Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2019;10:1s:216-222.

Telomerase and Oral Cancer

Arunachalam Meyyappan[1*] Sathish Kumar Mahadevan[2] Vinesh Ezhil Rajan[3] Mary Tresa Jeya Priya[4] Chandra Mohan. K[5] Deepak Velu[6]

[1]Senior Lecturer, Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.
[2]Professor and Head, Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.
[3]Reader, Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.
[4]Reader, Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.
[5]Senior Lecturer, Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.
[6]Reader, Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.

ABSTRACT

Background: The development of malignant neoplasms is a multistep process and it is believed that multiple genetic alterations are involved. There are various markers used to detect and to see the progression of cancers. One among them is telomerase. Telomerase has recently come into the limelight as one of the most prevalent tumor markers, due to its nearly ubiquitous presence in malignant tissues and absence from most somatic tissues. In view of the close association between telomerase and malignancy, this molecule may prove to be a useful marker for malignancy. The essential role of telomeres in unlimited cell proliferation and that of the enzyme in telomere maintenance have suggested that telomerase inhibitors may be effective in cancer therapy. This review focuses on structures of telomerase, its function and about the diagnostic and therapeutic potential of telomerase.

Keywords: Telomeres, telomerase, OSCC.

INTRODUCTION

The importance of telomerase came into lime light recently due to its presence in malignant tumors and absent in somatic tissues, so it has been used as a molecular marker in oral carcinogenesis more recently. In normal human somatic cells, the telomeres are critically short which suggests that they cause irreversible cell growth arrest and cellular senescence(1) . In contrast, in most human cancers telomere shortening are compensated mainly due to activation of telomerase (2). So with the help of telomerase, telomere become stable and grow permanently the repression of this enzyme activity in normal human somatic cells acts as a tumor suppressive mechanism.

One of the common cancer of oral cavity is Oral squamous cell carcinoma (OSCC), off late the treatment of OSCC is improved but the survival rate of OSCC still remains poor due to variety of reasons(3) . Many research and studies indicate that telomerase is a useful marker in cancer detection and evaluating prognosis. The enzyme that is present in telomerase maintenance and function of telomere in unlimited cell proliferation have suggested that telomerase inhibitors may be effective in treatment of cancer, so the diagnostic and therapeutic potential of telomerase could play a important role in prognosis of the cancer patients. In this article we review the structure and functions of telomere and telomerase and their role in carcinogenesis and senescence.

Telomere, telomerase-structure, function and homeostasis

Telomeres. telomeres cap each end of eukaryotic chromosomes, specialized structures which stabilize chromosomes by protecting chromosomes

Received: Aug. 12, 2019**: Accepted**: Oct. 17, 2019
***Correspondence Dr. Arunachalam Meyyappan.**
Department of Oral Pathology, Karpaga Vinayaga Institute of Dental Sciences, Maduranthakam, Tamil Nadu, India.
Email: Not Disclosed

pISSN 2278-0076
eISSN 2321-9270

from degradation and terminal fusion (4). Telomeres serves as attachment points to nuclear matrix(5) aiding the movement of chromosome within the nuclear matrix(4). and it may alter nearby gene transcription by a process called telomere silencing(6). Lastly, telomeres also acts as a buffer against the loss of terminal sequences inherent to the replication of linear DNA molecules (7)(8)(9).

Chromosomal ends are repetitive with telomere, shortens with each cell division because of incomplete replication of the 3' ends. DNA polymerase can synthesize DNA only in the 5' to 3' direction and needs a short RNA primer to initiate DNA synthesis, so lagging-strand synthesis remains incomplete. This phenomenon is called the end-replication problem(10).

Telomeres have a species-specific length setting which is constant over the generations. Telomere length is stable in several immortal human cell lines, suggesting that telomere elongation is maintained by a regulatory mechanism. In human cells, telomeric repeat binding factor proteins are shown to be important in regulating telomere length. Human telomeres contain two related TTAGGG repeat binding factors, TRF1 and TRF2(11)(12).Both proteins are located at chromosome ends where they function as protection and maintenance of telomeric DNA.

TRF1 helps in suppressing of telomere elongation and is involved in a negative feedback mechanism that stabilizes telomere length. Long-term overexpression of TRF1 in a telomerase-positive tumour-cell line resulted in gradual progressive telomere shortening. Conversely, telomere elongation was induced by expression of a dominant-negative TRF1 mutant that inhibited binding of endogenous TRF1 to telomeres(11) .

A recent study showed that a dominant-negative form of TRF2 increases the number of chromosome fusions in cancer cells and decreases the quantity of telomeric DNA 3' overhang.

Consequently, TRF2 prevents recombination between two telomeres by controlling the structure of the very end of chromosomal DNA(13) . The length of human telomeres is governed by a homeostatic mechanism.

Telomerase synthesizes telomeric DNA onto chromosome ends(14)(15). Telomerase plays an important role in maintaining telomere length. In 1985, telomerase was firstly identified from Tetrahymena cell-free extracts(14). In 1989, telomerase activity that satisfied the requirements for a human telomere terminal transferase was detected in crude human cell extracts(15). By 1994, it was found that telomerase activity was detected in germline cells and most cancer cells, whereas most normal somatic cells had not shown telomerase activity(16).

Telomerase. loss of telomeric DNA sequences and shortening of telomeres with each round of semiconservative DNA synthesis are predicted by the inability of DNA polymerases to replicate the termini of linear molecules(7)(8)(9). This 'end replication problem' can be overcome by addition of terminal sequences by transposition, as in *Drosophila* , or by recombination as sometimes occurs in yeast (17)(18)(19). Telomerase is active in the vast majority of tumours, but not in normal somatic tissues, and prevents progressive shortening of telomeres with cell division, probably giving tumour cells a growth advantage over normal cells.

Telomeres in human somatic cells differ in length and stability for adults from those in germline and fetal cells. In sperm, telomeric DNA tracts are =20 kb long(20)(21)(22)(23)(24)(25)(26) and are maintained at this length, or possibly even elongated, with increasing donor age(27) . on the other hand, in somatic tissues telomeres are significantly shorter and their size decreases as donor age increases(28) (21)(27)(26)(29)(30), a process that is accelerated in individuals with premature-aging syndromes(27) (30). Lastly, cell division plays a pivotal role in loss of telomeric DNA in cultured somatic cells. (28 ; Allsopp *et al,* submitted), and telomere length is a good predictor in the residual proliferative capacity of cells *in vitro* and *in vivo* (27) .

Cellular senescence

limited proliferative capacity of normal cultured cells are defined as cellular senescence (31). This point is termed mortality stage 1 (M1), and telomere length usually shortens to about 5 kb in human cells. When onco viral infection occurs, cells

can further extend their life span. When telomere shortening reaches its limit, cells cannot proliferate any more, This point is termed immortality stage 2 (M2)(32)(33) . However, after specific mutational events that result in telomerase reactivation, a rare immortal cell arises from this population of cells in M2. Activation of telomerase is considered an important step in immortalization. Thus, telomerase is activated in most malignant cells, resulting in permanent proliferation.

The molecular mechanisms underlying senescence have been poorly understood. However, in the last few years several progress has been made toward identifying the pathways executing senescence, one of which is the telomere aging clock theory(34)(35) .

Regulation of telomerase

hTERT

hTERT is one of the telomerase protein components and is the catalytic subunit of human telomerase(36). This component is also found in malignant tumour cells but is largely absent from normal cells. This protein mainly acts as a reverse transcriptase. Reconstitution experiments both in vitro and in vivo strongly suggest that hTERT is a major determinant of human telomerase activity (37)(38).

Activation of telomerase

Telomerase can be activated by oncogenes including c-myc [30±35], SV40 and H-ras human papilloma virus E6 [36±38](39), c-myc induces telomerase(40) and a cultured cell line showed a profound decrease in telomerase activity after c-myc antisense oligomer treatment, whereas cells treated with c-myc sense oligomers showed essentially no change in telomerase activity(41). down- regulation of p16 expression, in combination with induction of telomerase activity by E6, is able to immortalize epithelial cells efficiently (42). Moreover, the ectopic expression of hTERT in combination with two oncogenes, oncogenic allele of H-ras and SV40 large-T oncoprotein, results in direct tumourigenic conversion of normal human epithelial and fibroblast cells(39).

Inhibition of telomerase

cellular senescence is induced by introduction of normal human chromosome 3 into cancer cells, accompanied by suppression of telomerase activity and shortening of telomere length(43)(44)

It was reported that telomerase is activated and hTERT mRNA is upregulated by inhibition of histone deacetylase by trichostatin A in telomerase-negative cells. Therefore, repression of hTERT in human cells must be promoted by histone deacetylation(45) . Another paper reported that hTERT showed the presence of multiple alternately spliced transcripts(46) .

Thus, inhibition of telomerase may be of great therapeutic potential in the treatment of malignant tumours. Repression of telomerase activity may represent an effective mechanism for ensuring telomere shortening, and unexpected activation of this enzyme may prevent telomere shortening, leading to cellular immortalization and malignant progression.

Diagnostic potential

TRAP (telomeric repeat amplification protocol) assay, The highly-sensitive method based upon a polymerase chain reaction (PCR) provides the means to analyse telomerase in a wide variety of tissues(16). It is available since 1994, and has become standard method for detecting the telomerase activity. This method makes it possible to detect telomerase activity in a very small number of cells, a major advantage for examining clinical specimens. Evidence has accumulated that this assay may be useful as a potential diagnostic tool for cancer. For example, 80.1% of lung cancers(47), 85% of breast cancers(48) , 85% of gastric cancers(49), 87% of specimens of oesophageal cancer(50), 85% of hepatocellular carcinomas(51), 81% of colorectal cancers(52) , 71% of renal cell carcinomas(53), and 95% of pancreatic cancers (54) possess telomerase activity.

Apart from TRAP assay recently immunohistochemistry(IHC) were also used as an alternative method to detect the telomerase activity in cancers(55)

Therapeutic potential

Almost all types of cancer express telomerase activity, so the development of telomerase inhibitors may contribute to improved anti-cancer therapy. Treatment of subcutaneous tumours in nude mice with an antisense oligonucleotide against hTR significantly suppressed the tumour growth through induction of apoptosis(56). A hammer-head ribozyme directed against hTR could serve as an inhibitor of telomerase(57)(58). Azidothymidine and carbovir inhibited telomerase activity and induced senescence-like processes in cultures of immortal mouse fibroblasts(59)(60). New quinolones(61), an extracellular polysaccharide from marine microalga(62), and Protein Kinase C (PKC) inhibitors(63) also have an inhibitory effect on the telomerase activity.

Gene therapy for cancer implies that ideally selective tumour cell killing or inhibition of tumour cell growth can be achieved(64).

Role of telomerase in oral cancer and pre cancer

7.1. Telomerase in OSCC

telomerase activity are positive in About 80±90% of squamous cell carcinomas in the head and neck including oral carcinoma (65)(66). This frequency is similar to that of malignancy of other organs(2). This evidence indicates that telomerase plays a major role in telomere maintenance in OSCC.

telomerase activity shows stastically significant difference for T1 and T2 cancers compared with T4cancers(67).The proliferation marker, Ki-67 labeling index, is significantly higher in OSCC with high telomerase activity than in those with low or negative telomerase activity(68).

Telomerase in premalignant oral lesions

Several studies have suggested that some lesions of leukoplakia possess telomerase activity(65)(66). These results indicate that telomerase activity is a useful marker of oral carcinogenesis and malignant transformation from premalignant lesions and conditions. In some cases, tissue adjacent to OSCC also possessed telomerase activity(69). This activity is considered to originate from not only infiltrating lymphocytes, but also preneoplastic lesions or infiltrating tumour cells. Therefore, telomerase may be useful as a biomarker for assessing the risk of cancer in patients with precancerous oral lesions and conditions. Similarly to the case of OSCC, Ki-67 was significantly higher in leukoplakia with high telomerase activity than in that with negative or low activity(68). Accordingly, leukoplakia with telomerase activity is considered to have more proliferative capacity than that without telomerase activity.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

REFERENCES

1. Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mutation Research 1991;256:271±82.
2. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. European Journal of Cancer 1997;33:787±91.
3. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. New England Journal of Medicine 1993;328: 184±94.
4. Blackburn EH: Structure and function of telomeres. Nature 350: 569-573. 1991.
5. de Lange T: Human telomeres are attached to the nuclear matrix. EMBO J 11: 717-724, 1992
6. Karpen G: Position-effect variegation and the new biology of heterochromatin. Curr Opin Genet Dev 4: 281-291, 1994.
7. Olovnikov AM: Principle of marginotomy in template synthesis of polynucleotides. Doklady Biochem 201: 394-397, 1971.
8. Olovnikov AM: A theory of marginotomy: the incomplete copying of template margin in enzymatic synthesis of polynucleotides and biological significance of the phenomenon. J Theor Biol 41: 181-190, 1973.
9. Watson JD: Origin of concatemeric T7 DNA. Nature New Biol 239: 197-201, 1972.
10. Levy MZ, Allsopp RC, Futcher AB, Greider CW, Harley CB. Telomere end-replication problem and cell aging. Journal of Molecular Biology 1992;225:951±60.
11. Van Steensel B, deLangeT. Control of telomere length by the human telomeric protein TRF1. Nature 1997;385:740±3.
12. Smogorzewska A, van Steensel B, Bianchi A, Oelmann S, Shaefer MR, Schnapp G, de Lange T. Control of human telomere lengthby

TRF1andTRF2.MolecularandCellularBiology 2000;20:1659±68.
13. van Steensel B, Smogorzewska A, de Lange T. TRF2 protects human telomeres from end-to-end fusions. Cell 1998;92:401±13.
14. Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in tetra hymena extracts. Cell 1985;43:405±13.
15. Morin GB. The human telomere terminal transferase enzyme is a ribonucleoprotein that synthesizes TTAGGG repeats. Cell 1989;59:521±9.
16. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PL, et al. Specific association of human telomerase activity with immortal cells and cancer. Science1994;266:2011±5.
17. Biessmann H and Mason JM: Genetics and molecular biology of telomeres. Adv Genet 30: 185-249, 1992.
18. Pluta AF and Zakian VA: Recombination occurs during telomere formation in yeast. Nature 337: 429-433, 1989.
19. Lundblad V and Blackburn EH: An alternative pathway for yeast telomere maintenance rescues *estl~* senescence. Cell 73: 347-360, 1993.
20. Lejnine S, Makarov VL and Langmore JP: Conserved nucleoprotein structure at the ends of vertebrate and invertebrate chromosomes. Proc Natl Acad Sci USA 92: 2393-2397, 1995.
21. de Lange T, Shiue L, Myers RM, Cox DR, Naylor SL, Killery AM and Varmus HE: Structure and variability of human chromosome ends. Mol Cell Biol 10: 518-527, 1990.
22. Cross SH, Allshire RC, McKay SJ, McGill NI and Cooke HJ: Cloning of human telomeres by complementation in yeast. Nature 338: 771-774, 1989.
23. Cooke HJ and Smith BA: Variability at the telomeres of the human X/Y pseudo autosomal region. Cold Spring Harbor Symp Quant Biol LI: 213-219, 1986.
24. Allshire RC, Gisden JR, Cross SH, Cranston G, Rout D, Sugawara N, Szostak JW, Fantes PA and Hastie ND: Telomeric repeat from *T. termophila* cross-hybridizes with human telomeres. Nature 332: 656-659, 1988.
25. Cross S, Lindsey J, Fantes J, McKay S, McGill N and Cooke H: The structure of a sub terminal repeated sequence present on many chromosomes. Nucleic Acids Res 18: 6649-6657, 1990.
26. Hastie ND, Dempster M, Dunlop MG, Thompson AM, Green DK and Allshire RC: Telomere reduction in human colorectal carcinoma and with ageing. Nature 346: 866-868, 1990.
27. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW and Harley CB: Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 89: 10114-10118, 1992.
28. Harley CB, Futcher AB and Greider CW: Telomeres shorten during ageing of human fibroblasts. Nature 345: 458-460, 1990. Lindsey J, McGill NI, Lindsey LA, Green DK and Cooke HJ: *In vivo* loss of telomeric repeats with age in humans. Mut Res 256: 45-48, 1991.
29. Vaziri H, Schächter F, Uchida I, Wei L, Zhu X, Effros R, Cohen D and Harley CB: Loss of telomeric DNA during aging of normal and trisomy 21 human lymphocytes. Am J Hum Genet 52: 661- 667, 1993.
30. Haydick L. The limited in vitro lifetime of human diploid cell strains. Experimental Cell Research1965;37:614±36.
31. Wright WE, Shay JW. The two-stage mechanism controlling cellular senescence and immortalization. Experimental Gerontology 1992;27:383±9.
32. Shay JW, Wright WE, Werbin H. Defining the molecular mechanisms of human cell immortalization. Biochimica et Bio- physica Acta 1991;1072:1±7.
33. Ishikawa F. Aging clock: the watchmaker's masterpiece. Cellular and Molecular Life Sciences 2000;57:698±704.
34. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, et al. Extension of life-span by introduction of telomerase into normal humancells. Science1998;279:349±52.
35. Nakamura TM, Morin GB, Chapman KB, Weinrich SL, Andrews WH, Lingner J, et al. Telomerase catalytic subunit homologs from fission yeast and human. Science 1997;277: 955±9.
36. WeinrichSL, PruzanR, MaL, OuelletteM,TesmerVM,Holt SE,etal. Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT. Nature Genetics 1997;17:498±502.

37. Nakayama J, Tahara H, Tahara E, Saito M, Ito K, Nakamura H,etal. Telomerase activation by hTRTin human normal fibroblasts and hepatocellular carcinoma. Nature Genetics 1998;18:65±8.
38. Hahn WC, Counter CM, LundbergAS, Beijersbergen RL, Brooks MW, Weinberg RA. Creation of human tumour cells with defined genetic elements.Nature1999;400:464±8.
39. WangJ, XieLY, AllanS, BeachD, HannonGJ. Mycactivates telomerase. Genes and Development 1998;12:1769±74.
40. Fujimoto K, Takahashi M. Telomerase activity in human leu- kemic cell lines is inhibited by antisense penta deca deoxy nucleotides targeted against c-myc mRNA. Biochemical and Biophysical ResearchCommunications1997;241:775±81.
41. Kiyono T, Foster SA, Koop JI, McDougall JK, Galloway DA, Klingelhutz AJ. Both Rb/p16INK4a inactivation and telomerase activity are required to immortalize human epithelial cells. Nature 1998;396:84±8.
42. Tanaka H, Shimizu M, Horikawa I, Kugoh H, Yokota J, Barrett JC, et al. Evidence for a putative telomerase repressor gene in the 3p14.2-p21.1 region. Genes, Chromosomes and Cancer 1998;23:123±33.
43. Cuthbert AP, Bond J, Trott DA, Gill S, Broni J, Marriott A, et al. Telomerase repressor sequences on chromosome 3 and induction of permanent growth arrest in human breast cancer cells. Journal of NationalCancerInstitute1999;91:37±45.
44. Cong YS, Bacchetti S. Histone deacetylation is involved in the transcriptional repression of hTERT in normal human cells. Journal of Biological Chemistry 2000;275:35665±8.
45. Ulaner GA, Hu JF, Vu TH, Giudice LC, Ho man AR. Telo- merase activity in human development is regulated by human telomerase reverse transcriptase (hTERT) transcription and by alternate splicing of hTERT transcripts. Cancer Research 1998;58:4168±72.
46. Hiyama K, Hiyama E, Ishioka S, Yamakido M, Inai K, Gazdar AF, et al. Telomerase activity in small-cell and non-small-cell lung cancers. Journal of National Cancer Institute 1995;87: 895±902.
47. Landberg G, Nielsen NH, Nilsson P, Emdin SO, Cajander J, RoosG.Telomerase activity is associated with cell cycle deregulation in human breast cancer. Cancer Research 1997;57: 549±54.
48. HiyamaE, YokoyamaT, TatsumotoN, HiyamaK, Imamura Y, Murakami Y, et al. Telomerase activity in gastric cancer. CancerResearch1995;55:3258±62.
49. Takubo K, Nakamura K, Izumiyama N, Mafune K, Tanaka Y, MiyashitaM, et al. Telomerase activity in esophageal carcinoma. Journal of Surgical Oncology 1997;66:88±92.
50. Kojima H, Yokosuka O, Imazeki F, Saisho H, Omata M. Telomerase activity and telomere length in hepato cellular carcinoma and chronic liver disease. Gastroenterology 1997;112: 493±500.
51. Li ZH, Salovaara R, Aaltonen LA, Shibata D. Telomerase activity is commonly detected in hereditary nonpolyposis color- ectal cancers. American Journal of Pathology 1996;148:1075±9.
52. MehleC, PiatyszekMA, LjungbergB, ShayJW, RoosG. Telomerase activity in human renal cell carcinoma. Oncogene 1996;13:161±6.
53. Hiyama E, Kodama T, Shinbara K, Iwao T, Itoh M, Hiyama K, et al. Telomerase activity is detected in pancreatic cancer but not inbenigntumors.CancerResearch1997;57:326± 31.
54. Jayanthi palani, vidya Lakshmi narayanan, ranganathan kannan. immunohistochemical detection of human telomerase reverse transcriptase in oral cancer and pre cancer.ijdr,22(2),2011
55. Kondo Y, Koga S, Komata T, Kondo S. Treatment of prostate cancerinvitroandinvivowith2-5A-anti-telomeraseRNA component. Oncogene 2000;19:2205±11. Kanazawa Y, Ohkawa K, Ueda K, Mita E, Takehara T, Sasaki Y, et al. Hammerhead ribozyme-mediated inhibition of telomerase activity in extracts of human hepatocellular carcinoma cells. Biochemical and Biophysical Research Communications 1996;225:570±6.
56. Yokoyama Y, Takahashi Y, Shinohara A, Wan X, Takahashi S, Niwa K, et al. The 5H-end of hTERT mRNA is a good target for hammerhead ribozyme to suppress telomerase activity. Bio-chemical and Biophysical Research Communications 2000;273: 316±21.

57. Strahl C, Blackburn EH. E ects of reverse transcriptase inhibitors on telomere length and telomerase activity in two immortalized human cell lines. Molecular and Cellular Biology 1996;16:53±65.
58. Yegorov YE, Chernov DN, Akimov SS, Bolsheva NL, Krayevsky AA, Zelenin AV. Reverse transcriptase inhibitors suppress telomerase function and induce senescence-like processes in cultured mouse fibroblasts. FEBS Letters 1996;389: 115±8.
59. Yamakuchi M, Nakata M, Kawahara K, Kitajima I, Maruyama I. New quinolones, ofloxacin and levofloxacin, inhibit telomerase activity in transitional cell carcinoma cell lines. Can- cer Letters 1997;119:213±9.
60. Sogawa K, Sumida T, Hamakawa H, Yamada T, Matsumoto K, Matsuda M, et al. Inhibitory e ect of a marine microalgal polysaccharide on the telomerase activity in K562 cells. Research Communications in Molecular Pathology and Pharmacology 1998;99:259±65.
61. Ku WC, Cheng AJ, Wang TC. Inhibition of telomerase activity by PKC inhibitors in human nasopharyngeal cancer cells in culture. Biochemical and Biophysical Research Communications 1997;241:730±6
62. Davis BM, Koc ON, Lee K, Gerson SL. Current progress in the gene therapy of cancer. Current Opinion in Oncology 1996;8: 499±508.
63. Kannan S, Tahara H, Yokozaki H, Mathew B, Nalinakumari KR, Nair MK, et al. Telomerase activity in premalignant and malignant lesions of human oral mucosa. Cancer Epidemiol Biomarkers Prev 1997;6:413±20.
64. Sumida T, Sogawa K, Hamakawa H, Sugita A, Tanioka H, Ueda N. Detection of telomerase activity in oral lesions. Journal of Oral Pathology andMedicine1998;27:111±5.
65. CurranAJ, StDenisK, IrishJ, GullanePJ, MacMillanC, Kamel-ReidS. Telomerase activity in orals quamous cell carcinoma. Archives of Otolaryngology Head and Neck Surgery 1998;124:784±8
66. Liao J, Mitsuyasu T, Yamane K, Ohishi M. Telomerase activity in oral and maxillofacial tumors. Oral Oncology 2000;36: 347±52.
67. MaoL, El-NaggarAK, FanYH, LeeJS, LippmanSM, Kayser S, et al. Telomerase activity in head and neck squamous cell carcinoma and adjacent tissues. Cancer Research1996;56: 5600±4.