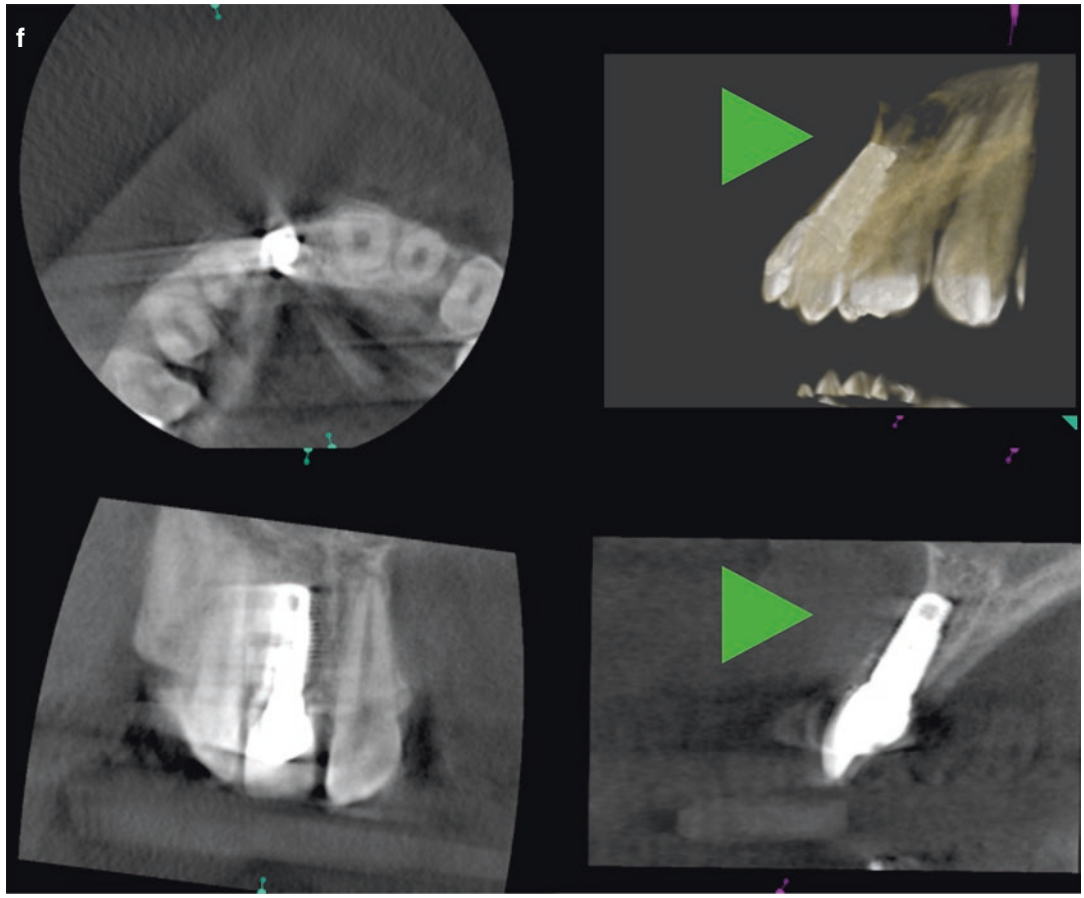


Fig. 6.2 A 22-year-old male patient with history of trauma to right central maxillary incisor. Case demonstrates the complexity and difficulties of implant restorations in the esthetic zone. Despite applying careful treatment planning and thoughtful execution of the clinical procedures, failure of the unit occurred. The mismatch of root versus implant shape and the non-integration of the bone grafting material will result in an extremely difficult situation for repair or replacement of the implant unit due to osseointegration of parts of the fixture, the



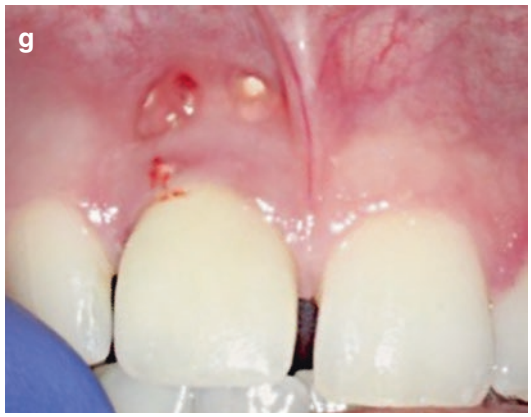


Fig. 6.2 (continued)

foreign body reaction to the grafting material, and possible damage to the gingival architecture after fixture removal and reimplantation. (**a**) Radiograph of endodontically treated tooth, multiple severe root resorptions (*arrows*), tooth was deemed not restorable; (**b**) preoperative clinical situation; (**c**) immediate implant placement with bone grafting; (**d**) temporary restoration after implant placement; (**e**) implant in situ with permanent restoration; (**f**, **g**) 3-year follow-up, CBCT, and clinical situation. CBCT demonstrates perforation of the buccal plate (*arrows*), clinical situation with non-integrated grafting material perforation of the buccal mucosa (Courtesy Dr. Luciano Retana, San José, Costa Rica, and Dr. Joon Park, Scarsdale, NY, USA)

diseases, Derks J. and Tomasi C. included 15 studies and reported peri-implant mucositis in 43 % (536 out of 1196 units, CI 32–54 %) and periimplantitis in 22 % (476 out of 2131 units, CI 14–30 %) of the respective study populations [127]. The authors noted the great impact of peri-implant disease on function time. However, the extent and severity of peri-implant disease were still rarely reported in original studies. Of 122 abstracts fulfilling all other inclusion criteria, the authors had to exclude 95 articles because mucositis or periimplantitis was not reported at all and six additional studies that did not report the actual prevalence of mucositis and periimplantitis or did not base the clinical diagnosis of periimplantitis on clinical signs of inflammation.

Esthetic complications also go frequently unreported. In particular in the esthetic zone, the final outcome is largely dependent on the placement of the implant fixture. This may be compromised by the available hard and soft tissues, the potential necessity of additional augmentative procedures or soft tissue surgery, as well as the clinician's and laboratory technician's skills. A single-unit implant restoration should match the contralateral tooth; however, if handled incorrectly, the esthetic outcome is often compromised by soft tissue recession from unpredictable healing following tooth extraction and implant placement [108]. Incisors have a distinctive undulation of the gingival margin and the cementoenamel junction. This results in long interproximal papillae, the integrity of which relies on healthy periodontal tissues. The gingiva of healthy natural teeth is supported by collagen fibers connected to the root cementum that are orientated in specific dentogingival, dentoperiosteal, circular, and transseptal fiber bundles. Modern dental implants are osseointegrated and are not supported by the periodontal attachment apparatus, as implants lack the cementum that is required for the attachment of collagen fibers as it occurs in natural teeth [128]. Moreover, even among young adults, with osseointegration essentially being equivalent to ankylosis, the natural long-term vertical dimension changes due to super-eruption of anterior maxillary teeth may lead to esthetically undesirable situations if they occur adjacent to single implants [129, 130]. Consequently, in situations with expected compromised esthetic outcome such as in patients with a thin-scalloped periodontal biotype or high esthetic demands, it has been suggested that greater efforts be made to preserve even a questionable anterior tooth to allow for the preservation of the soft tissue architecture [131, 132]. On the other hand, after root canal therapy in the anterior area, brown/reddish or gray discolorations of the clinical crown related to endodontic filling or repair materials are possible if the materials were placed too high in relation to the cementoenamel junction and were not sealed properly. This may compromise the esthetic outcome and indicate bleaching procedures and/or necessitate crown or veneer restorations.

6.5 Operator Training and Skills

A clinician's educational background and clinical training were shown to have a decisive impact on his or her recommendation whether to save a natural tooth or extract it with subsequent implant placement [133]. The study by Su et al. identified factors that demonstrated differences in opinion between professionals of different dental specialties by presenting clinicians with series of computer-generated scenarios where anterior teeth were compromised for different reasons. Various patient-related factors, such as patient's age, periodontal status, root morphology, root length, history of prior endodontic therapy, presence of posts, as well as the size of periapical radiolucencies, were shown to have a significant impact on the decision-making process. However, in agreement with previous studies [134–136], the authors' also demonstrated that the clinician's training significantly influenced the treatment decisions. Examples included the greater confidence of endodontists favoring tooth retention over implant placement in situations where nonsurgical or surgical endodontic therapy was indicated to preserve a tooth, including the treatment of large primary periapical lesions or endodontic re-treatment with or without the presence of a post [133].

The impact of the operator's training and experience was also demonstrated for the long-term outcome of endodontically treated teeth as well as dental implants. In a multicenter study, the difference in survival of 350 endodontically treated teeth after a 5-year follow-up was only 89.7 % after treatment by general dentists compared to 98.1 % if the treatment was rendered by an endodontist [137]. Dental implants are no longer an exclusive treatment alternative, but also increasingly being placed and restored by general practitioners with limited training. The impact of this development in general dentistry was assessed by Morris and Ochi, who compared the survival of dental implants placed by general dentists with limited experience and a history of infrequent implant therapy with the survival of units placed by implant specialists [41]. After 3 years of follow-up, 73.0 % of implants placed by general dentists and 95.5 % by specialized dentist were still in function.

Conclusion

Many clinicians face the decision of saving a tooth or extracting it with subsequent replacement by a dental implant on a daily basis. Although this may often seem to be a straightforward decision, treatment planning arguably has become more complex with the availability of dental implants. The preservation of teeth with endodontic therapy and an appropriate permanent restoration as well as implant restorations are both excellent and predictable treatment options for the preservation of oral health and the preservation of the patient's dentition. Outcome rates for both therapies have proven to be above 90 %, although recent data has demonstrated that the long-term prognosis of teeth may be better than that of dental implants. Inarguably, however, a dental implant is the gold standard of replacing a missing tooth.

Nevertheless, the topic of preservation versus replacement has been hotly debated in the past decade [138]. To complicate the issue, treatment planning of complex cases can often hardly be based on evidence due to the multifactorial nature of the clinical situation and the patient's medical and dental history. Hence, factors associated with the patient, the individual teeth, as well as the clinician may all play a role in deciding for the best possible and the preferred treatment. In regard to the patient, these may include age, medical history, current or past medications, social history such as smoking or drinking habits, past dental history, esthetic concerns or preferences, and finances [133]. Concerning the oral situation, the entire remaining dentition and the immediately adjacent teeth need to be part of the treatment planning process [110, 139].

For the individual tooth, periodontal condition, endodontic status, root morphology, remaining tooth structure, caries, the condition of the adjacent teeth and the opposing arch, the occlusion, and esthetic parameters are of concern [133]. If in the long term a tooth is potentially compromised for endodontic, periodontal, or prosthodontic reasons, it has to be considered that multiple risk factors may accumulate and increase the risk of long-term failure. As an example, surgical crown lengthening for a tooth that is already compromised by a large post preparation and also demonstrates a poor crown-to-root ratio may be at a higher risk for failure, and replacement rather than preservation may be indicated [110]. The added complexity of any additional adjunctive procedure may result in further complications and higher associated risks [140]. According to Torabinejad and Goodacre, added procedures also increase treatment costs and may compromise a patient's willingness to accept endodontic treatment and tooth preservation.

Nevertheless, a missing tooth is irreversibly gone, and tooth extraction should be only considered after worthwhile deliberation [3]. No lifetime guarantee can be given for either a natural tooth or a dental implant. With the increasing concerns regarding biological, technical, and esthetic complications associated with dental implants, the past exuberance of extraction and implant placement has been overshadowed by the recent evidence of long-term problems and a reduced life expectancy

of dental implants compared to natural teeth. A new critical analysis has recently taken place in particular from leaders in the field of periodontics and implant dentistry, suggesting to go back to saving teeth. In their editors' comment, Giannobile and Lang criticized that in many scenarios patients were advised the extraction of compromised tooth in favor of the "newer, better" implant (sic!), that the erroneous belief of a better long-term prognosis of dental implants compared to natural teeth has now been clearly rejected by various comparative studies, and called to action to revisit the long history of successful tooth maintenance for the preservation of the natural dentition [141]. In regard to the long-term success of implant, Lindhe stated that while most implants function without any problem, dental implant loss, failure, or complications are expected as much as for any other replacement part in the body [142]. He also concluded that while many dentists find it easy to remove a tooth and replace by an implant, it is done at the expense of evidence-based therapy of treating a tooth for its conditions and that an overuse of implants and an underuse of teeth as targets for treatment have been taken place.

Economic forces and market strategies have resulted in an ongoing commercialization of clinical practice and have left an undeniable mark on dentistry [3]. Dental education must not be dominated by companies, but delivered by educators or experienced clinicians. If fewer cases are handled or situations are complex, treatment by a specialist is advised, otherwise, an increasing number of implant or endodontic complications and failures may be the result [3].

Both options, preservation of the natural tooth and implant (re)placement, should be seen as complementary and not as competing procedures [31]. The overall goal in dentistry must be to provide long-term health and benefit of the patient, to be minimally invasive, and to incorporate function, comfort, and esthetics [3]. Thus, it is important for clinicians to be fully aware of the true long-term outcome of both implants and endodontically treated teeth [3]. However, the prognosis of either treatment outcome cannot be the sole decision-making factor, as outlined above, a complex array of factors must be considered during treatment planning. Nonsurgical or surgical endodontic therapy followed by an appropriate restoration is an excellent and predictable treatment option for the retention of compromised teeth. Treatment alternatives, such as dental implants or replacement by a fixed partial denture, are viable scenarios. However, priority should be given to preserving the natural dentition rather than extraction and replacement.

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7 Case Selection for the Use of Cone Beam Computed Tomography in Dentistry Based on Diagnostic Efficacy and Risk Assessment

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Abstract

Case selection for cone beam computed tomography (CBCT) for dental purposes is primarily based on individual risk-benefit assessment, balancing between the long-term radiation risks of CBCT and its ultimate benefit for each individual patient. Based on the currently available literature, the expected ultimate benefit to the patient, as evaluated by the level of diagnostic efficacy of CBCT in dentistry, is yet unclear, and it is mainly limited to its technical and the diagnostic accuracy efficacies. Even for these levels of efficacy, evidence is incomplete. Therefore, the efficacy of CBCT in supporting the practitioner's decision making, the treatment planning, and eventually in affecting treatment outcomes is not fully elucidated. On the other hand, the potential radiation risks of CBCT scan are uncertain and are stochastic in nature, thus requiring a preventive clinical approach. Consequently, cautious decision making is warranted when a CBCT scan is considered. This chapter reviews the current literature concerning the benefits of CBCT in dental practice, alongside its risks in this use, and presents a practical case-selection algorithm for the use of CBCT in dentistry.

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7.1 Introduction

Cone beam computed tomography (CBCT) was introduced in the late 1990s to construct three-dimensional scans of the maxillofacial region at a reduced radiation dose compared to the conventional CT [1–11] and has become a popular diagnostic technique in dentistry [1, 2, 12]. Although

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the effective radiation dose of CBCT scans is indeed reduced compared to multi-slice computed tomography (MSCT), it is still significantly higher than intraoral radiography or panoramic radiography [12, 13]. In addition, the long-term health risks of CBCT use in dentistry are unclear [2, 14–18]. It is therefore an acceptable practice that every effort should be made to reduce the overall effective radiation dose to the dental patient [2, 4, 12].

In recent years there has been a debate whether CBCT should be used as a standard preoperative imaging modality in dentistry [5–11, 19–23]. For example, it was stated in the American Association of Endodontists (AAE) and the American Academy of Oral and Maxillofacial Radiology (AAOMR) joint position statements from 2010 [2] and from 2015 [1] that CBCT should not be used routinely for endodontic diagnosis or for screening purposes in the absence of clinical signs and symptoms [1, 2]. However, the exact criteria for using CBCT for endodontic purposes are not sufficiently clear [2, 24–27], and the latest published data demonstrate that CBCT is being used also for routine endodontic purposes, such as preoperative evaluation of root canal system anatomy [28, 29], determination of root canal working length [30–33], identification of a healthy periapical tissue, or diagnosing vital teeth with irreversible pulpitis [12, 34, 35]. The increased usage rates of CBCT in dental practices, along with its unknown long-term health risks, present a significant long-term health concern [2, 4, 12, 36–38].

The decision to perform a CBCT scan must be justified on an individual basis by demonstrating that the benefits to the patient outweigh the potential radiation exposure risks [1, 2, 39]. Therefore, the case selection of CBCT is primarily a question of risk-benefit assessment [2, 12, 39]. These potential benefits to the patient should be largely based on the efficacy of the CBCT as a diagnostic imaging modality for each specific dental evaluation [2, 12, 39–41].

Diagnostic efficacy may be defined as "the probability of benefit to individuals from a system or test under ideal conditions of use" [12, 42]. A shallow view of the efficacy of diagnostic imaging would be that it should provide images of sufficient quality for diagnostic purposes that it was intended for [40, 41]. However, a more comprehensive point of view is required in order to evaluate the ultimate benefit of an imaging modality to an efficient and effective treatment of a patient [40, 41].

This comprehensive point of view on the efficacy of an imaging modality involves parameters that are beyond the technical characteristics and the accuracy of the imaging modality [12, 41, 42]. It should include also additional higher levels of efficacy evaluation such as the efficacy of this modality to support the practitioner's decision making and treatment planning and eventually to improve the treatment outcome [12, 41, 43].

This chapter reviews the current literature concerning the benefits of CBCT in dental practice, alongside its risks in this use, and presents a case-selection algorithm for the use of CBCT in dentistry.

7.2 The Potential Benefits

It has been stated that CBCT should be considered for diagnosis only if a review of the patient's health and imaging history together with a meticulous clinical examination lead to a conclusion that CBCT may significantly contribute to achieve an accurate and consistent diagnosis [2, 19, 39, 44, 45]. However, the need to achieve an accurate diagnosis is not the only factor that should be considered for adequate case selection – it is prudent that the decision to use CBCT be justified by demonstrating that the ultimate benefits to that particular patient outweigh the potential risks of radiation exposure [2, 12, 39].

The expected ultimate benefits of CBCT to the patient may be evaluated by levels of diagnostic efficacy. The diagnostic efficacy hierarchical model presented by Fryback and Thornbury [41] is a comprehensive tool for appraisal of the literature on efficacy of a diagnostic imaging modality [12]. It is comprised of six levels of imaging efficacy that include not only the technical characteristics of the imaging modality but also the

efficacy of this modality to support the practitioner's decision making and treatment planning and to eventually improve treatment outcome [12, 41, 43].

This model [40, 41] includes the following efficacy levels (in a hierarchical order, from the lowest to the highest efficacy level):

The *technical efficacy* – the technical quality of the images

The *diagnostic accuracy efficacy* – the diagnostic accuracy associated with interpretation of the images

The *diagnostic thinking efficacy* – the effect of the obtained radiographic information on clinician's estimate of the probability that a patient suffers from a disease or health condition

The *therapeutic efficacy* – the effects of the radiographic information on the patient's management plan

The *patient outcome efficacy* – the effect of the obtained radiographic information on patient's outcomes

The *societal efficacy* – the impact of the imaging modality on society as a whole [12]

This model is aimed to draw conclusions regarding the diagnostic efficacy of any imaging modality based on the currently available literature, and it has been used in recent years in dental research to evaluate the diagnostic efficacies of CBCT [12, 20, 21, 23, 40].

Numerous studies have been published on the applications of CBCT in dentistry, and the significant variability in their study designs generated inconsistent and confusing results [4–11, 13, 24, 25, 27–35, 45–47]. Evidence-based dentistry (EBD) is an approach to oral healthcare that integrates the best available clinical evidence to support a practitioner's clinical expertise for each patient's treatment needs and preferences [48–50]. Therefore, systematic reviews, which constitute the foundations of EBD, are of utmost importance in the evaluation of the diagnostic efficacy of CBCT in dentistry [48, 50, 51].

A recent systematic review [20] evaluated the evidence for the diagnostic efficacy of 3-D cephalometry in orthodontics and concluded that the current evidence for it is limited. In this systematic review, only six studies met the criteria for a moderate level of evidence, stressing the need for methodologically standardized studies on a 3-D cephalometric analysis [20].

Another study [21] evaluated the available clinical research and diagnostic efficacy studies in the oral and maxillofacial radiology literature and concluded that the current literature consists mostly of case reports, case series, and cross-sectional studies, assessing mostly technical efficacy and diagnostic accuracy [21]. In this review the authors stated that "such studies do not provide strong evidence for clinical decision making nor do they address the impact of diagnostic imaging on patient care" and that "more studies at the higher end of the study design and efficacy hierarchies are needed in order to make wise choices regarding clinical decisions and resource allocations" [21].

Another recently published study [43] evaluated the efficacy of CBCT for assessment of mandibular third molars using the hierarchical model by Fryback and Thornbury [41] and reported that only few high-evidence studies on the efficacy of CBCT for radiographic examination of mandibular third molars currently exist [43]. They stated that "periapical or panoramic examination is sufficient in most cases before removal of mandibular third molars. However, CBCT may be suggested when one or more signs for a close contact between the tooth and the canal are present in the two-dimensional image – if it is believed that CBCT will change the treatment or the treatment outcome for the patient" [43] (Fig. 7.1).

In a recent study [12], a systematic review of the literature was performed to identify and analyze studies evaluating the use of CBCT in endodontics. Initially 485 possible relevant articles were identified. However, following the application of strict inclusion criteria, only 58 articles (12%) met the inclusion criteria and were analyzed and allocated to levels of efficacy according to the Fryback and Thornbury model [41]. Most eligible articles ($n=52$, 90%) evaluated technical characteristics or the accuracy of

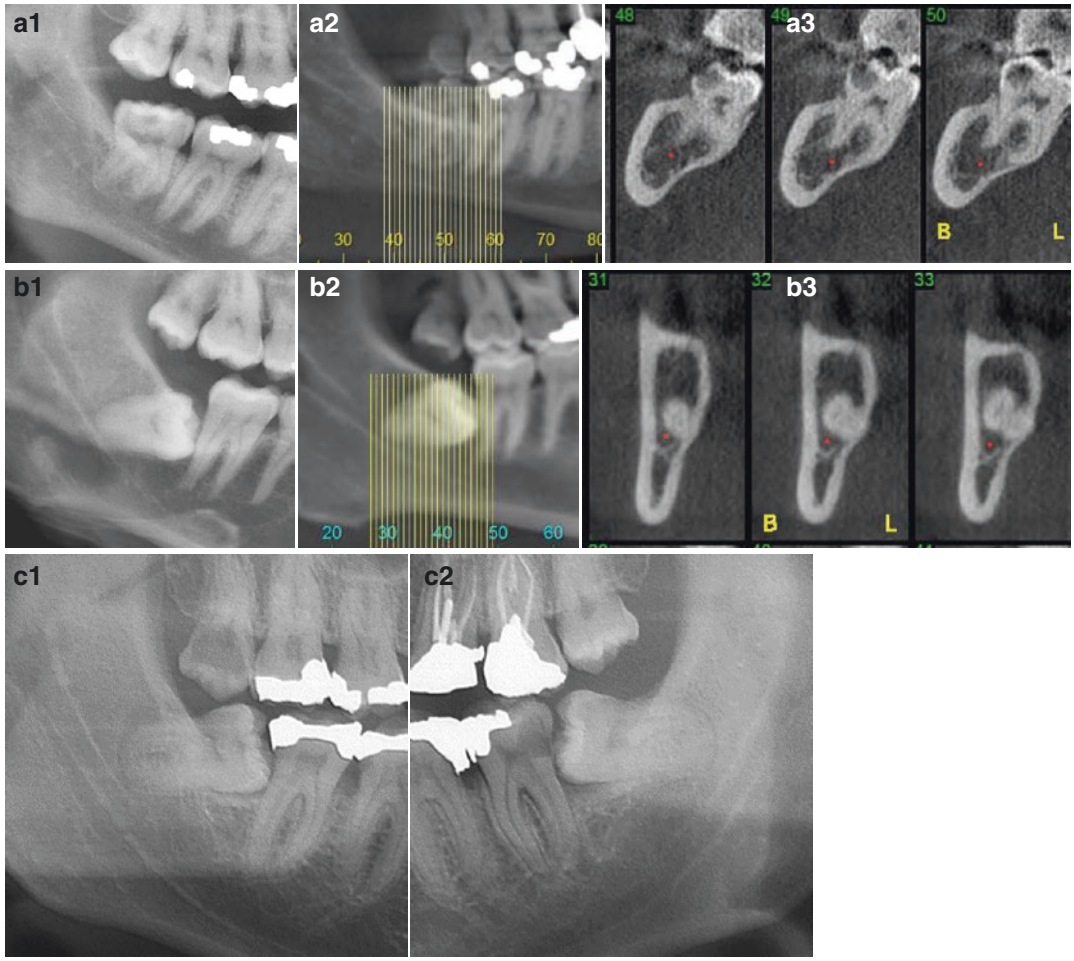

Fig. 7.1 (**a**–**c**) Presents three cases of assessment of mandibular third molars that are planned to be extracted. (**a**) The right mandibular third molar was scheduled for extraction. The initial panoramic radiograph (*a1*) was not sufficient in order to plan the procedure, and therefore CBCT evaluation was performed (*a2*, *a3*). (**b**) The right mandibular third molar was scheduled for extraction. The initial panoramic radiograph (*b1*) was not sufficient in order to plan the procedure, and therefore CBCT evaluation was performed (*b2*, *b3*). (**c**) The *left* (*c2*) and the *right* (*c1*) mandibular third molars were scheduled for extraction. The panoramic radiograph was sufficient in order to plan the procedures. Therefore, CBCT was not performed

CBCT, defined in this model as low levels of efficacy [41]. Only six articles (10%) proclaimed to evaluate the efficacy of CBCT to support the practitioner's decision making and treatment planning and ultimately to affect the treatment outcome, defined as higher levels of efficacy. They concluded that the expected ultimate benefit of CBCT to the endodontic patient as evaluated by its level of diagnostic efficacy is yet unclear and is mainly limited to its technical and diagnostic accuracy efficacies. They therefore concluded that a cautious and rational approach is advised when considering CBCT for endodontic purposes [12] (Fig. 7.2).

A comprehensive systematic review of the entire dental literature [40] assessed the risks and benefits of CBCT in dentistry. In that systematic review, it was reported that the understanding of CBCT's diagnostic efficacy in dentistry was largely limited to the first two lower levels of

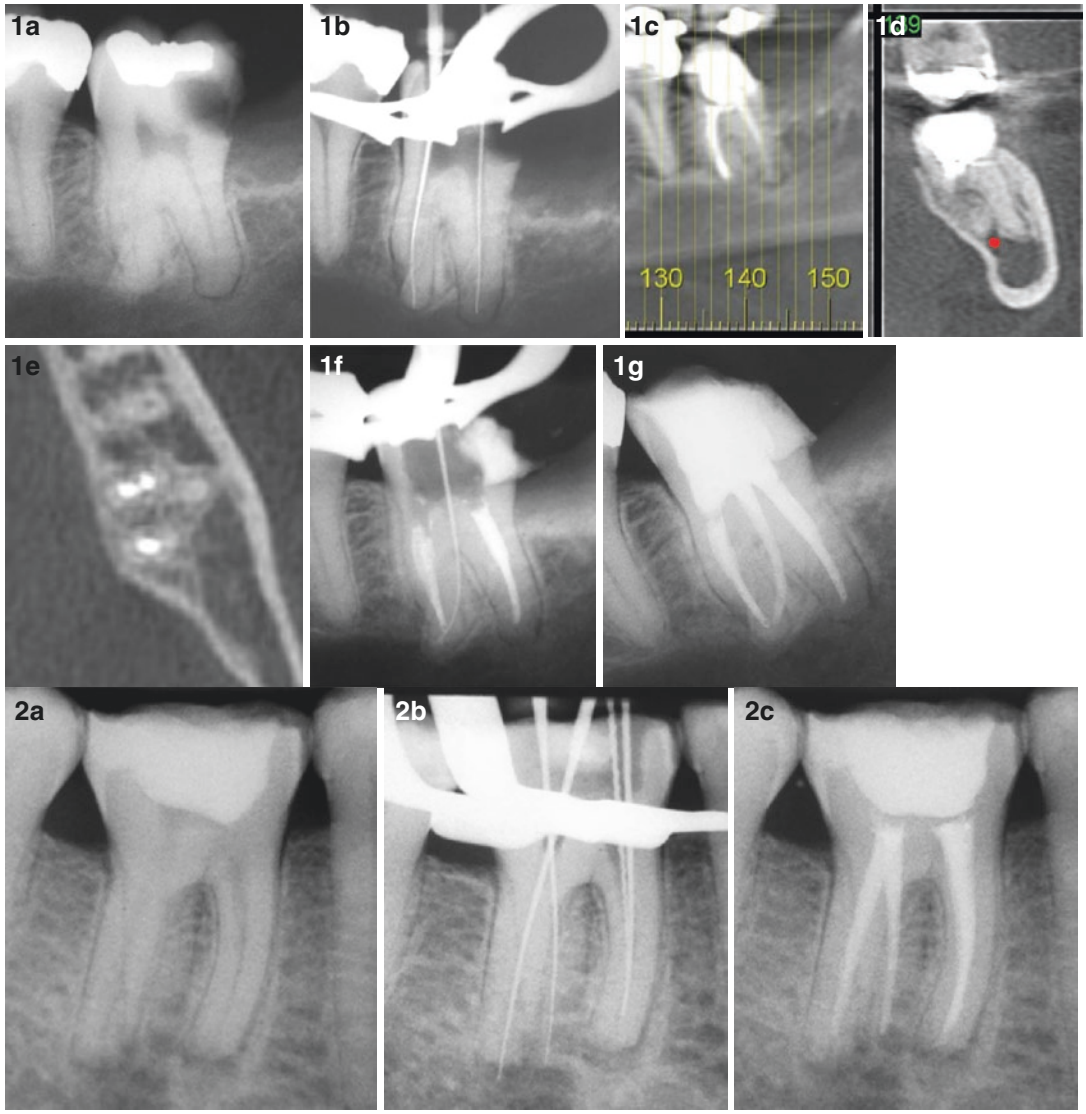

Fig. 7.2 Case selection of CBCT for the diagnosis and treatment of teeth with complex anatomy: two comparable cases of an additional third root in mandibular molar teeth scheduled for root canal treatment are presented. In case #1 CBCT was indicated, and in case #2 CBCT was not indicated. **Case #1a–1g** A lower second mandibular molar with an additional third root was scheduled for endodontic treatment. However, preoperative (**1a**) and intraoperative (**1b**) periapical Rx's, together with a thorough inspection by surgical operation microscope during the treatment did not provide sufficient information to locate the additional root. The patient was referred to CBCT that confirmed the presence and location of the additional third root (**1c**–**1e**). This root was endodontically treated (**1f**, **1g**). **Case #2a–2c** A lower first mandibular molar with an additional third root was scheduled for endodontic treatment. Preoperative (**2a**) and intraoperative (**2b**) periapical Rx's, together with a thorough inspection by surgical operation microscope during the treatment provided sufficient information to locate and endodontically treat the additional root (**2c**). Therefore, in this case CBCT was not indicated

efficacy (i.e., the technical and diagnostic accuracy efficacies) and that even for these, knowledge is incomplete. In this review only a few publications were identified which addressed higher levels of diagnostic efficacy [40, 41]. The authors concluded [40] that "development of guidelines with high evidence grades was precluded" and that it also "highlights the need for

clinical trials which will provide information on higher level efficacies, notably patient outcome efficacy"[40].

It is therefore evident that the current dental literature assessing the efficacy of CBCT as a diagnostic imaging modality is limited to the lower levels of efficacy, specifically to the technical characteristics, or to the accuracy of the imaging modality [40, 41]. These low levels of efficacy may be a prime interest for some clinicians; however, they provide only a partial view of the potential ultimate benefit of CBCT to patients [12, 40, 41]. Since the ultimate goal of medical diagnosis is to treat patients effectively and efficiently, only higher levels of diagnostic efficacies (e.g., therapeutic efficacy, patient outcome efficacy, and societal efficacy, defined as levels 4–6 of efficacies) are capable to provide a comprehensive view of the ultimate benefit of the modality to patients or to the society as a whole [12, 40, 41].

In this context, a high-quality imaging modality such as CBCT may be ineffective in certain instances, while an imaging modality of a lesser quality such as intraoral radiography may be of significant value in certain instances [12, 40, 41]. In addition, in order for an imaging modality to be considered efficacious at a higher level in this hierarchical model of diagnostic efficacy (e.g., therapeutic efficacy and patient outcome efficacy), it must be efficacious at lower levels, but not the other way around. In addition, improvements in the efficacy at a lower level (e.g., technical efficacy) will not guarantee an ensuing improvement at the higher efficacy levels (e.g., patient outcome efficacy) [12, 41, 42].

This asymmetry is often not well understood in dental research reports dealing with diagnostic efficacy levels 1 and 2 (e.g., technical efficacy) [40, 41], in which an improvement in some technical characteristics of CBCT or in its accuracy in a certain clinical scenario may incorrectly lead to a conclusion that these new findings also guarantee an improvement in higher levels of efficacy (e.g., the patient outcome) and in the expected ultimate benefit to the patient. It also highlights the need for additional clinical trials which will provide information on higher level efficacies, especially regarding patient outcome efficacy [12, 40].

Adequate professional standards for performing CBCT imaging in a certain patient should be based on selection criteria derived from the best available evidence [22]. However, the current available dental literature provides a very limited view on the ultimate benefit of CBCT to patients. In conclusion, as recently stated: "in this expanding era of CBCT imaging in dentistry, the apparent urgency of adopting glittering new technology should be balanced with diligent discovery and patience"[22].

7.3 The Potential Risks

In general, CBCT produces a higher radiation dose than traditional intraoral radiography, but less than that produced during a multi-detector CT scan [39]. However, the comparison of radiation doses by itself is too simplistic, as aside from the physical properties of the CBCT machine, estimation of radiation health effects requires an understanding of the nature of the X-ray radiation and its tissue effects and should also take into consideration a variety of other parameters such as the scanning parameters, the patient demographics, and the nature of the exposed tissues and organs [12, 13].

Diagnostic X-ray is an electromagnetic (EM) ionizing radiation with a small wavelength, deep penetration, and high energy transfer capabilities [4, 13, 39, 40, 52] that potentially may cause tissue damage and specifically DNA damage leading to chromosomal mutations and ensuing formation of malignancy [40]. These ionizing effects have no threshold radiation dose and are considered as "chance" ("stochastic") effects, making the distinction between "harmless" and "dangerous" exposures to radiation impractical [4, 13, 39, 40, 52]. Thus, any exposure to X-rays should not be considered as risk-free [4, 12, 13, 39, 40, 52].

The effective dose of CBCT scans, which takes into consideration also the specific radiosensitivity of the evaluated tissues [40], varies among scanners and depends on both clinical parameters such as the region of the jaw being scanned and on acquisition parameters, such as

the field-of-view (FOV) dimensions, exposure time, and the tube electric current and potential [13]. A recent meta-analysis of the literature [53] analyzed the reported effective dose estimations of dental CBCT examinations and found large variations: the reported adult-effective doses ranged from 46 to 1073 μSv for large FOVs, between 9 and 560 μSv for medium FOVs, and between 5 and 652 μSv for small FOVs. The reported child-effective doses ranged from 13 to 769 μSv for large or medium FOVs and from 7 to 521 μSv for small FOVs. They concluded that "large exposure ranges make CBCT doses difficult to generalize" [53].

In addition, the radiation damage experienced by an exposed group and its descendants is gender and age dependent [36–38, 40]. At all ages, the reported risks for females are slightly higher than for males [13]. It has been reported that the risk is tripled in children under 10 years old in relation to the risk at age 30 [40]. Children's cancer risk per unit dose of ionizing radiation is higher than adults, and they have a longer lifetime risk of developing radiation-induced cancers [2, 17, 39]. Therefore, additional strict considerations should be weighted prior to the exposure of children to CBCT scanning [36–38].

Radiation risk management is the assessment of future-associated health risks, including the effect of uncertainty, followed by efforts to minimize the probability and impact of these suspected adverse effects [36–38, 54]. CBCT radiation risk management requires a combination of two principles: *justification*, defined as "doing more good than harm to the patient," and *optimization* based on the "ALARA" principle – as low as reasonably achievable, meaning to obtain the necessary diagnostic information using the lowest radiation dose that can be reasonably achieved [40]. However, the uncertain long-term and stochastic nature of radiation risks requires a preventive clinical approach [2, 13, 39, 54], which may not always be easy to implement [12, 36–38].

The traditional nonpreventive approach to health hazards, *late lessons from early warnings* [55], is described as delayed learning from historical early worrying events [55]. A historical medical example of this approach is the story of asbestos: in 1898, Lucy Deane, a United Kingdom (UK) industrial inspector, observed and reported about *the evil effects of asbestos dust* [55]. However, only in 1998 the UK government, followed by the European Union (EU), decided to ban the use of asbestos [55], and current future estimates suggest that the number of asbestos-related fatalities in Western Europe would reach about a quarter of a million over the next 35 years [56]. This devastating outcome is an example to a misuse of the concept of precaution when dealing with a potential health hazard and to the need to adopt a modern preventive approach [55].

In this context, preventing long-term health hazards sometimes requires acting before there is an established proof of harm [55]. The *precautionary principle* represents a modern preventive approach to health hazards that can be defined as a "better safe than sorry approach suggesting that action should be taken to avoid harm even when it is not certain to occur"[57]. However, this preventive approach may be especially difficult to implement when the impacts of the potential health hazard are far into the future and the immediate perceived benefits from avoiding current preventive measures are significant [12, 55–58].

In the context of CBCT imaging, the potential immediate benefit to the individual patient from the use of CBCT imaging in dental practice may be perceived as substantial [2, 12, 59]. However, the relatively high radiation doses associated with CBCT compared to conventional radiography [13] still raise long-term health concerns especially regarding a potential increase in the risk of malignancy and especially in children [2, 14–18, 26, 36–38, 60]. Furthermore, the adverse effects of the CBCT radiation exposure may not be seen until years after the actual exposure [2, 13–18, 36–38]. Thus, implementing the precautionary principle in the decision making when considering a CBCT scan for dental purposes is prudent [2, 12, 55, 57].

With the growing popularity of CBCT technologies among dental practitioners [2, 13], concerns have also been expressed about the level of

training, education, and experience required to interpret the CBCT data [39]. In addition to CBCT data on the region of interest, CBCT scans usually include additional adjacent anatomical structures that are usually not visible in the FOV of routine intraoral radiographs, and the practitioner who performs a CBCT study is obligated to systematically examine the entire CBCT image data and report on any anatomical abnormalities or pathological conditions observed [2, 39, 40, 61]. However, this diagnostic obligation requires a comprehensive radiology knowledge of head and neck anatomy and pathology that may be beyond the dental practitioner qualifications, thus subjecting the patient to risks of undiagnosed or misdiagnosed pathological conditions and the practitioner to an ensuing medicolegal liability risk [54, 61].

7.4 Case Selection Algorithm for the Use of CBCT in Dental Practice: Benefit Versus Risk

The potential benefits to the patient as judged by the imaging diagnostic efficacy of CBCT should be weighed against the potential radiation risks to that particular patient by applying the precautionary principle to eliminate the uncertainty regarding the long-term health concerns of the radiation exposure. This process must be evidence based [12, 48, 51, 54]. Dental practitioners must stay scientifically updated with the ongoing research and development of the CBCT technology, and with the associated potential long-term radiation risks [14–17, 36–38, 40, 55, 60], and apply an evidence-based approach in case selection for performing CBCT [12, 39, 49].

When the decision whether to use CBCT is not based on solid systematic evidence-based foundations, it may lead to misuse or overuse of CBCT, exposing the patient to unnecessary radiation risks without any clinical justification [13, 39]. As an example, it became acceptable and common to use CBCT for the diagnosis of vertical root fractures (VRF), a complex endodontic condition [62], assuming that CBCT is clinically effective for this purpose and that it possesses superior efficacy over conventional radiography [26, 46, 63–76]. Nevertheless, recent published data, including a recent meta-analysis of the literature [25], raises a concern regarding the alleged superiority of CBCT over conventional intraoral radiography for the detection of VRF [24, 25, 27], especially in the presence of metal posts [27]. The exact extent of CBCT scans performed for the diagnosis of VRF is unknown, but is clearly extensive [26]. However, the limited evidence raises a significant concern regarding its clinical effectiveness for the diagnosis of VRFs [12, 13, 24, 25, 27, 39], regarding its superiority over alternative lower-dose conventional dental radiography modalities [13, 24, 25, 27, 39], and regarding its potential ultimate benefit to the patient compared to its potential radiation risks [2, 14–18, 26, 60].

A number of position statements [1, 2, 39] suggested several clinical scenarios when CBCT may be indicated. However, according to the currently available scientific literature on the diagnostic efficacy of CBCT in dentistry, these recommendations are not well supported by a high level of efficacy evaluation [40]. In addition, the caution that is required due to the associated radiation risks of CBCT is commonly presented without a thorough explanation and without adequate implementation of the precautionary principle in light of the uncertainty regarding its possible unknown long-term health risks [12]. Therefore, it is recommended that the selection of patients to be referred to CBCT should be based on an assessment of the need for additional imaging, the benefit of CBCT in that clinical scenario, and the risks of performing CBCT to that particular patient as follows:

Need Assessment: Assessment whether the patient's anamnesis, clinical examination, and lower-dose conventional dental radiography are sufficient or not for the specific diagnostic process

Benefit Assessment: Assessment whether the diagnostic efficacy of CBCT is scientifically established, not only for the technical characteristics of the CBCT but also for the efficacy of CBCT to improve the practitioner's decision

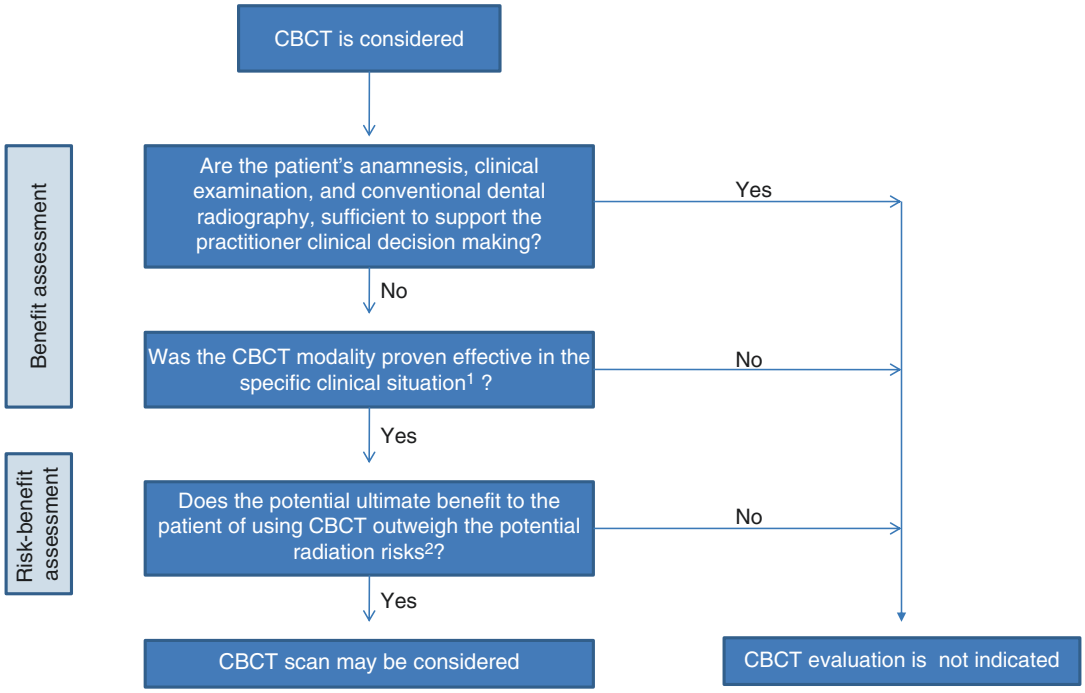

Fig. 7.3 Case selection algorithm for CBCT scan in dentistry.[1] The diagnostic efficacy of CBCT for the specific clinical situation is scientifically supported not only for the technical characteristics of the CBCT but also for the efficacy of CBCT to support the practitioner's decision making, the treatment planning, and ultimately the treatment outcome, in that particular clinical scenario.[2] The potential radiation risks to the particular patient should be assessed by applying the precautionary principle, considering the uncertainty regarding the long-term health concerns of exposure to radiation

making and treatment planning and ultimately the treatment outcomes

Benefit Versus Risk Assessment: Assessment whether the potential ultimate benefit to the patient of using CBCT outweighs the potential radiation risks to the particular patient, assessed with the precautionary principle regarding the long-term health concerns of exposure to radiation

The application of these criteria in the case selection for CBCT will ensure the efficient and cautious use of CBCT in dentistry (Fig. 7.3).

Conclusions

The selection of cases requiring CBCT in dentistry is primarily based on a risk-benefit assessment. The expected ultimate benefit to the patient, as evaluated by the level of diagnostic efficacy of CBCT in dentistry, is not fully elucidated, and it is mainly limited to its technical and the diagnostic accuracy efficacies. Even for these levels of efficacy, evidence is incomplete. On the other hand, the potential radiation risks of CBCT scan are uncertain and stochastic in nature, thus requiring the implementation of the precautionary principle by a preventive clinical approach. Based on these principles, a practical algorithm for the use of CBCT in dentistry is proposed (Fig. 7.3).

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8 Evolving New Strategies for Periodontal, Endodontic, and Alveolar Bone Regeneration

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8.1 Tooth-Associated and Implant-Associated Loss of Support

The continuous presence of bacteria at the tooth-epithelium or implant-epithelium junction results in a progressive inflammatory process, which leads to the destruction of the gingival connective tissue and subsequently of the alveolar bone, periodontal ligament (PDL), and cementum on the root surface. This process, when left undisturbed, will lead eventually to the loss of the involved tooth or implant. Not only is this loss of periodontal support detrimental to the stability and function of the tooth or implant, it also hampers the restoration of the diseased area with implants following the removal of the ailing tooth/implant. Therefore, the clinical art of periodontology has been paying a tremendous amount of attention to periodontal regeneration.

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8.2 Current and Future Periodontal and Bone Regenerative Treatments

This chapter describes evolving experimental approaches that are geared toward periodontal/bone regeneration. Currently, the pinnacle of regenerative periodontal treatment is the use of bone substitutes combined with barrier membranes, which already demonstrates how far we have progressed from the old resective approaches that dominated the field. Thus, the focus of the clinical repertoire shifted from a purely surgical to biologically oriented treatment of the detrimental effects of periodontal disease.

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8.3 Tissue Engineering

Tissue engineering (often referred to as regenerative medicine) is a rapidly evolving multidisciplinary research and treatment field, aimed at reconstructing and regenerating lost tissues, using a combination of biological, medical, and biomechanical (engineering) tools. The ultimate goal of tissue engineering procedures is to restore tissue mass, integrity, and function, thus improving the health of the host.

In general, the ability to rebuild lost tissues relies on the three key elements of tissue engineering (Fig. 8.1):

8.3.1 Scaffolds (Matrices), Signaling Molecules (Biologics), and Cells [1]

Scaffolds, in the form of implantable biomaterials, are necessary for several functions, namely, maintenance of the space in which the tissue is to be grown, guidance (conduction) of host or donor cells into that space, assistance in restoring blood supply to the defect area, and potential delivery of signaling molecules into the regenerating site. The most common scaffolds are either naturally occurring molecules (such as collagen, hyaluronic acid, demineralized and mineralized bone particles), synthetic polymers (like polylactic/polyglycolic acid (PLGA), polypropylene fumarate, and others), or calcium-based particles (calcium phosphate, calcium sulfate, etc.). Whatever their formulation, these biomaterials must be biocompatible, biodegradable, and porous if possible with sufficient biomechanical properties. Classically, these are divided into the following categories: autografts, allografts, xenografts, and alloplasts.

Signaling molecules usually belong to the family of growth and differentiation factors, capable of inducing proliferation and/or differentiation of local primitive cells into mature cells of the desired tissue. They can be delivered into the regenerating site either as recombinant proteins (which is the most common form that have been

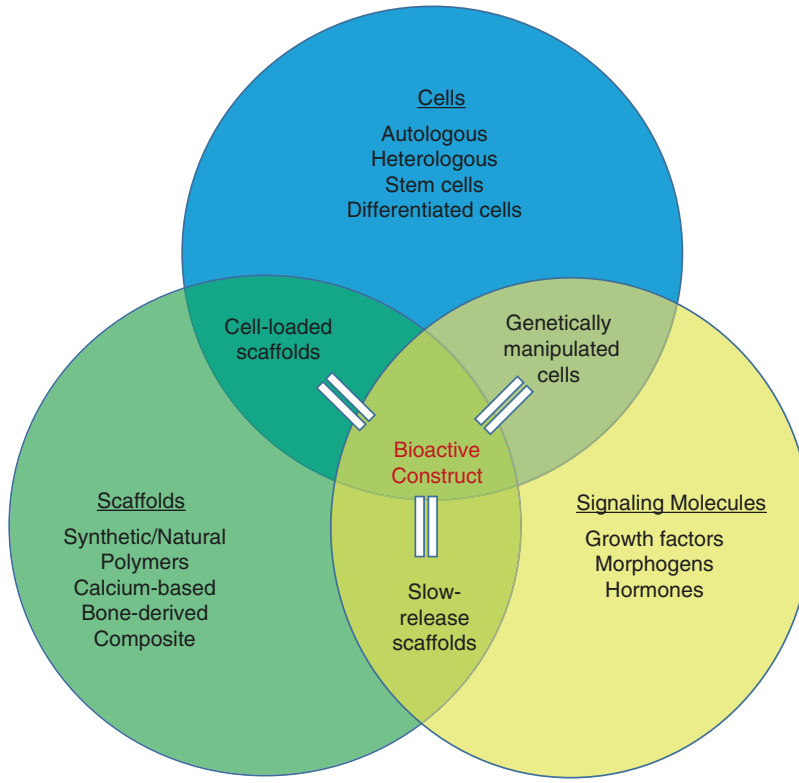

Fig. 8.1 The three key elements of tissue engineering and their combinations

tested to date) (i.e., *protein/peptide therapy*), as the respective gene (i.e., *gene therapy*) in a vector (viral or other) that will induce host cells to produce that protein, or in the form of cells that have been engineered in vitro to produce the desired protein and are then transplanted into the deficient site. The biological principles that have led to the nascence of this experimental approach are based on mimicry, since most of the inductive molecules that are being tested for periodontal regeneration (growth factors as well as enamel matrix proteins) have profound effects during the natural genesis of the periodontal apparatus. Thus, the most promising molecules in the field of mesenchymal tissue engineering are bone morphogenetic proteins (BMPs), enamel matrix proteins (EMPs), and other growth factors such as basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and transforming growth factor beta 1 (TGF-ß1). With the exception of EMPs, whose mode of action has not yet been fully elucidated, all these growth factors interact with their respective receptors on many cell types and elicit a cascade of intracellular signaling, which results in an altered cellular behavior (primarily gene expression and subsequent protein production).

Lastly, any meaningful regeneration of lost tissue volume must involve recruitment of appropriate progenitor *cells*, their timely migration into the allotted space, their differentiation into mature cells, and ultimately the production of the required tissue constituents. These cells can originate from the host at the site after a proper induction by the scaffold or biological inducer or can be delivered into it as a graft (i.e., *cell therapy*). The most common cells used for tissue engineering of mesenchymal tissues are mesenchymal stem cells, bone marrow stromal cells, and various progenitor cell preparations (from PDL, skin, adipose tissue, etc.).

8.4 Periodontal Regeneration Using Tissue Engineering

Periodontal regeneration is defined as reconstruction of lost periodontal tissues (cementum, PDL, and alveolar bone) and restoration of tooth support. In recent years, the frequency of implant placement increased dramatically and with it, the recognition that inflammation-related bone loss around implants is a clinical challenge. Thus, peri-implantitis was added to the indications for which periodontal regenerative treatments are sought.

The introduction of guided tissue regeneration (GTR) and bone replacement grafts has cast the foundations for modern tissue engineering of periodontal tissues. Current tissue engineering of periodontal tissues rests on two important pillars: firstly, membranes (whether absorbable or non-absorbable), which secure the space for the regenerating tissue, exclude gingival tissues from the site and prevent epithelial migration onto the root surfaces. Secondly, bone replacement grafts, whose purpose is to maintain the regenerating space, guide host cells into it and possibly stimulate progenitor cells, including autografts (from the same patient), allografts (from another human), xenografts (from another species), and alloplasts (synthetic inorganic particles) [2]. Most grafts used to date (all alloplasts such as hydroxyapatite, beta-tricalcium phosphate, and bioactive glass as well as freeze-dried bone allografts (FDBA) do not possess any inductive properties and therefore only conduct host cells into the regenerating site (i.e., are "osteoconductive"). They constitute the first element of tissue engineering (scaffolds/matrices). Autografts and DFDBA (demineralized FDBA) were believed to possess some bone inductive properties due to their alleged content of BMPs. However, this notion has recently been challenged [3], and in any case the concentrations of BMPs in commercial DFDBA are probably too small to exert any substantial inductive effect. Nevertheless, the quest for bone fillers with substantial osteoinductive properties (primarily without the addition of inductive molecules) is still ongoing [4, 5].

This has led researchers to search for more efficient methods of induction of periodontal regeneration, namely, the introduction, into the regenerating site, of inductive molecules (biologics), the second key element of tissue engineering.

For successful regeneration of periodontal tissues to occur, several cell types must be recruited in a synchronous fashion: cemento-

blasts, osteoblasts, fibroblasts, and endothelial cells. That the PDL contains progenitor cells for all the periodontal tissues (bone, cementum, and PDL) is well accepted [6, 7]. Many in vitro studies have shown that various growth factors are mitogenic (i.e., stimulate proliferation) toward cells residing in the periodontium. Most notably, PDGF is mitogenic for periodontal cells [8–10], cementoblasts [11], and osteoblasts [12, 13], and bFGF is mitogenic for periodontal ligament cells [14, 15]. These molecules are also chemotactic for several cell types, resulting in their migration toward a concentration gradient [16]. Other growth factors, namely, BMPs and TGFß, which are basically morphogens that play a pivotal role in embryonic development of bone and cartilage, are powerful inducers of osteogenic differentiation of mesenchymal precursors and thus capable of inducing de novo bone formation [17]. These agents have also significant stimulatory effects on proliferation and gene expression of PDL cells [18]. Given the multitude of in vitro studies showing the power of PDGF, FGF, and BMPs to induce various anabolic activities in periodontal cells, these molecules have become natural candidates for use in periodontal reconstructive surgery [19].

8.5 Protein/Peptide Therapy in Periodontal Regeneration

Today's availability of recombinant proteins has boosted the experimental use of peptide growth factors in bone and periodontal regeneration. There are many published studies exploring the use of PDGF-BB and BMPs in humans and laboratory animals [16, 20–27]. With BMPs (mainly BMP-2 and BMP-7), periodontal regeneration experiments are encouraged by the vast number of studies exploring their use in orthopedic indications. As a shining example, BMP-2 and BMP-7 have been approved by the FDA for treatment of lumbar spine fusion (InFUSE™ (Medtronic)) and long bone nonunions (OP-1™ (Stryker)), respectively.

The most popular animal models for investigating the potential of growth factors in periodontal regeneration are furcation and fenestration defects. The understandable biological, clinical, and financial interests in using recombinant growth factors for periodontal regeneration are driving the research efforts, and the emergence of products that combine osteoconductive materials with osteoinductive growth factors is to be expected. The harbinger of this kind is GEM 21S ® (BioMimetic Therapeutics), which combines recombinant PDGF with beta-tricalcium phosphate (β-TCP) granules. The outcome of studies using PDGF-BB or FGF-2 toward periodontal regeneration is summarized in [28].

In recent years, two "new" players have been added to the list of candidates for peptide therapy in periodontal regeneration. These are FGF-2 (also called basic fibroblast growth factor (bFGF)) [29–31] and growth/differentiation factor 5 (GDF-5), which is closely related to the bone morphogenetic protein (BMP) family and a member of the TGF-beta superfamily [32, 33].

Despite the introduction of several commercial products, attempts to enhance the regenerative process beyond conduction have been made in all areas of periodontology/implantology. Different carriers containing the same molecule, combinations of molecules attached to the same carrier [34], biologics coated on titanium implants [35], and efficacy in different periodontal applications are all subjects of intense research, some of which has reached the human trial phase [36–41] are only some examples (see also [25]).

8.6 Gene Therapy

As stated before, several animal and human studies described the potential efficacy of local surgical application of recombinant growth factors toward periodontal regeneration. However, the main problem with this approach (i.e., a single application of the therapeutic peptide) is the short half-life of the implanted molecules, resulting in an inadequate maintenance of therapeutic levels of the protein at the defect site [42]. The major routes of growth factor elimination from the regenerating site are proteolytic breakdown, solubility of the delivery vehicle, and intracellular

endocytosis [42]. Therefore, gene therapy may serve as an alternative, probably more efficient, method of longer-term targeting proteins to a diseased tissue. Genes are specific portions of DNA that code for (contain the required information for the production of) specific proteins. When genes are "activated," their transcription, in the nucleus, into messenger RNA (mRNA) molecules occurs. These are transported to the cytoplasm into the rough endoplasmic reticulum, where they dictate the assembly of amino acids into the respective protein. Thus gene therapy relies on the delivery of the gene of interest into the regenerating site, with the hope that it will eventually bring about the local continuous (or at least longer-term) production of the desired protein. Currently there are two major ways in which genes of interest can be administered into a disease-compromised site. The first is "in vivo gene therapy" (Fig. 8.2), which involves a direct delivery of the genetic material into the desired anatomical site, either by itself or combined with an appropriate scaffold, hoping that it will integrate into and transduce (convert) local host cells, resulting in their production of the protein [43]. Most systems to date use replication-defective viral vectors (primarily adenoviruses and adeno-associated viruses) for gene delivery; however several types of nonviral constructs (e.g., liposomes, calcium-based nanoparticles, and complexes between DNA and polymers such as PLGA, chitosan, and gelatin) are being tested [24–26]. They are considered superior when compared to viral vectors due to their nonimmunogenicity and low toxicity and are less likely of being introduced into the host cell genome; however they usually display a lower transduction efficiency.

8.7 Gene Therapy in Periodontal Regeneration

The most common method of delivering DNA material into surgical sites is via adenoviral vectors or DNA-lipid complexes. There are many

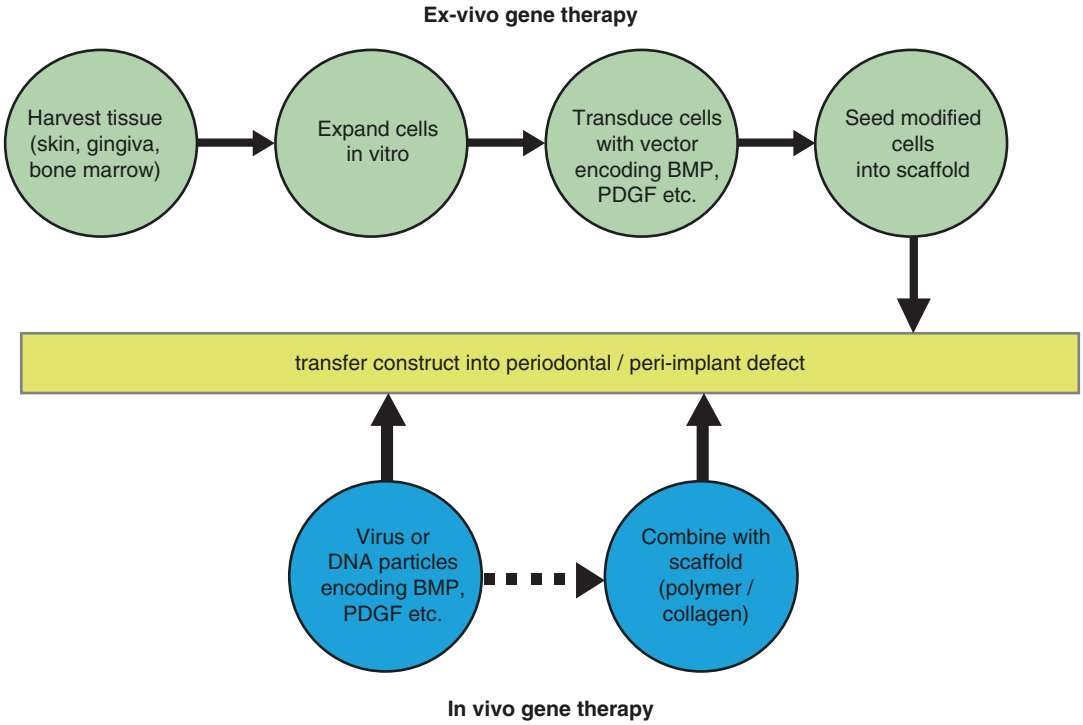

Fig. 8.2 The two strategies of gene therapy for periodontal regeneration

studies that describe the usage of gene therapy in orthopedic bone regeneration [44–50]. These studies either administered viral particles alone or combined them with a scaffold from which they would be released post-surgery. This approach was attempted in several studies toward periodontal and peri-implant regeneration. Jin et al. [51] implanted a collagen matrix containing adenovirus particles, encoding the PDGF-B gene, into experimental fenestration defects in rats and observed a greater number of proliferating cells in the defect and a greater amount of newly formed bone and cementum, compared to all control groups. Similar animals receiving a collagen matrix with a gene encoding a light-producing enzyme (luciferase) showed that local gene expression could be observed up to 21 days postimplantation (Fig. 8.3).

Other studies investigating the use of PDGF-B in this manner have also been published [52–54]. Furthermore, Dunn et al. [55] implanted a collagen matrix containing adenoviral vectors encoding BMP-7 into osseous defects created around implants placed in rats and found local gene expression for up to 10 days and a better bone fill of the defects compared to control viruses. Other studies using BMP vectors also exist [56, 57].

Last but not least, successful regeneration of bone or periodontal defects relies on the timely reestablishment of blood supply to the regenerating tissues; therefore the treatment of large defects poses a significant clinical challenge. Thus, the use of growth factors with angiogenic properties has become a vital option in aiding the regenerative process. Vascular endothelial growth factor (VEGF) is a signal protein produced by several cell types that stimulates vasculogenesis and angiogenesis. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate or helps supply new blood vessels when new tissue formation is required. Several groups have assessed the effect of administering VEGF into periodontal defects as peptide/protein treatment either by itself or in

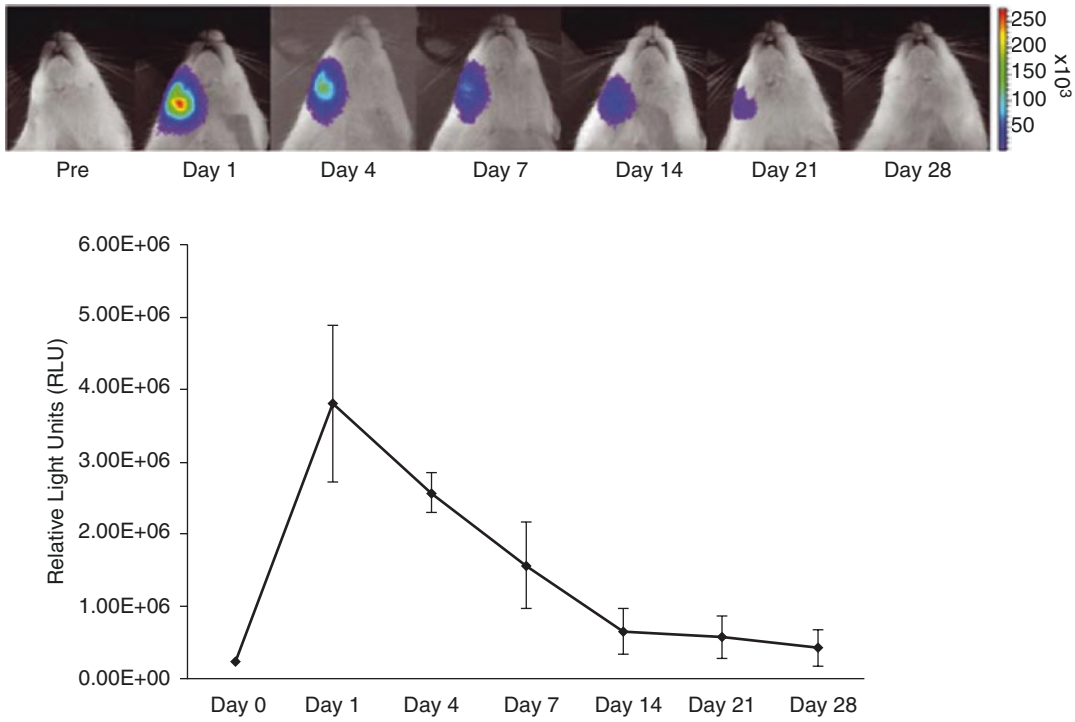

Fig. 8.3 Noninvasive in vivo visualization of gene expression following gene therapy. Images of a rat receiving the luciferase-encoding adenovector to the mandible, showing the kinetics of luciferase expression (as light emission) post-administration [51] (With permission from Nature Publishing Group)

combination with other growth factors (e.g., BMPs) [35, 58, 59] or as gene therapy [60].

While these studies demonstrate the feasibility of direct in vivo gene delivery for periodontal and bone regeneration, this approach is limited by two factors: the inability to target the genes to specific cells within the regenerating site and the relatively short time period in which gene expression can be expected to last, perhaps due to a limited exposure of cells to the viral plasmids and/or a low transduction efficiency in vivo. These disadvantages can be overcome by using the second method of gene therapy, i.e., "ex vivo gene therapy" (Fig. 8.2), whereby cells (either autologous or allogenous) are expanded and treated in vitro with the viral vectors and later transplanted into the regenerating site [43]. This topic will be reviewed later in this chapter.

8.8 Cell Therapy

As mentioned above, the third key element in tissue engineering is the successful recruitment of progenitor cells, their proliferation, differentiation, and production of matrix constituents. While conductive methods rely solely on migration of host cells and inductive methods are aimed at recruiting more host progenitors to the process, the availability of cells for the regenerative process is a rate-limiting step for both approaches. Cell therapy is aimed at overcoming this difficulty by transplanting into the regenerative site progenitor cells that have the potential to differentiate into the desired cell type. This procedure provides the regenerative process with a greater number of progenitors, compared with relying on the recruitment of host progenitors. This advantage may become even more critical in situations in which the regenerative capacity of the host is diminished. Another advantage of this approach is that the cells, which are expanded and later implanted, can be obtained from the patient himself, avoiding the possibilities of disease transmission and immune rejection. For example, an FDA-approved cell therapy protocol (Carticel ®) is based on harvesting chondrocytes from a healthy zone of a damaged knee joint, their expansion in vitro, and subsequent reimplantation into the diseased zone of the joint.

8.9 Cell Therapy in Periodontal Regeneration

Since periodontal regeneration and bone (orthopedic) regeneration share a common feature, namely, the need to reconstruct mesenchymal tissues, these two applications share some of the repertoire of cells that can be used for cell therapy. The first cell types suitable for the job are somatic (differentiated) cells such as osteoblasts, PDL fibroblasts, and cementoblasts [25, 61]. All of these cells can be isolated from their natural habitat, expanded and even immortalized, and all have shown the capacity to form mineralized tissue in vitro, making them candidates for cell therapy.

However, these cells usually lack self-renewal capabilities and have a limited multipotency. Therefore, the most common cells used for regeneration of mesenchymal tissues are mesenchymal stem cells (MSCs) that do have self-renewal capabilities and can differentiate into a significant number of cell types, including osteoblasts, chondroblasts, adipocytes, myocytes, fibroblasts, and cementoblasts [25, 27, 61, 62]. MSCs have been obtained from various tissues, including the bone marrow, skeletal muscle, adipose tissue, oral mucosa, and dental pulp. Regardless of their origin, MSCs can be isolated, expanded in vitro, and, if necessary, manipulated before their transplantation. Bone marrow stromal cells (BMSCs) are another popular type of cells that are used for mesenchymal cell therapy [63]. They also are pluripotential cells, albeit with a narrower range of plasticity. Many examples of orthopedic bone regeneration via cell therapy of MSCs or BMSCs have been published. For example, calvarial and long bone defects were repaired with bone marrow stromal cells or mesenchymal stem cells [64–68]. In a similar direction, Kawaguchi et al. [69] used autologous bone marrow-derived MSCs loaded in a collagen gel to regenerate class III furcation defects in dogs and reported increased cementum and bone

formation compared with collagen transplanted alone. Other investigators used similar cells for different periodontal applications such as intrabony defects e.g., [70, 71].

In addition, MSCs have been isolated from PDL [72–74], and another study showed that MSCs, when cultured in contact with native PDL cells, acquire the characteristics of PDL cells [75], making them suitable for periodontal regeneration purposes. Several groups demonstrated the feasibility of using PDL-derived cells for periodontal regeneration. Dogan et al. [76] retrieved cells from a regenerating periodontal defect in dogs, expanded them in culture and transplanted them into a small number of class II furcation defects of the same animals for 6 weeks. They reported variable results, in that they noted a trend toward better bone formation but less cementum formation. In contrast, Nakahara et al. [77] obtained autologous PDL-derived cells from dogs, then expanded and transplanted them into fenestration defects. They reported better cementum formation but equal bone formation in the cell-seeded sites. Murano et al. [78] retrieved PDL cells from a healing site undergoing a GTR procedure and transplanted them into furcation defects reporting superior bone formation vs. controls.

Other investigators adopted a different approach: PDL cells are cultured on specialized surfaces and induced to form extracellular collagen until they form a continuous sheet. These "PDL cell sheets" are lifted off the culture plate and transferred into various defects [79–81]. Histological analysis revealed better cementum formation or better bone-fill in cell-seeded sites. Although there is some in vivo evidence that these cell sheets also form a cementum-like substance with PDL-like fibers attached when transplanted ectopically [82], these essentially pilot studies (summarized in [83] and [84]) need further validation.

Several groups have isolated human [85], murine [86], and bovine [87] cementoblast progenitor cells, which are natural candidates for periodontal regenerative procedures. When these cells were transplanted subcutaneously in vivo into immunodeficient mice, they formed a cementum-like tissue [88]. One group went ahead and tested the efficacy of these cells in periodontal regeneration. Zhao et al. [89] transplanted these cells (OC-CM) or dental follicle cells loaded onto PLGA sponges into fenestration defects of athymic rats. Histological analysis revealed a cementum-like mineralized tissue which formed adjacent to the roots only in the cementoblast-seeded group. Bone formation and PDL organization were also noted in these defects.

Another cell type – periosteum-derived cells – was suggested as a candidate for bone regeneration [25]. This tissue is relatively easier to obtain, and these cells were tested in various models such as class III furcations [90], peri-implant defects [91], or rat calvarial critical-size defects (Fig. 8.4) showing successful bone regeneration.

Another recent commercial addendum to the repertoire of implantable cells are Ixmyelocel-T ® (Vericel) which is an autologous preparation of human bone marrow cells in which CD90+ stromal

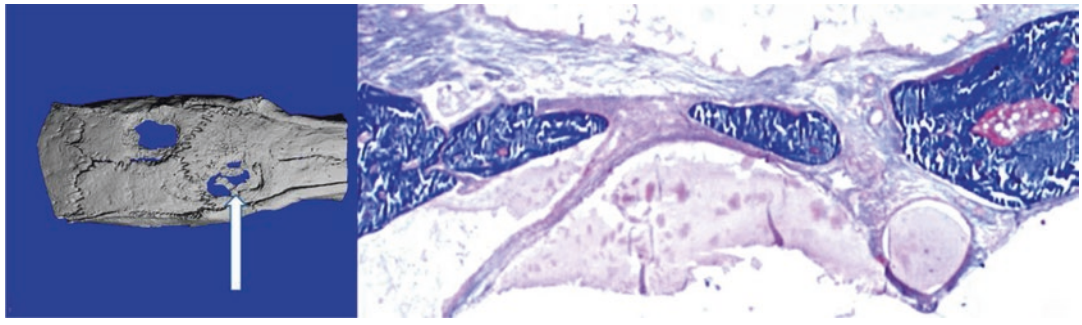

Fig. 8.4 Bone formation in a rat calvarial defect by implanted periosteal cells (M. Weinreb 2002)

cells and CD14+ macrophages are enriched while CD45+ hemopoietic cells are depleted. These cells have been used to augment human jaw defects and were compared with GBR techniques [92]. These cells were also used in attempts to regenerate other tissues (e.g., cardiac muscle).

Naturally, all these implantable cells must be seeded onto or into biocompatible and biodegradable scaffolds in order to transport them into the defect and allow their matrix-dependent survival ([93–95] to name just a few studied materials).

An important advance in this field is the establishment of induced pluripotent stem cells (iPSCs). The most pluripotent cells in the body are embryonic stem cells (from the inner cell mass of the blastocyst), which can divide for long periods and can differentiate to all cell types. However, their obtainment is difficult and fraught with ethical issues. In contrast, iPSCs are pluripotent stem cells that can be generated from adult somatic cells (e.g., fibroblasts) by the forced expression (via gene therapy) of several genes that are unique to embryonic stem cells. Mouse iPSCs were first reported in 2006, and human iPSCs in late 2007. Both are capable of generating cell characteristic of all three germ layers. Notably, these cells are of great potential for regenerative procedures and have already been tested in several periodontal applications [96–99]. It will be up to future studies to assess primarily the safety of using these cells, mainly in terms of integration of viral genes into the host, immunogenicity, and tumorigenicity.

In summary, there are numerous options for "cell therapy" strategies toward periodontal and peri-implant regeneration; however we need many more reproducible studies before this approach can be estimated for its routine clinical value.

8.10 Combined Cell + Gene Therapy

As mentioned previously, "ex vivo gene therapy" is the second option for delivering therapeutic genes into the regenerating site. This method is based on culturing (mostly autologous) progenitor cells, manipulating them in vitro by transducing them with the gene(s) of interest, and transplanting them into the regeneration site. This approach enhances the regenerative process in at least three ways:

1. It allows the selection of cells that have the potential to differentiate into the desired cells (e.g., MSCs, BMSCs, etc. in our case) so that they can participate in the formation of the desired tissue. The product (protein) of the introduced gene may have paracrine effects (inducing host progenitor cells) as well as autocrine effects (on the transplanted cells themselves), thus amplifying the inductive effect.
2. It usually ensures a higher efficiency of transducing the cells and allows confirmation that the introduced gene has been integrated into the progenitor cells prior to transplantation.
3. The resulting protein production is usually sustained for a longer period than by introduction of the gene alone, giving the therapeutic protein a better chance of influencing the regenerative process.

Most studies published to date on bone regeneration have infected BMP genes into MSCs or BMSCs, since these cells are known to differentiate into osteoblasts. For instance, Lieberman et al. [100] have used BMP-2-transduced BMSCs to repair femoral defects in rats, while Chang et al. [101] have used similar cells to repair calvarial defects. Rutherford et al. [102] and Krebsbach et al. [103] have used BMP-7-transduced fibroblasts to regenerate calvarial defects, while Lee et al. [104] used BMP-2 containing muscle-derived cells for the same purpose. In addition, Peterson et al. [105] used BMP-7-transduced MSC derived from adipose tissue to repair femoral defects in rats. Finally, Zhao et al. [106] used MSC, which they had transduced with combinations of genes for BMPs 2, 4, and 7, and showed that subcutaneous transplantation of cells expressing more than one BMP was more efficient in inducing ectopic bone formation than that of cells expressing only one

of the BMPs. These data suggested that such a strategy could be applied to genuine bone regeneration too.

With these studies in mind, Jin et al. [107] tested the efficacy of BMP-7-transduced dermal fibroblasts in healing of fenestration defects in rats for 10–35 days. They reported that defects treated with BMP-expressing cells displayed a significantly greater amount of bone and cementum formation compared with cells expressing a control (dye encoding) gene. Chen et al. [108] used autologous bone marrow mesenchymal stem cells (MSCs) engineered by replication-defective adenovirus to express the BMP-2 gene and Pluronic F127 (PF127) for the treatment of periodontal defects. Another interesting approach was recently taken by Huang et al. [109] who transplanted subcutaneously BMSCs together with viral vectors encoding BMP-4 and VEGF. The idea was that these two growth factors will stimulate simultaneously osteogenic differentiation and angiogenesis, respectively, thus enhancing bone formation at the implantation site. They reported that the combined delivery of all three elements (cells + two growth factor genes) resulted in a significant increase in the quantity of regenerated bone compared with any factor alone or any combination of two factors.

A variation on the BMP gene therapy theme was recently described [110], in which gingival fibroblasts and periosteal and fat-derived stem cells were transduced with the sonic hedgehog (shh) gene and used to regenerate critical-size calvarial defects in rabbits. Shh, a member of the hedgehog gene family, is a key protein involved in craniofacial morphogenesis and causes differentiation of pluripotent mesenchymal stem cells into the osteoblastic lineage by upregulating the expression of BMPs. In this paper, bone regeneration was evident only where transduced cells were transplanted.

In addition to the use of BMP-infected cells as described above, another group has tested the utility of utilizing PDGF production toward periodontal regeneration. PDGF is a growth factor, which is released from platelets and other cell types, and has a major role in the promotion of wound healing. It is a mitogen and chemoattractant for many cell types, including those derived from the periodontium (PDL fibroblasts, osteoblasts), and thus a natural candidate for use in periodontal regeneration [111]. This group had shown previously that local administration of the PDGF peptide enhances periodontal regeneration significantly but not completely [112], making gene therapy a worthy attempt. They first transduced cells residing in PDL (fibroblasts, osteoblasts [111], and cementoblasts [42]) with adenoviral vectors containing the PDGF-A gene and found that the manipulated cells expressed PDGF-A mRNA for at least 7 days and responded by increased proliferation. With these encouraging data (attesting to successful in vitro transduction and prolonged gene expression), they then examined the behavior of the transduced cementoblasts in vivo by implanting them subcutaneously in immunodeficient mice [113]. Surprisingly, continuous production of PDGF-A in the implantation site *delayed* the formation of mineralized tissue, compared with cells that were not transduced at all. The authors suggested that PDGF was produced at the implantation site for a period which was too long and suggested that shorter exposure of the cells to PDGF may have a positive effect. Future studies might test whether PDGF-BB expression results in different outcomes. Similar attempts with cells transfected with VEGF have also been made [114].

This brings us to another problem that the combined cell/gene therapy faces and that is controlling the expression of the therapeutic genes. For some gene products, a short period of gene expression is desirable, while for others a longer period is necessary. Furthermore, it may be necessary to carefully control the level of expression of the osteoinductive molecules such that their activity is sufficient to promote local bone/cementum formation but will not promote undesirable bone formation (whether ankylosis or bone tumors). Whatever duration of gene therapy we may seek, we may need to formulate mechanisms to exogenously control the expression of the therapeutic gene in the transplanted cells. Recently this has been achieved by introducing into various cell type genes engineered in such a way that their activity can be turned on and off

exogenously by administration and cessation, respectively, of certain antibiotic drugs such as tetracycline, doxycycline, and rapamycin [115, 116]. For example, when MSCs were transduced with a doxycycline-controlled BMP-2 gene and transplanted into a calvarial defect, bone formed only in animals that received doxycycline in their drinking water, indicating that the expression of the therapeutic gene can be turned on and even more importantly, turned off whenever desired [117].

8.10.1 3-D Bioprinting

After describing all the options for future periodontal regeneration (peptide, gene, and cell therapy), it is appropriate to highlight another important advance in the field. It is obvious that periodontal and peri-implant defects vary considerably in size and 3-D anatomy (one to three walled). Currently, bone grafts and implantable scaffolds are being placed surgically without a preadaptation process to the configuration of the specific defect being treated. The introduction in the last couple of years of 3-D bioprinting allows to change that notion. Three-dimensional printing devices use inkjet-like technology to produce complex predetermined structures made of extracellular peptides, DNA molecules, and cells as desired. Alternatively, a 3-D mold is designed based on the anatomy of the patient's defect derived from CT scans and can be later converted into a scaffold made of biocompatible/biodegradable materials such as polycaprolactone or poly(lactic-co-glycolic)acid (PLGA). Several attempts to treat periodontal or peri-implant bone deficiency using this technology have already been reported [41, 118–121].

The cumulative research efforts described hitherto in this chapter have taught us that all nonconductive forms of periodontal tissue engineering (protein, gene, and cell therapy) may have potential beneficial effects on periodontal regeneration, but more consistent studies are needed before any of the protocols is validated for clinical use. Several problems still need to be resolved in a robust manner [122]:

- Induction of bone vs. cementum/PDL fiber formation
- Selection of optimal scaffolds for the various treatment modalities
- Ankylosis and its resolution
- Safety of continuous exposure to growth factors and introduction of viral materials
- Controlling the exposure of the regenerating site to the inductive molecules
- Administration of single/dual/multifactor biologics
- Cost-effectiveness of any form of regenerative treatment
- The difference in size between experimental periodontal defects in rodents vs. humans, which affects cell survival, revascularization, and healing kinetics

Given the progress made in bone and cartilage regeneration using similar methods, there is hope for these methods to mature and become more predictable and user-friendly for successful periodontal regeneration. In addition, the safety (e.g., local side effects, systemic spread of biologics, immunogenicity) of the various treatments must be thoroughly investigated (e.g., [52]).

8.11 Enamel Matrix Proteins in Periodontal Regeneration

Since the discovery that enamel matrix proteins (EMPs) are expressed by epithelial cells during root formation and are involved in cementogenesis in addition to their natural role in amelogenesis, a huge number of in vitro, animal, and human studies have been carried out to examine the potential usefulness of these proteins in periodontal regeneration. The current EMP product (Emdogain ®, Straumann) is made of a preparation of EMPs called enamel matrix derivative (EMD) and the carrier propylene glycol alginate (PGA). It contains mainly amelogenin and its fragments and other proteins such as enamelin, ameloblastin (also called amelin or sheathlin), amelotin, apin, and various proteinases. It is indicated for the treatment of one-wall, two-wall, and three-wall intrabony defects, some class II

furcation defects, and recessions. Many clinical and preclinical studies documented the efficacy of Emdogain in periodontal regeneration (e.g., [123–127], reviewed in [21, 128–130]). Studies involving histology showed that it induces true periodontal regeneration, i.e., the de novo formation of tooth support, namely, cementum, PDL, and alveolar bone [131, 132]. Among the reported biological (cellular/molecular) effects of EMPs are enhanced proliferation of PDL cells [133–135], osteoblasts [136] and cementoblast-like cells [137], inhibited proliferation of epithelial cells [138, 139], as well as increased mineralized nodule formation by PDL cells [133] and bone marrow cells [140], all of which help explain the beneficial effects of EMPs in the periodontal regeneration arena (summarized in [141–143]).

Beyond the widespread application of Emdogain in periodontal regeneration, the last *several years have witnessed four developments in its use and understanding*:

1. The precise molecular mechanism(s), by which EMPs induce all their biological and clinical effects, have not been elucidated; however the expanding use of modern molecular biology tools to analyze these effects has helped deciphering this issue. Notably, the introduction of microarray technology (="gene chips"), which reveals global gene expression changes consequent to cell or tissue treatment, and bioinformatic analyses into periodontal research is instrumental in advancing our understanding of the molecular pathways which participate in these effects [144–150].
2. It is quite clear that Emdogain is a mixture of EMPs, with many full or fragmented protein species. This fact makes it harder to pinpoint molecular mechanisms in any given cellular effect. Therefore, several attempts were made to separate this mixture to its components or at least subfractions with greater homogeneity, mainly based on their molecular weight (e.g., [151, 152]). Consequently, several groups have tried to attribute a specific cellular effect of EMD (e.g., proliferation, angiogenesis, osteoblastic differentiation) to various subfractions of EMD [151–155]. On one hand, finding a fraction with activity greater than the whole EMD mixture (either due to increase in relative concentration or removal of some internal hindrance from other molecules) would augment the effect expected in vivo. On the other hand, finding the molecular mechanism for any effect becomes simpler with more homogeneous protein mixtures.
3. Clinical studies suggested that better periodontal regeneration may be achieved when Emdogain is combined with a bone substitute. Since the current product is in a gel form, its adsorption to particulate substances is not ideal. This has led to the development of a liquid form of EMD (Osteogain ®) with better reported adsorption of the enamel proteins to bone grafts such as natural bone mineral (NBM) or demineralized freeze-dried bone allograft (DFDBA). The clinical efficacy of this formulation in regeneration and cellular signaling is being tested [150, 156, 157].
4. The possible beneficial effects of EMPs on gingival tissue were not thoroughly investigated. This research direction is prompted by sporadic clinical observations that Emdogain treatment during periodontal therapy has beneficial effects on gingival tissue. For instance, application of Emdogain® during coronally positioned flap procedures for correction of gingival recession resulted in an increased width [158, 159] and thickness [160] of the keratinized gingiva compared with control treatment. This finding could suggest an effect of EMPs on cells of the gingival connective tissue, separate from their effect on PDL or alveolar bone cells. We have recently performed a series of studies on the effects of EMD on human primary gingival fibroblasts and found that it increases their in vitro proliferation and extracellular matrix production in rats [140] and humans [161]. Searching for possible mechanisms for this effect, our studies revealed that the mitogenic effect of EMD on gingival fibroblasts is dependent on the activation of the extracellular signal-regulated kinase (ERK) pathway [161] and involves signaling through the epidermal growth factor (EGF) receptor (EGFR)

[162]. In addition to promoting gingival fibroblast proliferation, EMD effectively protects these cells from the cytotoxic effect of tumor necrosis factor (TNF), a known periodontal disease-associated cytokine [163]. Since increased cell death and reduced healing capacity (i.e., proliferation and matrix production) are hallmarks of the sequelae of periodontal disease in gingival tissue, the summation of these three effects of EMPs (stimulation of proliferation, stimulation of matrix production, and prevention of cell death) suggests that they may exert an anabolic effect on gingival fibroblasts in vivo. In addition, many reports have shown that EMD stimulates in vitro the proliferation and migration of endothelial cells and is angiogenic in several in vivo models [141–143]. Based on these in vitro findings, the first two pioneering studies in this area have shown that Emdogain promotes healing of rat oral mucosa wounds by stimulating several aspects of the healing process (mainly vascularization and collagen production [164, 165], see Fig. 8.5).

On a closing note (and somewhat closing a circle), similar effects of EMPs described for gingival fibroblasts (induced proliferation and matrix production) were noted in PDL fibroblasts [166, 167]. Analysis of gene expression of these cells in response to EMD [144, 168] using cDNA microarrays revealed that the expression of several growth factors (PDGF-A, VEGF, TGFß, BMP-4) and growth factor receptors (BMPRII, VEGFRI, PDGFR) is increased following exposure to EMD. Similar analysis of other cells also showed growth factor induction by EMD (e.g., [148]). These data highlight another possible mechanism of action of EMPs, namely, that they induce the expression (and presumably the production) of several known growth factors and facilitate their activity, thus linking two artificially separated treatment modalities in periodontal regeneration (EMPs and growth factors). These issues will hopefully be clarified in the future.

8.11.1 Future Trends in Bone Regeneration

Advanced alveolar bone atrophy may prevent appropriate implant placement. Various alveolar bone augmentation approaches have been suggested to enlarge the bone volume before or at the time of implant placement. These surgical procedures are demanding for both clinicians and patients and often involve the use of autologous or allogeneic bone grafts. In large defects, graft incorporation requires a long time; this depends on the residual bone, the graft material, the grafting procedure, and the patient's response to grafting, mainly related to age, smoking habits, and systemic condition. Moreover, the use of autogenous grafts implies the need for a second surgical site, thereby increasing the morbidity of the

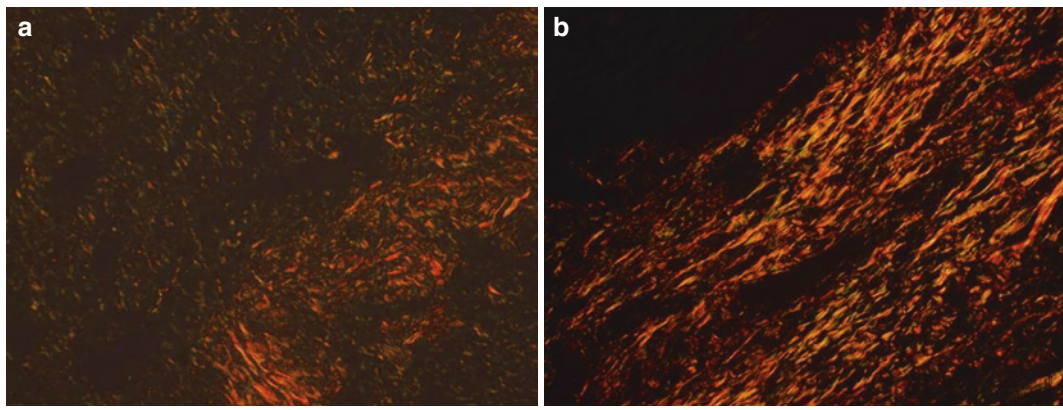

Fig. 8.5 Collagen fibers stained with picrosirius red and viewed under polarized illumination in the gingival connective tissue 9 days after an incisional wound was treated with Emdogain (**b**) and control PGA (**a**) (M. Weinreb)

procedure, while the use of non-autogenous grafts could be associated to the risk of immunogenic reactions and markedly increase the cost of the procedure. During the recent years, many different cytokines and growth factors have been proposed in order to achieve fast and effective bone regeneration in oral surgery procedures. It is known that different soluble growth factors and cytokines are involved in different stages of tissue healing, while acting for different periods. Therefore, it is likely that delivery of a single bout of high-concentration growth factors in the tissues at the time of surgery does not exploit its potential optimally. The development of a controlled spatial-temporal delivery could provide an effective way to maximize the effect of growth factors on tissue healing process.

Biodegradable polymeric devices for controlled distribution and temporal release of growth factors could have positive effects on bone regeneration.

One pivotal discovery that has fueled the research in regenerative medicine and tissue engineering has been the fundamental role that cytokines and growth factors play in the process of tissue repair [169–171]. Hence, providing the injured tissue a milieu of biological signals may functionally accelerate tissue repair [172].

Although the role of all certain growth factors involved in tissue regeneration has been only partially elucidated, the biological effects of many of them have been fully understood during the last decade. This has led to the potential clinical use of different cytokines and growth factors as therapeutics in a wide range of diseases and the repair or regeneration of certain tissues [173, 174]. Such a strategy comes from the determination that all the phases of tissue repair process are mediated and controlled by a pool of biologically active growth factors that modulate cell function through direct physical interactions with extracellular domain of transmembrane receptors. The latter transduce secondary signals, thereby, modulating cell response and controlling diverse aspects of subcellular biology.

However, despite a long history of preclinical evaluation with promising results, the routine use of growth factors as therapeutic agents for bone and periodontal regeneration in dentistry is not yet a reality. Recombinant human platelet-derived growth factor BB (rhPDGF-BB) isoform and some recombinant human bone morphogenetic proteins (rhBMP-2 and rhBMP-7) are among the most promising substances clinically evaluated for bone and periodontal regeneration. BMPs, the most specific and potent osseoinductive factors, are currently in clinical use in the orthopedic field for complicated cases (nonunion, open tibiae fractures, and spinal fusions) but are still not fully approved for oral and maxillofacial applications. Clinical trials using BMP-2 for maxillary sinus augmentation provided good but not enthusiastic results [175, 176]. rhPDGF-BB (also known among clinicians as GEM-21S) was first introduced in dentistry in the field of periodontology and has been shown to be mitogenic and chemotactic for periodontal ligament cells, with the additional effect of promoting regeneration of bone, ligament, and cement [177, 178]. The effect of rhPDGF-BB, combined with certain bone grafts, is still controversial [179–183]. One of the main reasons that limit the use of such recombinant factors is their high cost-efficacy ratio. While high developmental and therapeutic costs might appear justified for severe skeletal conditions such as nonunions, open fractures, spinal fusion, and large bone defects, the same cannot necessarily be said for relatively small and non-life-threatening defects like alveolar defects where preventive and maintenance measures are still mandatory and therapeutic alternatives exist. An important concerning especially BMPs, whose action in physiological condition is confined within bone tissue, is the risk for ectopic bone formation in case of uncontrolled release out of the site of application (e.g., through the bloodstream). Finally, a critical point to the use of single recombinant molecules is that a pool of growth factors, cytokines, and proteins are likely to be required according to the complex intricacy of the healing and tissue-repairing processes. Considering one specific growth factor as a magic bullet might only conduce to impaired tissue regeneration [184]. Therefore, clinical needs for devices, being at the same time safe, effective,

and inexpensive, oriented the research and the market toward the development of alternative solutions.

A number of growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta 1 (TGF-beta1), and insulin-like growth factor (IGF) have been shown effective in enhancing bone regeneration.

In 2008, a group of the Columbia University, NY, published a study in which alginate microspheres and microcapsules were used as carriers for controlled release of several growth factors [185]. They observed that factor release profiles varied as function of the carrier and the bioactivity of the released factors was maintained in vitro, promoting human osteoblast-like cell proliferation and alkaline phosphatase (ALP) activity. This study represented the proof-of-principle that growth factors can be incorporated in devices for controlled delivery and can preserve its effects on the surrounding tissues after release. However, the hydrogel-based releasing device must be coupled with (or consist of) a scaffold having mechanical properties suitable for supporting newly forming bone. Finally, based on the basic rules of tissue engineering, the addition of a sufficient amount of progenitor cells to the device should complete its capability of enhancing tissue regeneration.

Different types of releasing devices with different delivery profiles (e.g., microspheres and microcapsules) could be combined together, within a polymeric scaffold, for a better mimicry of the natural healing process, in order to enhance bone regeneration.

To be effective as a therapeutic agent, a GF has to reach the site of injury without degradation, and then, it has to remain in the target location long enough to exert its action(s) [186]. GFs that are provided exogenously in solution into the site to be regenerated are generally not effective because GFs tend to diffuse away from wound locations and are enzymatically digested or deactivated.

The lack of cell response, thereafter, leads to failure to induce tissue morphogenesis and regeneration. There is an increasing evidence that GFs may exert their biological function efficiently in tissue engineering only if the design and development of release technologies provides controlled spatiotemporal delivery of key signaling molecules and prevents unwanted and potentially harmful side effects. Conventional routes of GF delivery, either topically or as a single dose local administration, are unlikely to be effective for many, if not all, GFs. Advances in understanding the critical pathways involved in healing of a specific tissue are leading to guide in the therapeutic administration of GFs, i.e., which factors, dose, and release pattern of delivery should be applied, for the regeneration of a number of homologous tissues [122]. A broad range of biomaterial-based deployment technologies are becoming available that could have a significant potential to control the spatial presentation and release kinetics of different biological cues for diverse biomedical applications including dentistry, oral implantology, orthopedics, ulcer treatment, sports medicine and tissue engineering, and others [170].

Designing systems that achieve desirable tissue exposure to growth factors requires an understanding and prediction of their distribution in vivo; moreover, appropriately designed release technology may in turn reduce the amount of protein required to achieve a desired effect, which may essentially increase the potency of the GFs in some cases. The incorporation of multiple GFs into cell-based tissue engineering systems, therefore, may be a promising approach for more efficient and effective tissue regeneration procedures.

The sequence of events leading to bone formation (chemotaxis, cell migration, proliferation, and differentiation) is regulated by different soluble growth factors and cytokines, many of which are present in platelets. It is likely that delivering a single bout of high-concentration growth factors in the tissues at the time of surgery is definitely not the optimal mode for exploiting its potential due to a premature and simultaneous release of the relevant stimulatory factors [187]. A more precise control of the kinetic release of all these multiple growth factors, aiming to mimic as much as possible the natural injured tissue requirements during the different regeneration phases, is of paramount importance [188]. The

reduced half-lives and local bio distribution of the growth factors may require in some therapeutic conditions their association or incorporation into biomaterials or drug delivery systems in order to better control their pharmacokinetics [189, 190]. Last but not least, the excessive costs of the synthetic growth factors and the variability of results with a single dose application make them unsuitable for regular clinical.

From a critical review of the current published evidence, some considerations can be done: both recombinant (PDGF, BMPs) and autologous growth factors (platelet concentrates) can be generally useful for enhancing tissue healing in different types of oral and maxillofacial bony defects. Several new biomaterials and biomedical technologies have been explored in the recent years with the aim of providing a control over growth factor release kinetics. One important challenge in the field has been to produce three-dimensional matrices and rendering them deliverable locally through minimally invasive techniques [191, 192]. Some of these approaches are based on the combination of the growth factors and autologous, natural, or synthetic biomaterials. The combination of polymers and growth factors might provide a controlled release into the local microenvironment to yield desirable concentrations over a period ranging from days to months [188, 193]. The new generation of biomaterials and technologies promises to allow greater control over cell fate and ultimately tissue structure and function. Some examples of polymers used for bioactive factor release include synthetic materials such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymers (PLGA) [194] and nitrocinnamate-derived polyethylene glycol (PEG-NC) hydrogel systems [195], natural polymers such as alginate [196, 197] or gelatin [198], and autologous materials such as fibrin [199].

A polymer-based device for controlled release of growth factors over time acting as a slow-releasing device (SRD) would solve the problem of simultaneous delivery of the GF at a single time, immediately after the surgical procedure, with a consequent waste of a major part of the effect of the GFs. The scaffold should have the following properties:

1. Initial putty-like consistency so as to be easily adapted to the bony defects and accordingly shaped
2. Possibility of being hardened in situ with light/UV exposure, to provide mechanical support
3. Osteoconductive properties
4. Porosity of the order of 300–400 microns that may allow non-covalent immobilization of GF-enriched microspheres and microcapsules, ingrowths of a microvascular network from neighboring vascularized tissues, and easy diffusion of nutrients from microcirculation, permit homogenous diffusion of growth factors as they are released from microspheres and microcapsules, allow homing of osteoprogenitor cells that might be attracted within the porous scaffold by a soluble factors and cytokine gradient, and find a comfortable niche to proliferate and induce new bone formation
5. Degradation rate similar or slightly slower than new bone formation, to preserve the desired volume during the osteogenic process
6. Degradation by-products that do not interfere with new bone formation

This device should allow for:

1. Precise control, and possibility of modulation, of growth factor release in the surrounding tissues after application and throughout the healing process
2. Maximize the growth factor effects: with the current techniques, apparently, most GFs are present in excess or at inappropriate timing, thus, becoming inactivated by tissue cleavage shortly after being released and, therefore, with minimal effect on the actual healing process
3. Possibility to control the mechanical properties of the polymeric device to serve as a three-dimensional scaffold to support its replacement by the newly formed bone
4. Possibility to test the efficiency of the device in vitro, taking advantage of the hydrogel properties for three-dimensional tissue regeneration

Different polymers with different features in terms of degradation rate, affinity for biologic substances, and mechanical consistency must be tested to determine the optimal combination of characteristics needed for optimal bone regeneration, namely, the release of active factors during at least 4 weeks, which is the minimum period necessary for early bone formation in humans.

Such polymer-based device by means of a hardware system that may be applied chairside without the need of a specialized laboratory for assembling the polymer and the patient-derived growth factors previous to clinical use. Ideally, such hardware should have the able to incorporate the inductive proteins at the desired concentration into polymeric microspheres or microcapsules, which will thereafter be mixed with a soft porous scaffold. This compound bone graft could be placed and adapted into the bone defect, conformed to the desired shape and then hardened by light or UV exposure, similar to many dental composite materials.

This achievement would represent a real breakthrough in the dental field, since no similar device is currently available. Providing the clinicians with a versatile, effective, and safe device for enhancing tissue regeneration in a predictable way is in fact one of the main goals of the project. However, such device should be prepared, adapted, and hardened chairside, within the surgical session, thus avoiding the needs for specialized laboratories to prepare the final product, which further rises treatment time and costs.

A different type of device consists of a multiple layer membrane where the recombinant growth factors may be embedded. The latter applies the same principle as the microspheres, where the different layers of the membrane are characterized by different degradation rates. In this way, the membrane can be used similarly to the currently applied membranes for guided tissue regeneration; however, the side with the degrading layers containing growth factors faces the bone defect. The first layers will release the growth factors mainly involved in the early stages of bone healing (e.g., PDGF, TGF-β1, IGF), and the deeper layers will release other growth factors, involved in subsequent stages (e.g., VEGF, TNFα), thus providing a continuous, timely, and specific support for defect regeneration, closely mimicking the natural healing process. This membrane may be easier to develop but, evidently, requires a greater initial financial investment since the different recombinant factors must be integrated in the device. However, this type of membrane could be commercialized ready to use and would certainly be rapidly adopted by clinicians, as most of them are acquainted with guided bone regeneration techniques.

This multilayer membrane, in which the deeper layers (those facing the bony defect) are embedded with specific recombinant growth factors, will have a known degradation rate so that the GF release can be controlled. Ideally, the first layer facing the healing site should contain those GFs that are known to act in the early period of the healing process, and its degradation rate should be faster than the deeper layer. The latter will contain those GFs that act in the subsequent period and will be released thereafter. The degradation time of the first layer should be of about 1 week, while the inner layer will have a longer degradation time so as to allow GF release for at least 4 weeks of the surgical procedure. The outer layer of the membrane could be composed of collagen or polymer with a longer degradation time, to allow GF release from the inner layer toward the defect site. The outer layer will act as a protective membrane avoiding infiltration of soft tissues in the healing site. The concentration of the recombinant growth factors embedded in the multilayer membrane will be determined to provide their constant release of a similar concentration as present in the coagulum of each of the GFs, for the predetermined period.

8.11.2 Future Trends in Endodontic Regenerative Therapy

There are two aspects for tissue regeneration in endodontics: *regenerative endodontic procedures*, defined as "biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of

the pulp-dentin complex" [200], and *guided tissue regeneration* (*GTR*) *procedures* that are performed during surgical endodontic treatments in order to improve the outcome of the surgery and to promote periodontal bone healing [201].

8.12 Regenerative Endodontic Procedures

Traditionally, long-term calcium hydroxide root canal dressing was used to induce apexification of immature teeth with pulpal necrosis before placing an obturation material. However, calcium hydroxide apexification has several limitations including a required long duration for formation of the calcified barrier (months to years), multiple appointments needed, the adverse effect of long-term calcium hydroxide dressing on the mechanical properties of the tooth dentin, and the risk of infection due to the absence of a definitive root canal filling during the long-term dressing period [200, 202].

Mineral trioxide aggregate (MTA) has been successfully used as a modern alternative treatment for calcium hydroxide apexification, with success rates of over 90 %. MTA induces apexification and enables an immediate obturation of open apex teeth, due to its ability to induce cementum-like hard tissue, its sealing property, its ability to set up in the presence of moisture, and its biocompatibility [202] (Fig. 8.6).

However, it had been claimed that calcium hydroxide- or MTA-based apexification treatments may not enable further root development and that the immature teeth remain vulnerable to fractures. In contrast, regenerative endodontic procedures (sometimes termed "revascularization") were recently proposed as an alternative to the apexification procedures in immature teeth with

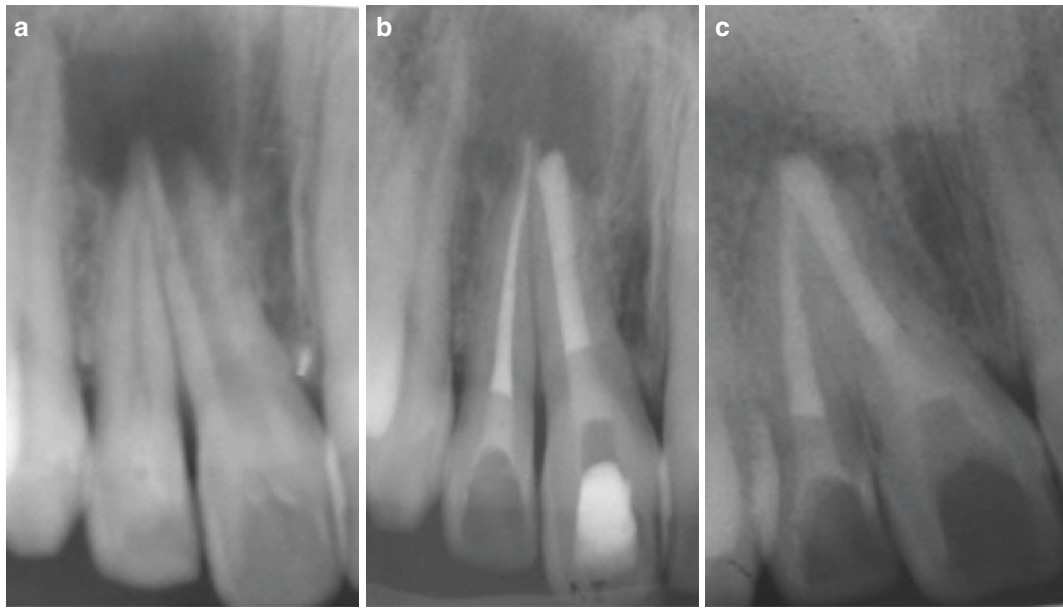

Fig. 8.6 A 15 yrs old female patient presented with an open apex right upper central incisor, diagnosed with pulp necrosis, acute apical abscess, and a large periapical lesion (The adjacent lateral incisor was also diagnosed with pulp necrosis, and was scheduled for a routine endodontic treatment) (**a**). Following non-surgical root canal treatment, a calcium hydroxide paste was used as an inter-appointment intra-canal medicament. Two weeks later, the tooth was a-symptomatic, and a 5-6 mm MTA apical plug was placed. The remainder of the canal system was restored with glass ionomer applied directly to the MTA (**b**). A bonded composite material was later used to restore the tooth crown. At 12 months follow-up, the tooth remained a-symptomatic, and the radiographic evaluation revealed a process of periapical healing (**c**)

pulpal necrosis and are aimed to enable restoration of pulpal function and subsequent completion of root development and, thus, may offer better long-term prognosis, higher resistance to fractures, and capability for immune response of the regenerated pulp-dentin complex [200] (Fig. 8.7).

Due to its alleged advantages, regenerative endodontics has gained much attention and popularity in the past decade. However there are not enough scientific evidences in the literature regarding this new treatment. A recent systematic review found that there are only a few cohort studies and many low-level studies, mainly case series or case reports, that assessed the outcome of regenerative endodontic therapy [203]. In addition, another recent study reported on significant missing concepts in pulp regeneration which may explain why it may be difficult to establish pulp-dentin regeneration and called for further animal studies and testing of its safety via clinical trials [204]. This lack of adequate high-level studies assessing the biological and clinical

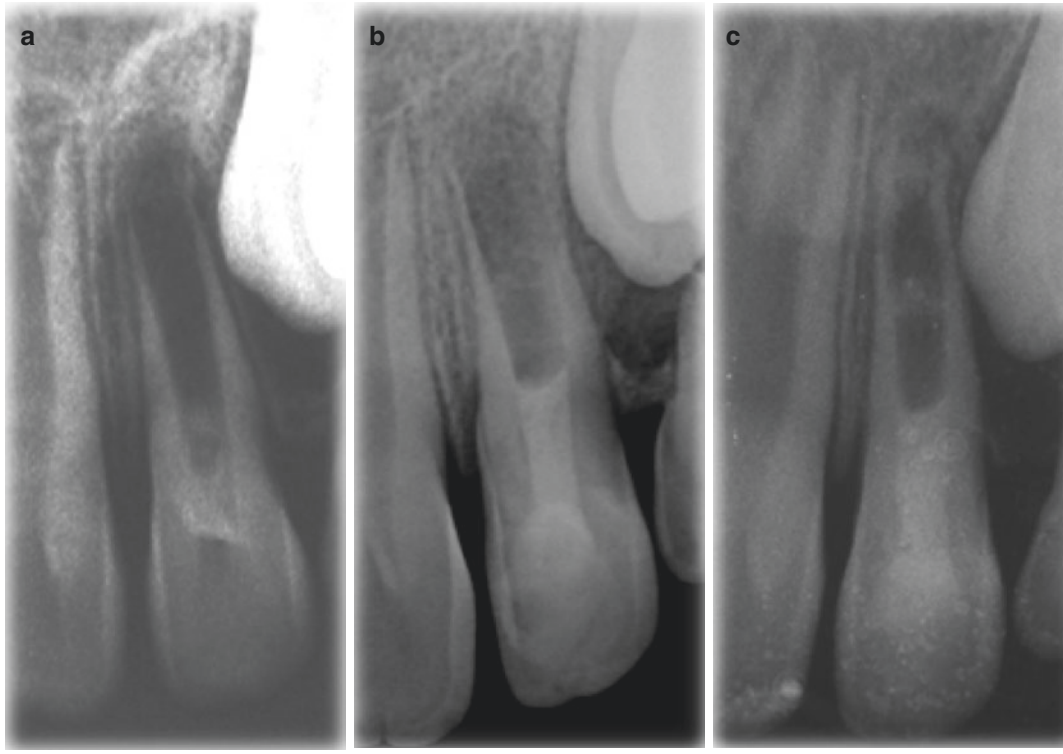

Fig. 8.7 Regenerative endodontic procedure ("revascularization") in an immature lateral incisor with an open apex (Courtesy of Dr. Shlomo Elbahary): 9 yrs old male patient presented with an immature left upper lateral incisor, diagnosed with pulp necrosis and chronic apical abscess (**a**). During the 1st appointment, the tooth was isolated, anesthetized and a standard endodontic access cavity was prepared. The root canal was irrigated with 20ml NaOCl, followed by saline. A calcium hydroxide paste was used as an inter-appointment intra-canal medicament. At the 2nd appointment 3 weeks later, the tooth was a-symptomatic and without any signs of persistent infection. The tooth was isolated and anesthetized with 3% mepivacaine without vasoconstrictor, the root canal was irrigated with 20ml of 17% EDTA and dried with paper points. Bleeding into the root canal space was achieved by over-instrumenting and rotating a pre-curved K-file at 2-3 mm past the apical foramen until the canal was filled with blood to the level of the cemento-enamel junction. The stimulated bleeding is aimed to deliver stem cells into the root canal and to create an intra-canal scaffold (the ensuing blood clot). The bleeding was stopped and a 2-3 mm layer of Mineral Trioxide Aggregate (MTA) capping was placed over the blood clot, covered with a layer of glass ionomer. A bonded composite material was used to restore the tooth crown (**b**). At 5 months follow-up, the tooth remained a-symptomatic, and the radiographic evaluation revealed a process of periapical healing and subsequent continued root development (**c**)

aspects of regenerative endodontics constitutes a significant knowledge gap in the endodontic literature [203, 204], thus advocates a rational decision-making and strict case selection.

8.13 Guided Tissue Regeneration During Surgical Endodontic Treatments

Surgical endodontic treatment may be indicated for teeth with periapical pathology when nonsurgical retreatment is impractical [205–207]. Modern endodontic surgical technique uses magnification and illumination devices, minimal root resection bevel, ultrasonic root-end preparation to a depth of 3–4 mm, and biocompatible root-end filling materials [201, 208]. A success rate of over 90% has been reported with this technique [205, 206, 208, 209].

Complete periapical healing following endodontic surgery includes regeneration of alveolar bone, periodontal ligament, and cementum [210]. The use of GTR techniques has been proposed as an adjunct to endodontic surgery in order to promote periodontal hard tissue healing [201, 210–227]. However, there is a debate regarding the effectiveness of GTR in endodontic surgery and its specific indications in that use [201, 210–213, 215–227].

The main difference between endodontic and periodontal therapy is that in endodontic surgery, flap elevation procedures are performed only to achieve surgical access since the marginal periodontium is usually healthy. In contrast, periodontal treatments are performed in diseased periodontal tissues in order to treat them [201, 210, 228]. In addition, the periodontal lesion is considered as an open wound, whereas the endodontic periapical lesion is primarily a closed wound [201, 210, 229].

From the evidences in the current literature, it seems that endodontic surgery GTR may be indicated to improve the outcome of bone regeneration only in cases with certain periapical lesions, such as large periapical lesions and "through-and-through" lesions [201].

Evidently, present knowledge on new strategies for periodontal, endodontic, and alveolar bone regeneration is being continuously enlarged. New evidence concerning application of new methodologies for tissue regeneration in the different disciplines as has been presented in this chapter will lead to clinical applications that will apparently allow to treat even the most extreme cases. Today's evidence shows definite limits on tissue and organ regeneration, especially in the dental field. Everyday clinical practice is hardly applying most of these uprising technologies; on the other hand, these must be evaluated on the long term: tissue stability and behavior throughout time, and mainly possible side effects, not only locally but systemically, will have to be evaluated before we will be able to apply them as regular clinical routine based on the evidence.

Naturally, the evidence on new technologies is still sparse, and in most cases it is based on in vitro and research animal studies, where human evidence and especially controlled long-term clinical evaluations are indispensable to base their application.

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