Abstract. Radiation therapy plays a critical role in women with advanced-stage cervical cancer worldwide, particularly in developing countries, and most of the time it may be the only available treatment. The efficacy of radiation largely depends on the radiosensitivity of the tumor. The high radiation dose associated with therapy for cervical cancer may have severe side-effects and low-dose radiation has little effect on cervical cancer. A safe and effective radiosensitizing agent is required to allow reduction of radiation doses used and of side-effects associated with radiation for cervical cancer. In recent years, great knowledge has been gained about the effects of apoptosis, cyclo-oxygenases, angiogenesis, hypoxia and temperature on radiation, making it possible to manipulate the radiation response of cervical cancer to achieve a better treatment outcome. In this mini review, some of these factors associated with the radiosensitivity of cervical cancer are discussed.

Cervical cancer is a malignant tumor arising from cells originating in the cervix of the uterus. It is a very common malignant tumor in women and still remains one of the leading malignancies in women worldwide. About 12,360 new cases of cervical cancer were projected to occur in the USA in 2014 (1). Treatment for cervical cancer includes surgery in early stages, chemotherapy and radiation therapy in more advanced stages. Radiation has been used to treat patients with cervical cancer in advanced stages for a long time and has been of a great benefit to them. However, radioresistance has been an obstacle since application of radiation in clinical treatment for patients with cervical cancer. Enhancing radiosensitivity and reducing the dose of radiation would be one of the most promising strategies to obtain a better survival rate. In recent years, great knowledge has been gained about the effects of apoptosis, cyclo-oxygenases (COXs), angiogenesis, hypoxia and temperature on radiation, making it possible to manipulate the radiation response of cancer to achieve a better treatment outcome. In this mini review, we focus on some of these factors associated with the radiosensitivity of cervical cancer.

Apoptotic Proteins and Radiosensitivity of Cervical Cancer

Apoptosis is also called programmed cell death. It is an active process of cell death involving the sequential activation of a series of caspases (2, 3). Apoptosis is initiated through the extrinsic or the intrinsic pathway. The extrinsic pathway is triggered after binding of death receptors of the tumor necrosis factor (TNF) receptor superfamily and corresponding ligands such as FAS vs. FAS ligand (FASL) and death receptor 5 (DR5) vs. TNF-related apoptosis-inducing ligand (TRAIL) (5, 6). This signal is further propagated through caspase-8 (2, 3, 7-13). Fas-associated death domain-like IL-1β-converting enzyme inhibitory protein (FLIP) is an important inhibitor for receptor-mediated apoptosis by inhibiting caspase-8 (14, 15). The intrinsic pathway is characterized by the release of cytochrome c from the mitochondria. B-cell lymphoma extra large (BCL-XL) and B-cell lymphoma-2 (BCL2) are two important anti-apoptotic molecules. BCL2-associated death promoter protein (BAD) and BCL2-associated X protein (BAX) are two important pro-apoptotic molecules. They all belong to the BCL2 family and play important roles in intrinsic apoptosis by regulating mitochondrial membrane potential and cytochrome c release (4-6, 16, 17). BAX was the first identified pro-apoptotic member of the BCL2 protein family. BAX promotes...
apoptosis by binding to and antagonizing the BCL2 protein. Protein p-53 is traditionally regarded as an anti-proliferative protein, however, in recent years, it has been shown to be pro- and anti-apoptotic in human testicular cancer depending on cell context (18). In response to extrinsic or intrinsic stimulus including radiation, cervical cancer cells undergo organized degradation of cellular organelles by activated proteolytic caspases. Cervical cancer cells undergoing apoptosis exhibit a characteristic morphology, including blebbing, loss of membrane asymmetry and attachment, shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation.

The radiosensitivity of cervical cancer mainly depends on the balance between pro- and anti-apoptotic proteins in cancer cells. Kitahara and colleagues studied nearly 20 tumors and identified a set of corresponding proteins associated with radiosensitivity of cervical squamous cell carcinomas, and established a predictive method to detect the cell response to radiation (19). Thus, it is possible to predict cancer radiosensitivity by identifying some specific molecules in cancer. To date, several proteins such as BCL2, BAX, and p53 have been identified to be associated with radiosensitivity of cancer cells.

**BCL2 and BAX**

Apoptosis plays an important role in cancer cell radiation sensitivity. BCL2 family proteins such as BCL2, BCL-XL and BAX are some of the most important apoptosis regulators associated with radiation. These proteins also modulate mitochondrial morphology (20-22) and cellular metabolism (23) independent from cell death mechanisms. BCL2 and BCL-XL function to repress apoptosis and are important anti-apoptotic proteins (16, 24). They are stably inserted in intracellular membranes, including endoplasmic reticulum, and inhibit apoptosis by sequestering the pro-apoptotic BCL2 family proteins, such as BAD and BAX, into inactive complexes (25).

In cervical cancer, the expression of BCL2 and BAX might correspond to disease stage progression or cell radiosensitivity. Saegusa et al. compared 46 cervical intraepithelial neoplasias (CIN) I/II, 75 CIN III, and 60 invasive squamous cell carcinomas (ISCC) by immunohistochemical staining for BCL2 and BAX. They also investigated the presence of human papillomavirus (HPV)-DNA. They found that BCL2 may play an important role in a relatively early stage of cervical tumorigenesis, in association with BAX expression and HPV infection (26). Crawford et al. used immunohistochemistry to determine prognosis in patients with cervical cancer. They studied 46 patients with primary cervical cancer and 28 women with recurrent carcinoma and found that positive staining for BCL2 was associated with a better 5-year survival (27). Mukherjee et al. studied 78 cases of cervical cancer that were the same stage (II A and B) (28). All patients were treated with radiotherapy with a dose varying from 35 to 50 Gy. Subsequent to the completion of radiotherapy, all patients underwent surgery 4-6 weeks later. By pathological examination, 51% of the cases (40/78) showed a complete response to therapy with no viable tumor cells; 49% of cases (38/78) had residual tumors ranging from a small focus to lesions extending through more than half the thickness of the cervical wall. BCL2 and BAX proteins were studied using IHC on the paraffin sections of the biopsies (pre-treatment) of those patients who failed to respond to radiotherapy and compared to similar studies on biopsies of patients who had a complete response to radiotherapy. In the radioresistant cases, 15% showed positivity for BCL2. None of the radiosensitive tumors were positive for BCL2; 75% of the radiosensitive tumors were positive for BAX, whereas only 19% of the radioresistant tumors were positive for BAX. These data strongly suggest that BCL2 and BAX could play a role in determining which tumors are likely to respond to radiotherapy.

Furthermore, Harima et al. studied a group of 44 patients with cervical cancer, including three with recurrent cervical stump carcinomas, and these patients were treated with definitive radiotherapy (29). They investigated the relationship between the expressions of the BAX and BCL2 proteins and the response to radiotherapy after the administration of 10.8 Gy in these patients. BAX and BCL2 protein expressions prior to radiotherapy did not correlate with response and survival. However, the BAX and BCL2 protein expressions after radiotherapy correlated with both response and survival. Those patients with BAX-positive tumors showed significantly better responses than those with BAX-negative tumors after 10.8-Gy radiation. In contrast, those with BCL2-positive tumors showed significantly poorer responses than those with BCL2-negative tumors after radiation. Increased BAX expression after the 10.8 Gy radiotherapy was found to be correlated with good survival. In contrast, increased BCL2 expression after such radiotherapy was correlated with poor survival. The levels of BAX and BCL2 expression after radiotherapy are useful prognostic markers in patients with human cervical carcinoma.

In line with this, overexpression of the anti-apoptotic protein BCL2 is associated with resistance to radiation in several types of cancer cells. Hara et al. transfected a human cervical cancer cell line (HeLa/BCL2) with a BCL2 expression plasmid. Compared with the parental wild-type cells, the transfected cell line was more resistant to radiation (30).

On the other hand, overexpression of BAX causes apoptosis in multiple cervical cancer cell lines and primary cervical cancer cells. Huh et al. infected cell lines and primary cervical cancer cells with recombinant BAX adenovirus. They found significant cytotoxicity and apoptosis was detected in all infected cervical cancer cell lines and infected patient-derived primary cervical cancer cells (31). Ohno et al. investigated 20 patients with cervical...
cancer by biopsy before and after radiation. They found that the positive rate for BAX increased from 15% (in three out of 20 patients) before irradiation to 60% (in 12 out of 20 patients) after 9 Gy was administered. In addition, there was a significant correlation between BAX expression and apoptosis positivity after the 9 Gy were administered (32). Thus, checking the expressions of BAX and BCL2 of cervical cancer cells could predict the outcome of radiation treatment for cervical carcinoma.

p53

p53 is a transcription factor. As a tumor-suppressor protein, p53 is regarded as an anti-proliferative protein and its ability to suppress tumorigenesis has been extensively investigated (33). p53 regulates the transcription of a large number of genes with a myriad of anti-oncogenic functions that include cell-cycle arrest, such as p21 and growth arrest and DNA damage inducible 45 (GADD45), as well as apoptosis, such as FAS and BAX. p53 also plays a transcription-independent role in the cellular response to radiation-induced DNA damage. The inactivation of p53 or its mutation has been demonstrated in 50% of human tumors (33). Some studies have shown that p53 is mainly inactivated or mutant in carcinomas associated with HPV infection in cervical carcinomas and this is associated with progression of cervical cancer and its response to radiotherapy, however, this idea is challenged by other studies. Shin et al. investigated the effect of HPV16-E6 (HPV 'early' gene) oncoprotein on in vitro radiosensitivity of HPV-negative/p53 mutant C33a cervical cancer cells. They found that HPV 16 E6 increases the radiosensitivity of p53-mutated cervical cancer cells (34). Ishikawa et al., reviewed 52 patients with International Federation of Gynecology and Obstetrics stage IIIB squamous cell carcinoma of the cervix who received radiation therapy-alone. There was a significant correlation between the existence of HPV and p53 status. The p53 mutation had a significant correlation with local tumor recurrence. Conversely, no obvious correlation with any clinical outcome for patients with cervical carcinoma was found concerning HPV infection. It is possible that the p53 gene may be used as a predictive factor in radiation therapy for patients with stage IIIB squamous cell carcinoma of the cervix (35). However, studies from other groups do not seem to support this conclusion. Rantane et al. observed the correlation between p53 tumor-suppressor gene mutations and the presence of high-risk HPV DNA with the in vitro radiosensitivity of gynecological malignancies by studying 26 cell lines derived from gynecological cancer of 23 patients. They found that inactivation of the p53 gene through mutation or binding with HPV-DNA does not increase the resistance of gynecological malignancies to ionizing radiation in vitro (36). In the study by Harima et al. mentioned previously (29), the authors also analyzed the presence of mutations of p53 gene by a single-strand conformation polymorphism analysis and DNA sequencing. Surprisingly, fewer than 10% (4/44) of patients studied had mutant p53 (29). In line with this, Crawford et al. used immunohistochemistry to determine the prognosis in 46 patients with primary cervical cancer and 28 women with recurrent carcinoma and found that positive staining for p53 was associated with a survival disadvantage (27). Thus, the effect of p53 on radiosensitivity of cervical cancer is still controversial and further studies are required to address this.

COXs and Radiosensitivity of Cervical Cancer

COXs are critical enzymes in the biosynthesis of prostanoids (37-40). In recent years, great interest has been shown in COXs because they are involved in the development and progression of cancer, including cervical cancer. There are two isoforms of COXs: COX1 and COX2. COX1 is constitutively expressed in many cell types and plays a role in the maintenance of homeostasis. However, COX2 is an inducible enzyme for Prostaglandin E2 (PGE2) production during inflammation (37-40). The mechanisms by which COX2 exerts its tumorigenic effect are not yet known. It has been proposed that its products may cause free radical-induced damage of DNA (37-40). In addition, PGE2 has been shown to promote tumor growth by stimulating PGE receptor signaling (37-40). Jeon et al. utilized three cervical cancer cell lines (HeLa, HT-3, and C33A) and clonogenic assays to determine whether COX expression is related to radiosensitivity. They found COX expression to be associated with the radiosensitivity in cervical cancer cell lines. They further found that COX1 might have a more important role than COX2 in this regard (41). However, another study emphasized on the critical role of COX2 in radiosensitivity in cervical cancer. Celecoxib is a selective COX2 inhibitor. Wang et al. found Celecoxib inhibited HeLa human cervical cancer cell proliferation in a dose- and time-dependent manner. They further found that Celecoxib radiosensitized the HeLa cell line via a mechanism dependent on reduced COX2 (42). Thus, manipulating the level of COXs might be a very promising strategy to increase the radiosensitivity of cervical cancer.

Epidermal Growth Factor Receptor (EGFR), Vascular Endothelial Growth Factor (VEGF), Angiogenesis and Radiosensitivity of Cervical Cancer

EGFR is a member of the Erythroblastic Leukemia Viral Oncogene Homolog (ERBB) family of receptors, a subfamily of four closely-related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). It has been shown that mutations
affecting EGFR expression or activity can result in cancer (43) and EGFR has been reported to be frequently overexpressed in carcinoma of the uterine cervix (44). Pérez-Regadera et al. studied the expression of EGFR in 112 patients with advanced cervical cancer treated with chemoradiotherapy. They found that patients with overexpression of EGFR had a higher probability of pelvic relapses and decreased disease-free survival. The poor prognosis of these tumors may be a consequence of an increase in radioresistance (45). Thus, the expression level of EGFR can be used to predict response to radiation and survival in cervical cancer (45). In line with these data, anti-EGFR drugs, such as AG1478, significantly suppressed cervical cancer development and progression in a mouse xenograft model by inhibiting the function of EGFR. Thus, anti-EGFR therapy may benefit patients (46). Despite the fact that EGFR is frequently overexpressed in carcinoma of the uterine cervix, Cerciello et al. studied the role of pre-treatment EGFR expression level and the change of expression induced by ionizing radiation (44). They found EGFR expression changes unpredictably during radiation. Thus, it is not clear if EGFR can be used as a target for radiotherapy of cervical cancer.

VEGF is a key regulator in the initiation and regulation of angiogenesis in various tumor tissues. Mounting evidence has shown that VEGF also plays an important role in cancer radiotherapy. Cooper et al. studied 74 patients with locally advanced carcinoma of the cervix and found that women with highly vascular tumors had poorer 5-year survival than those with poorly-vascular tumors. Thus, tumor vascularity is a significant prognostic factor for cervical carcinoma treated with radiotherapy (47). Loncaster et al. further studied 100 patients with advanced cervical cancer and found that high VEGF expression was associated with a poor prognosis (48). Hu et al.’s research had similar findings. In their study, VEGF expression was knocked-down with RNAi in cervical carcinoma cells. They found that inhibition of VEGF expression enhances radiosensitivity in cervical cancer (49). In fact, some clinical studies have directly explored the association between angiogenesis and the clinical outcome in cervical cancer. Alcázar et al. studied tumor vascularity in predicting response to concurrent chemoradiotherapy for locally advanced cervical cancer by transvaginal color Doppler sonography. They studied 21 patients with locally advanced cervical cancer and found that transvaginal color Doppler sonography may be useful in predicting clinical response to concurrent chemoradiation in patients with locally advanced cervical cancer (50). Mayr et al. studied the temporal changes of dynamic contrast-enhanced magnetic resonance imaging perfusion patterns during the radiation therapy course and their influence on local control and survival in cervical cancer. They found that longitudinal tumor perfusion changes during radiation correlate with treatment outcome. Persistently low perfusion in pre-radiation, early radiation, and mid-radiation therapy indicates a high risk of treatment failure, whereas outcome is favorable in patients with initially high perfusion or subsequent improvements of initially low perfusion. These findings likely reflect re-oxygenation and may have potential for non-invasive monitoring of intra-treatment radiosensitivity and for guiding adaptive therapy (51).

It is clear that new knowledge about the effect of angiogenesis on radiosensitivity of cervical cancer will provide new opportunities for developing new drugs targeting angiogenesis.

**Cancer Hypoxia and Radiosensitivity of Cervical Cancer**

Cancer hypoxia is a characteristic status in solid types of cancer, including cervical cancer (52-54). A hypoxic region in a tumor is defined as the area with oxygen tension value of 10 mmHg or lower. Increasing evidence suggests that tumor hypoxia contributes to radiation therapy resistance by direct or indirect mechanisms (52, 55). On one hand, hypoxia directly induces tumor resistance to radiation therapy by deprivation of oxygen, because adequate intratumoral oxygen is required to achieve maximal cytotoxic effects. On the other hand, hypoxia modulates expression of genes associated with proliferation, apoptosis, angiogenesis, cancer invasiveness and metabolism. Thus, hypoxia may contribute to resistance to radiation therapy (52, 55, 56). Suzuki observed the relationship between intratumoral oxygen partial pressure (pO2) and outcome in patients with cervical cancer. The mean intratumoral pO2 before radiation therapy was 17.3 mm Hg. The 3-year local control rate of patients with pO2 of 20 mmHg or less before radiation therapy was 52% and that of those with pO2 greater than 20 mmHg was 100%. At 9 Gy, the mean intratumoral pO2 was 23.6 mm Hg, a significant increase compared to the value before radiation therapy. The 3-year local control rates of tumors with pO2 of 20 mmHg or less and pO2 greater than 20 mmHg at 9 Gy were 35% and 93%, respectively. The significantly better local control for oxygenated tumors at 9 Gy, as well as before radiation therapy, indicate that the oxygen effect and re-oxygenation by radiation plays an important role in local control in radiation therapy for cervical cancer (57). Dehdashi et al. investigated if pre-treatment for tumor hypoxia assessed by positron-emission tomography with Cu-60 diacetyl-bis(N4-methylthiosemicarbazone) predicts responsiveness to subsequent therapy in cervical cancer. Fourteen patients with cervical cancer were studied before initiation of radiotherapy and chemotherapy. Six out of nine patients with normoxic tumors were free of disease, whereas all five patients with hypoxic tumors developed recurrence. This study strongly
indicates that tumor oxygenation might be predictive of tumor behavior and response to therapy (58). Evidence also showed the expression of hypoxia markers such as hypoxia-inducible factor-1α (HIF1α) in oligodendrogliomas might impact prognosis, neoangiogenesis and cell radiosensitivity. HIF1α plays a key role in the adaptation of cells to hypoxia by stimulating angiogenesis via regulation of VEGF and by metabolic adaptation to O₂ deprivation. Birner et al. investigated the expression of HIF1α protein in 51 specimens of supratentorial pure oligodendrogliomas. They found that strong expression of HIF1α was observed in 12 (23.5%) specimens, moderate expression in 21 (41.2%) specimens, weak expression in eight (15.7%) cases, and no expression was found in 10 samples (19.6%). Their study suggests that overexpression of HIF1α might indicate a diminished prognosis in oligodendrogliomas. This finding may be explained by the strong vascularization of these tumors that prevents hypoxia and allows O₂ diffusion and tumor progression (59). Ishikawa et al. analyzed 38 patients with cervical cancer treated with radiation therapy-alone. All patients received combination therapy of external-beam irradiation and low-dose-rate intracavity brachytherapy. HIF1α expression in cancer tissues was examined by immunohistochemical staining. There was a significant positive correlation between high HIF1α expression and disease recurrence. Furthermore, HIF1α had a significant correlation with the recurrence-free survival rate. No statistical correlation was noted between high HIF1α expression and the local control rate, whereas the HIF1α status predicted distant metastasis with strong significance. Conversely, other factors demonstrated no impact on the clinical outcome. This study strongly suggests that HIF1α is an important prognostic factor, especially for predicting future metastasis after radiation therapy for patients with cervical cancer (60). Liu et al. further found that both HIF1α and N-Myc downstream-regulated gene 2 contribute to hypoxia-induced tumor radiosensitivity and that the latter acts downstream of HIF1α to promote radioresistance through suppressing radiation-induced BAX expression (61). Carbonic anhydrase-9 (CA9) is a transmembrane protein overexpressed in a wide variety of tumor types and is induced by hypoxia. It is a new predictor for radiation-resistant hypoxic cells (62). Olive et al. studied the expression of CA9 and pimonidazole (a hypoxia marker) in formalin-fixed sections from tumors of 18 patients with cervical cancer. Excellent co-localization was observed, although the area of the tumor section that bound antibodies to CA9 represented double the number of cells that bound antibodies to pimonidazole. Occasional regions stained with pimonidazole but not CA9 could be indicative of transient changes in tumor perfusion. Their results support the hypothesis that CA9 is a useful endogenous marker of tumor hypoxia (62).

Clearly, monitoring and manipulating the level of tumor hypoxia might be a very promising strategy to increase the radiosensitivity of cervical cancer.

**Temperature and Radiosensitivity of Cervical Cancer**

Hyperthermia therapy is a type of medical treatment in which body tissue is exposed to slightly higher temperatures in order to damage and kill cancer cells, or to make cancer cells more sensitive to the effects of radiation and certain anti-cancer drugs (63). Techniques that may bring local tissues to high temperatures, such as radiofrequency ablation, are not generally regarded as "hyperthermia"; When hyperthermia is combined with radiation therapy, it is called thermoradiotherapy. Hyperthermia treatment might increase tumor oxygenation and perfusion, and affect the outcome of radiotherapy as a result. Research was performed by Kim et al. to investigate this hypothesis in patients with cervical cancer undergoing regional hyperthermia treatment. They found that relatively mild temperatures (40-41.5˚C) can sensitize human cells to radiation. Therefore, there may be a therapeutic benefit by adding mild hyperthermia to brachytherapy regimens for the treatment of cancer. However, the required heating times are long (approximately 48 h), which renders this approach somewhat impractical. A novel alternative is to combine pulsed brachytherapy with pulsed hyperthermia to enable the total radiation dose to be given at an elevated temperature while the total heating time is kept short. A treatment schedule in which 1 Gy radiation pulses were given once per hour during 5-min heating pulses also delivered once per hour, was investigated in vitro in the human cervical carcinoma line, SiHa. Pulsed heating alone caused little cytotoxicity. However, when pulsed heating was added to pulsed radiation, the level of cytotoxicity was greater than for pulsed radiation alone or radiation alone. The effect was also greater than would be predicted from a simple additive effect of pulsed radiation and pulsed heating. Thus, pulsed heating at 45˚C sensitized cells to pulsed radiation without the development of thermal tolerance (64). Radiochemotherapy combined with regional pelvic hyperthermia could induce high response and resectability rates in patients with nonresectable cervical cancer. Interestingly, Sreenivasa et al. studied 32 patients with nonresectable cervical cancer confined to the pelvis treated with radiochemotherapy and weekly regional pelvic hyperthermia. Responders underwent hysterectomy, if possible, whereas patients in whom disease was still unresectable underwent definitive hyperthermic radiochemotherapy. Feasibility and toxicity, as well as response, resectability, local progression free- and overall survival rates, were evaluated. They found that preoperative hyperthermic radiochemotherapy (45-50 Gy) induces high
response rates and enables curative surgery in a high proportion of patients with nonresectable cervical cancer. Therefore, the use of hyperthermia in conjunction with standard chemo/radiotherapy with/without surgery may allow for more effective tumor treatment while reducing the risk of complications in patients with locally advanced cervical cancer (65).

Hyperthermia treatment might be also useful for cervical cancer. Cryotherapy is the use of extreme cold produced by liquid nitrogen to destroy tissue. Cryotherapy can be used to treat skin cancer and also used to treat tumors inside the body, including cervical cancer, through a cryoprobe. Typically, cryotherapy is not used for cervical cancer, but Burton et al. assessed the effect of cooling temperatures on cellular radiation response. An established human cervical carcinoma cell line (HTB35) was subjected to holding temperatures of 0, 5, or 15°C for up to 24 h before irradiation. They found that cooling enhanced in vitro radiation sensitivity, which is dependent upon cooling temperature, duration, and rewarming interval before irradiation (66). Thus, it is possible to sensitize cervical cancer cells by modulating temperature.

In this mini review, some of the factors associated with the radiosensitivity of cervical cancer such as apoptosis, COXs, angiogenesis, hypoxia and temperature were discussed. Since cervical cancer is still one of the leading malignancies in women and radiation plays a critical role in treating women with advanced-stage cervical cancer worldwide, further studies regarding the effect of factors associated with radiation are required to improve patient treatment. Therefore we need to push research forwards regarding the key events involved in the process of malignant transformation and progression of cervical cancer. New insight might allow the manipulation of the radiation response of cervical cancer in order to achieve a favorable outcome. Here we are expecting the development of safer and more effective radiosensitizing agents to benefit patients with cervical cancer in the near future.

Acknowledgements

This study was supported by a grant from Des Moines University to Yujiang Fang.

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Received April 5, 2014
Revised July 5, 2014
Accepted July 5, 2014