CHAPTER 1

INTRODUCTION
1. Introduction:

Squamous cell carcinoma of the oral cavity (OSCC) is the most prevalent cancer in males of the Indian subcontinent, predominantly associated with the tobacco-chewing habit [1] and the absolute number of cancer deaths is projected to increase because of population growth and increasing life expectancy [2]. Despite recent advances in surgical treatment and radio/chemo therapy, the long term survival of oral cancer patients has not changed significantly [3]. Several factors are associated with poor prognosis of OSCC. Firstly, majority of the oral cancer patients are diagnosed at an advanced clinical stage, which may be possible due to ignorance or inaccessibility of medical care as knowledge of oral cancer or precancerous lesions and its risk factors among Indian population is limited [4]. Second, the development of multiple primaries has major impact on survival and outcome. About 40% of oral cancer patients die from uncontrolled loco-regional disease alone and 24% show metastases to distant sites [5]. Therefore, it is an urgent need to improve the early detection of oral carcinomas and in depth study of mechanisms involved in the development and progression of oral cancer [6]. Oral carcinogenesis is a multistep process involving functional deregulation of several genes including those involved in cell proliferation and apoptosis and OSCC’s have also been repeatedly linked to apoptotic dysregulation [7]. Altered expression or mutation of genes encoding key apoptotic proteins can provide cancer cells with both intrinsic survival advantage and an inherent resistance to therapy [8].

Apoptosis or programmed cell death is controlled by a diverse range of cell signals and effected via two major pathways namely extrinsic and intrinsic [9]. The extrinsic pathway is triggered by binding of extracellular ligands and oligomerization of transmembrane receptors. The intrinsic or mitochondrial pathway is regulated by Bcl-2 family members comprised of pro- and anti-apoptotic proteins. The dynamic balance between these opposing members play a critical role in regulating cell survival [10]. Over expression of anti-apoptotic members of the Bcl-2 family like Bcl-2 & Bcl-XL, has been shown to be associated with radioresistance [11,
12]. Bcl-2 members might, therefore, function as indicators of response to radio/chemotherapy. Mcl-1 (Myeloid cell leukemia-1), is an important anti-apoptotic member of the Bcl-2 gene family, essential for development, differentiation and proliferation [13]. Elevated levels of Mcl-1 have been detected in a variety of hematopoietic, lymphoid and solid s including head and neck carcinoma [14, 15]. Overexpression of Mcl-1 has been associated with poor prognosis and resistance to treatment in breast, cervical & gastric cancers [16-18].

Recent studies from our laboratory have demonstrated significant overexpression of Mcl-1 transcripts and protein in oral cell lines and tumors [19]. Further, we have also demonstrated Mcl-1 to be a prognostic factor in oral cancer patients treated with definitive radiotherapy [20]. Our earlier studies have also demonstrated a five to ten fold higher expression of anti-apoptotic Mcl-1L transcript, versus the pro-apoptotic Mcl-1S in oral tumors [19]. Mcl-1 has been shown to contribute in resistance of cancer cells to chemo/radio therapy [21, 22]. However there are no reports on role of Mcl-1splice variants in radiation induced apoptosis and radioresistance.

Therefore, in the present study we wanted to investigate the association of Mcl-1 isoforms with oral cancer prognosis and with radioresistance and/or chemoresistance of oral cancer cells.