ISSN 2449-8947
3(2) 2015

Volume 3
Number 2
July-December 2015

MicroMedicine

formerly
Archives of Biomedical Sciences

MNiSW points 2015: **8**
Index Copernicus 2014: **91.01**

http://www.journals.tmkarpinski.com/index.php/mmed
e-mail: mmed@interia.eu

MicroMedicine

ISSN 2449-8947

List of Peer-Reviewers
http://www.journals.tmkarpinski.com/index.php/mmed/pages/view/reviewers

Author Guidelines
http://www.journals.tmkarpinski.com/index.php/mmed/about/submissions

More information
www.journals.tmkarpinski.com/index.php/mmed

Publisher and Editor's office: Tomasz M. Karpiński, Szkółkarska 88B, 62-002 Suchy Las, Poland, e-mail: mmed@interia.eu

Contents

ISSN 2449-8947 MicroMedicine Case Report

Conservative management of adherent retained placenta: report of 4 cases

Minakshi Rohilla*, N. Pramya, G. R. V. Prasad, Vanita Jain, Jaswinder Kalra

Department of Obstetrics and Gynecology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

* Corresponding author: Dr. Minakshi Rohilla, Add. Prof., Department of Obstetrics and Gynecology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh (U.T.), 160012, India, Mobile: +91-9914209354, Fax: 0172-2747909, e-mail: minurohilla@yahoo.com

Received: 07 May 2015; **Revised submission:** 12 June 2015; **Accepted:** 22 June 2015

ABSTRACT

The frequency of adherent placenta is increasing due to growing number of caesarean deliveries. The optimal management of this condition remains unclear**,** resulting in complications in the peripartum period such as severe haemorrhage, a possible need for caesarean hysterectomy, and even severe injuries to pelvic organs. We report cases of conservative management of adherent retained placenta following midtrimester abortion, preterm normal and caesarean delivery. All were managed conservatively with antibiotics, and followed up with 2-4 weekly USG. There was complete resorption of placenta by 3-6 months postpartum in all the cases. No complications developed during the conservative management and all women resumed normal menstruation by 5-6 months post procedure. Conservative management of abnormally invasive placentation can be effective and fertility can be preserved which should be considered in highly selective cases. Further research with prospective evaluation for conservative treatments versus different approaches for adherent retained placenta is necessary.

Keywords: Retained placenta, Adherent, Conservative management, Pregnancy.

1. INTRODUCTION

Placenta accreta is one of the most feared complications in obstetrics in which entire or focal placenta is abnormally adherent to the myometrium. Morbidly adherent placenta is frequently associated with severe maternal morbidity. An increased incidence over the recent years may be secondary to the increased caesarean section rates. The most severe form is placenta percreta, in which placenta penetrates through the full thickness of the myometrium, through the serosa, and may invade adjacent pelvic organs such as the bladder. If invasion is limited to myometrial invasion, it is placenta increta. The incidence reported in literature varies but averages 1:1000 [1]. The aetiology of placenta accreta has been thought to be due to the absence of the spongiosus layer of the decidua and the histology correspondingly shows trophoblast invasion into the myometrium without intervening decidua. The common end-result is massive haemorrhage often as a result of attempted manual

placental separation from its poorly formed decidual bed which opens up large-caliber spiral vessels and sinuses.

Risk factors include uterine scarring from previous uterine curettages, caesarean sections, myomectomies, and placenta previa. A high index of suspicion is required for diagnosis, and ultrasonographic (USG) features suggestive of accreta must be sought in cases with risk factors [2]. Magnetic resonance imaging (MRI) is currently being studied as an imaging modality to better define the topography and area of placental invasion to aid planning of surgery. There has been a paradigm shift in terms of treatment, from the historical caesarean hysterectomy to more conservative methods of management involving uterine conservation and leaving the placenta in situ with adjuvant treatment of methotrexate in some cases, or simply awaiting spontaneous resorption of the placenta. The conservative management is facilitated by development of methods of controlling blood loss during surgery, such as embolisation, ligation or balloon occlusion of the arterial supplies, as well as the enhanced availability and safety of blood transfusions and good modern intensive care support.

We report cases of adherent placenta which were retained and managed expectantly without additional intervention.

2. CASE REPORTS

2.1. Case 1

A 27 years old gravida 4, previous 3 abortions was transferred to our institution 9 hours post-delivery with retained placenta and failed manual removal following preterm breech vaginal delivery at 32 weeks gestation with vaginal pack in situ. Antenatal period was apparently uncomplicated. She was haemodynamically stable, uterus was well retracted, 24 weeks gravid uterus size and there was no excessive bleeding per vaginum. Transabdominal ultrasound at admission showed a 9 x 6 cm placenta at fundus with no distinct myometrium beneath. The patient was counseled regarding the management options, their risks and benefits. In view of desire for fertility preservation the patient wanted conservative management of retained placenta. She was started on broad spectrum antibiotics and haemoglobin, leucocytes count, temperature was monitored. She remained afebrile throughout and two units packed red blood cells was transfused. On day 4 postpartum, she expelled some products spontaneously and USG showed placenta of 9 cm with minimal liquefaction in the centre at fundus. She was discharged on day 15 and followed on outpatient basis. Intermittent urinary tract infections developed and treated with appropriate antibiotics. She was followed up with 1-2 weekly USG and there was complete resorption of placenta by 3 months postpartum during which USG showed a 0.8x3.4 cms hyperechoic area in cavity suggestive of calicfication. No complication developed further and she resumed normal menstruation by 5 months postpartum period.

2.2. Case 2

32 years old multiparous lady with previous 3 caesarean sections and one living newborn admitted as a partial retained placenta following preterm caesarean section one day back. She had suspected adherent placenta which was left in situ partially during caesarean section (5 x 6 cm on USG at fundus). There was history of postpartum haemorrhage (PPH) which was medically managed successfully. Increased risk of bleeding and possibility of hysterectomy was explained to her, she was interested in nonsurgical management. Broad spectrum antibiotics were started after written informed consent for conservative management. One fever spikes of 38^0C noticed on 2nd post operative day, which was manage conservatively. There were no further episodes of fever or vaginal bleeding. At 5 months follow up only calcification around 2 x 3 cm was noticed at fundus. She resumed menstruation at 6 months postpartum.

2.3. Case 3

30 years old multiparous lady (P3013) with 3 living children admitted on day 3 postabortion as retained placenta following mid trimester abortion (3 x 3 cm mass at fundus of uterus). There was no history of post abortal haemorrhage. She was febrile on admission, for which antibiotics were continued for 2 weeks. At 3 weeks follow up, she presented

with history of expulsion of mass per vaginum. There was no history of fever or vaginal bleeding. No placental tissue was seen inside uterus on USG.

2.4. Case 4

36 years old multiparous lady (P_{1101}) with previous caesarean section admitted with partially retained placenta following preterm delivery and early neonatal death. On USG, there was hypercehoic area about 6 x 5 cm seen at inside uterus. Increased vascularity on Doppler USG was also noticed. BhCG was 329 IU. On serial monitoring BhCG decreased to 50 IU. There was no history of fever or excessive vaginal bleeding. At 3 months follow-up placental tissue resorbed to 2 x 3 cm in size. There was no increased vascularity. At 5 months follow-up BhCG decreased to 5 IU, she resumed normal menses. She conceived spontaneously and delivered a healthy child after 1 year of last child birth.

3. DISCUSSION

Over the past 50 years, the incidence of abnormally invasive placentation has increased atleast 10-fold, the risk of which is extremely low in primigravida patients, but rises significantly if associated with placenta previa or repeated cesarean section. The importance of a proper management plan in such a case is obvious. The approach most often recommended is extirpative. However, the standard management as described by Fox in 1972 of immediate Cesarean hysterectomy has devastating consequences for future fertility in such women [3]. An alternative therapeutic approach is conservative rather than extirpative which was first described by Arulkumaran et al. in 1986 where systemic methotrexate 50 mg as an intravenous infusion (total dose 250 mg) was administered on alternate days and the placental mass was expelled on day 11 postnatally [4]. Early diagnosis is important so that the patient can be adequately counseled with regard to treatment options and their possible consequences. This includes obtaining consent for caesarean hysterectomy and informing the patient of the risks of sepsis and delayed haemorrhage that may result in situations where the uterus is conserved and the placenta is left in situ.

Nowadays, the use of USG combined with color doppler provides an accurate record of the size of the placental mass, the depth of myometrial invasion, plane of cleavage and blood flow within this mass the sensitivity of which varies between 57 to 93%. Alternatively, MRI when available may provide a more accurate assessment of placental invasion in particular circumstances such as a posterior placenta. Histopathological evidence of placental basal plate within myometrial fibers will support the diagnosis of placenta increta, but their absence does not refute the clinical diagnosis [5].

In present series all 4 cases were managed conservatively and had spontaneous resorption of placental tissue. One women had spontaneous expulsion of placenta after mid trimester abortion at 3 weeks follow-up. Rest of three women had retained placenta following preterm delivery. All women had history of recurrent curettage or previous repeat caesarean section, as risk factor for adherent placenta.

Conservative management should only be considered in highly selected cases when patient is hemodynamically stable, and there is desire for fertility preservation. The various additional interventions reported in literature are methotrexate, arterial embolization, uterotonic agents and radiofrequency ablation. Systemic administration of methotrexate reduces placental vascularity leading to necrosis and rapid resolution although the route of administration, treatment schedule and total doses prescribed varies. The outcome when the placenta is left in place ranges from expulsion at 7 days to progressive resorption in roughly 6 months. Bilateral uterine artery embolisation has been employed with varying success. According to Descargues et al. a series of 7 women who had uterine artery embolisation carried out in emergency or prophylactic control of postpartum haemorrhage described a success rate of 72%, compared with an expected success rate of over 90% in the absence of abnormal placentation [6]. Whereas in a study by Bodner et al. prophylactic balloon occlusion and arterial embolisation before hysterectomy in patients with abnormally invasive placentation did not reduce intraoperative blood loss [7]. The interval between treatment and resolution varies from case to case, so careful follow-up of these patients is vital. The use of β-human chorionic gonadotropin, although corresponding to placental activity, may not be an

accurate predictor of treatment success or reduction in the size of the placental mass [8]. Conservative management has some disadvantages, including postpartum infection, treatment failure, and restrictive follow-up. The administration of antibiotics might be effective in preventing uterine infection, but their efficacy remains to be proven.

Kayem et al. [9] studied the impact of conservative and extirpative strategies for placenta accreta on maternal mortality and morbidity comparing two protocols of treatment, one of which was to leave the placenta in situ (20 cases), as compared to manual removal of the placenta (13 cases). It was found that there was a reduction in the hysterectomy rate from 15% to 84% in the conservative management group. However, there were 3 cases of sepsis in patients in which placenta was left in situ, compared to 1 in the other group, and at least 2 cases of women with conservative management with subsequent successful pregnancies. Similar to the present case series, Panoskaltsis and colleagues described a case with successful outcome in which no intervention was taken [10].

Over the past 20 years (1985 to 2006), around 48 case reports have described outcomes of 60 women who were treated conservatively for abnormally invasive placentation [11]. Twenty-six women were managed without any additional interventions. In 19/26, the placenta had been partially removed and therapy failed in 4 of these 26. Twenty-two women received adjuvant methotrexate. The entire placenta was left in situ in 19/22, in which therapy failed in 5. Twelve women were managed with arterial embolisation. The placenta was completely left in situ in 9/12 out of which therapy failed in 3. Overall, infection developed in 11/60, vaginal bleeding in 21/60, disseminated intravascular coagulopathy in 4/60 women. Spontaneous placental expulsion occurred in 16 women and subsequent pregnancies in 8 women. In a recent review different uterus preserving treatment options were discussed in managing invasive placentation but no conclusions could be drawn about the superiority of any modality. 90% of the total women in whom expectant management were considered, had subsequent menstruation and 67% had next pregnancy [12].

4. CONCLUSIONS

Management of placenta accreta is multidisciplinary and patients must be informed of all options. Treatment is decided according to obstetric history of the patients, operative findings and peripartum blood loss [13, 14]. Conservative management decrease blood loss during delivery and allows patients to preserve fertility. Side effects of this therapy are secondary haemorrhage, sepsis, long-term follow-up. Embolization can be a very useful adjunct, whenever massive haemorrhage occurs. There are few studies reporting fertility after conservative management, but it seems to be a safe option of planning for future pregnancies.

AUTHORS' CONTRIBUTION

MR: Conception and design, Acquisition of data, Review and revision of the manuscript; NP: Writing of the manuscript; GRVP: Administrative and material support; VJ: Administrative and material support; JK: Administrative and material support. All authors read and approved the final manuscript.

TRANSPARENCY DECLARATION

The authors declare no conflicts of interest.

REFERENCES

1. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. Am J Obstet Gynecol. 2005; 192: 1458-1461.
2. Comstock CH. Antenatal diagnosis of placenta accreta: a review. Ultrasound Obstet Gynecol. 2005; 26: 89-96.
3. Fox H. Placenta accreta 1945-1969. Obstet Gynecol Surv. 1972; 27: 475-479.
4. Arulkumaran S, Ng CS, Ingemarsson I, Ratnam SS. Medical treatment of placenta accreta with methotrexate. Acta Obstet Gynecol Scand. 1986; 65: 285-286.
5. Khong TY, Werger AC. Myometrial fibers in the placental basal plate can confirm but do not necessarily indicate clinical placental accreta. Am J Clin Pathol 2001; 116: 703-708.
6. Descargues G, Clavier E, Lemercier E, Sibert L. Placenta percreta with bladder invasion managed by arterial embolisation and manual removal after caesarean. Obstet Gynecol. 2000; 96: 840.

7. Bodner LJ, Nosher JL, Gribbin C, Siegel RL, Beale S, Scorza W. Balloon-assisted occlusion of internal iliac arteries in patients with placenta accrete/ percreta. Cardiovasc Intervent Radiol. 2006; 29: 354-361.
8. Jaffe R, DuBeshter B, Sherer DM, Thompson EA, Woods JR. Failure of methotrexate treatment for term placenta percreta. Am J Obstet Gynecol. 1994; 171: 558-559.
9. Kayem G, Davy C, Goffinet F, Thomas C, Clément D, Cabrol D. Conservative versus extirpative management in cases of placenta accreta. Obstet Gynecol. 2004; 104: 531-536.
10. Panoskaltsis TA, Ascarelli A, de Souza N, Sims CD, Edmonds KD. Placenta increta: evaluation of radiological investigations and therapeutic options of conservative management. Br J Obstet Gynaecol. 2000; 107: 802-806.
11. Timmermans S, van Hof AC, Duvekot JJ. Conservative management of abnormally invasive placentation. Obstet Gynecol. 2007; 82(8): 529-539.
12. Steins Bisschop CN, Schaap TP, Vogelvang TE, Scholten PC. Invasive placentation and uterus preserving treatment modalities: a systematic review. Arch Gynecol Obstet. 2011; 284(2): 491-502.
13. Héquet D, Ricbourg A, Sebbag D, Rossignol M, Lubrano S, Barranger E. Placenta accreta: screening, management and complications. Gynecol Obstet Fertil. 2013; 41(1): 31-37.
14. Doumouchtsis SK, Arulkumaran S. The morbidly adherent placenta: an overview of management options. Acta Obstet Gynecol Scand. 2010; 89(9): 1126-1133.

ISSN 2449-8947 MicroMedicine Short Communication

Multiparametric qualimetric microsurgical scanning chip-lancet model: theoretical metrological and biomedical considerations

A. Jablokov[1], Oleg Gradov[2,3]*

[1]Russian National Research Medical University, Moscow Faculty, Moscow, Russia; [2]Institute of Biology and Chemistry (MPSU), Department of Anatomy and Physiology of Humans and Animals, Moscow, Russia; [3]Institute of Energy Problems of Chemical Physics, Russian Academy of Sciences, Moscow, Russia.
* Corresponding author: Oleg Gradov, Lelninsky pr., 38, bld. 2, Cab. 18, Moscow, 119334, Russia; e-mail: o.v.gradov@gmail.com; neurobiophys@gmail.com

Received: 04 May 2015; **Revised submission:** 26 June 2015; **Accepted:** 29 June 2015

ABSTRACT

The construction of a novel surgical instrument is considered, which is also a probing device providing a signal to the measuring equipment, which after its interpretation allows to obtain useful information about the section quality and the biomaterial properties. We propose here some formalized considerations on the possibility of its implementation for different variables registration. The idea is also extrapolated into the field of micrurgy which refers to the microelectrode techniques and the local potential registration in situ.

Keywords: Phenomenological qualimetry, Metrology, Microsurgery, Imaging, Scanning lancet, Quasi-optics.

1. INTRODUCTION

Let us assume that there is a scalpel/lancet combined with a detecting head (see Fig. 1) with the known transfer function in the diagnostic spectral range. Spectral distribution pattern, that is a position sensitive spectral data frame detected at the output of the tissue, i.e. at the detecting device input, depending on the changeable chemism of the tissue (flap) points, has the form $\Theta_{in}(x, y, t, \lambda)$, where (x, y) are the plane coordinates, t - time and λ - wavelength. This is true for both optical and mass spectra, but in the latter case mass to charge ratio or the ion current intensity dependence on the mass to charge ration M instead of λ is detected. The presence of the time variable t allows the flap or a tissue fragment diagnostics within dynamic chemistry, since the function dimension for a statistic pattern is reduced by one to the function of three variables $\Theta_{in}(x, y, \lambda)$ or $\Theta_{in}(x, y, M)$.

The sample scanning obviously includes a coordinate transformation at a scale equal to the moving / scanning rate of a spectrometric or a mass spectrometric head relative to the movement of the non-fixed tissue flap in the course of the operation - the analytical signal deconvolution. Similar to the discretization with respect to the argument λ by

considering not the entire set of the $\Psi(\lambda)$ function values, describing the optical emission spectrum of the sample area, but only its additive RGB ranges $\Psi_R(x,y,t)$, $\Psi_G(x,y,t)$, $\Psi_B(x,y,t)$, used in multispectral digital photography, in the case of a mass-spectrometric control it is expedient to analyze only the most interesting from the diagnostic point of view mass-spectral distribution areas with different masses. Suppose that we know that a diagnostic agent for certain a disease *N* belongs to the mass range *N*, while the diagnostic agent for another disease *M* lies in the *M* mass range. Than it is possible to divide the $\mathbb{M}$ area into two regions $\Theta_N(x,y,t,\mathbb{M})$ and $\Theta_M(x,y,t,\mathbb{M})$ for determination of the particular diagnostic agent of interest (see Fig. 2 and 3). This reduces the data aquisition representativeness but significantly simplifies the procedure and increases the rate of the intraoperative agent distinction.

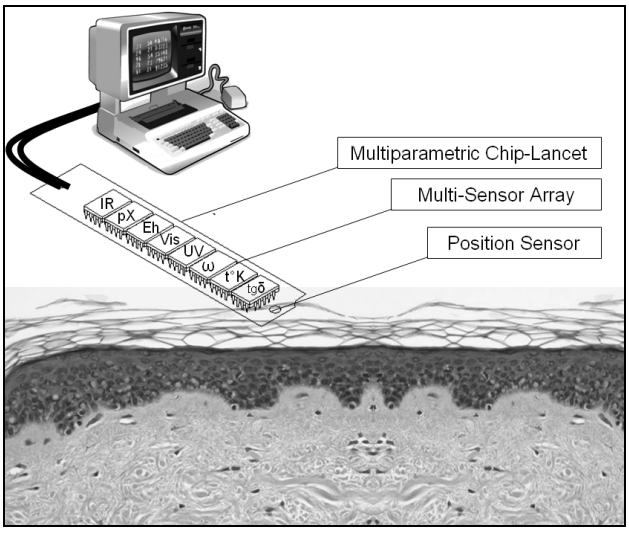

Fig. 1. The component scheme of the Multiparametric Chip-Lancet for epitelial surgery.

2. PHENOMENOLOGICAL MODEL

For the dynamic control it is necessary to consider discretization with respect to the argument t, performed by the signal recording at the intervals corresponding to the frame changing periods. Herewith the four-dimensional function describing the signal transforms (is converted) into a sequence of two-dimensional functions due to the spectral scanning mechanism. In the case of the analysis at the exactly known wavelengths or molecular fragment mass ranges we can write

$$\Theta_{N_1}(x,y),\Theta_{N_2}(x,y),\ldots,\Theta_{N_{\mathbf{Z}}}(x,y),$$

$$\Theta_{M_1}(x,y),\Theta_{M_2}(x,y),\ldots,\Theta_{M_{\mathbf{Z}}}(x,y)$$

where $\mathbf{Z}$ is a set of integers (full sampling of the spectral frame, which can be rewind either forward or backward for the corresponding $\mathbf{Z}$ which is in principle unlimited). In a general case for any arbitrary wavelength λ or any mass $\mathbb{M}$

$$\Theta_{\lambda_1}(x,y),\Theta_{\lambda_2}(x,y),\ldots,\Theta_{\lambda_{\mathbf{Z}}}(x,y)$$

$$\Theta_{\mathbb{M}_1}(x,y),\Theta_{\mathbb{M}_2}(x,y),\ldots,\Theta_{\mathbb{M}_{\mathbf{Z}}}(x,y)$$

where $\forall\lambda\in$ and $\forall\mathbb{M}\in$. In other words, the data frame sequence for spectroscopic or mass-spectrometric image-guided surgery can be obtained either from single masses or diagnostic wavelengths, or from the wide range spectral distributions.

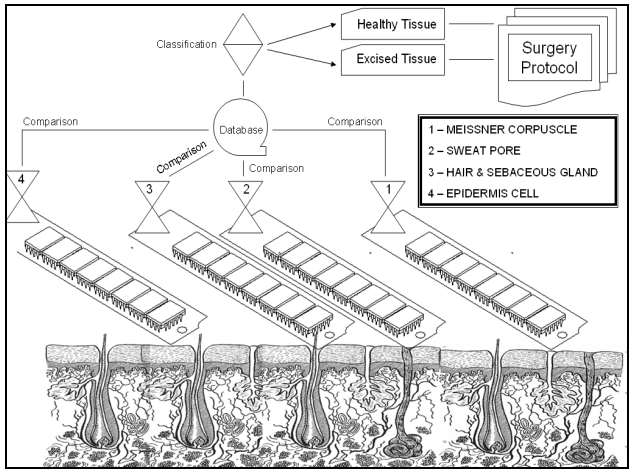

Fig. 2. Example of the intraoperative multiparametric analytical signal classification from derma.

Let us now introduce an operator $\varphi[...]$ that shows the way we should impact the function determining the input signal in order to obtain the output signal function. When the detection is performed along the scalpel movement line the signal which forms the data frame is one-dimensional and can be expressed by the function $\Theta(\vartheta)$, where ϑ stands for the spatial coordinates, time and wavelengths (or masses detected), besides the input and output functions are related as

$\Theta_{out}(\vartheta) = \varphi[\Theta_{in}(\vartheta)]$. Then it is obvious that the input signal of the registration device during the analyte sampling in a mass-spectrometric scalpel or during the optical gap opening in the optical-spectroscopic control can be expressed by the delta-function $\Theta_{in}(\vartheta) = \delta[\vartheta - \vartheta_1^{\vartheta}]$, where ϑ_1^{ϑ} stands for the pulse coordinate at the input. It follows that the impulse response function at the output is $\Theta_{out}(\vartheta, \vartheta_1^{\vartheta}) = \varphi[\delta(\vartheta - \vartheta_1^{\vartheta})]$, resulting in a limited temporal resolution which correlates with the limited spatial intervals at the line of resection and registration when they are synchronized. If the system is linear, it satisfies the superpositoin principle. Thus, if we connect the 2D-input and output signals by the ratio

$\Upsilon_{out}(x, y) = \varphi[\Upsilon_{in}(x, y)]$, then

$$\varphi\left[\sum_m a_m \Upsilon_{in_m}(x, y)\right] = \sum_m a_m \varphi\left[\Upsilon_{in_m}(x, y)\right].$$

Suppose further that during the analyte sampling we fed an infinitesimal spatial impulse, characterized by the delta-function

$\Upsilon_{in}(x, y) = \delta(x - x_1, y - y_1)$, where x_1, y_1 stand for the spatial impulse coordinates at the input of the detection system, to the input of the spectral imaging registration device. The impulse dissipation and scattering occurs in the course of the detection process, therefore it is better to consider the point spread function rather then the point of analysis, which can be denoted Υ_{τ}

$$\Upsilon_{out}(x,y;\ x_1,y_1) = \Upsilon_{\tau}(x,y;\ x_1,y_1) = \varphi[\delta(x - x_1, y - y_1)]$$

As a result of the input signal decomposition into several points located at short distances at the scalpel trajectory X_1 along the $0x$ axis and Y_1 along $0y$ axis we can obtain a unified expression for the input signal:

$$\Upsilon_{in}(x,y) \cong \sum_n \sum_k \Upsilon_{in}(nX_1, kY_1)\delta(x - nX_1, y - kY_1)X_1Y_1$$

and, therefore,

$$\Upsilon_{out}(x,y) \cong \varphi\left[\sum_n \sum_k \Upsilon_{in}(nX_1, kY_1)\delta(x - nX_1, y - kY_1)X_1Y_1\right]$$

and

$$\Upsilon_{out}(x,y) \cong \sum_n \sum_k \Upsilon_{in}(nX_1, kY_1)\Upsilon_{\tau}(x,y;\ nX_1, kY_1)X_1Y_1$$

It is also advisable to replace the sums in the above expression with the double integral:

$$\Upsilon_{out}(x,y) = \iint_{-\infty}^{\infty} \Upsilon_{in}(x_1, y_1)\Upsilon_{\tau}(x,y;\ x_1, y_1)dx_1dy_1$$

Assuming that the scalpel and the sampler are always located at the same angle to the fixed operated flap, i.e. the sampler or the optical gap projections remain isoplanar and do not change their shape during the scanning procedure, one can obtain a two-dimensional convolution of the input function with the point spread function:

$$\Upsilon_{out}(x,y) = \iint_{-\infty}^{\infty} \Upsilon_{in}(x_1, y_1)\Upsilon_{\tau}(x - x_1, y - y_1)dx_1dy_1.$$

For the linear and isoplanar (i.e. spatially invariant) registration system at the qualimetic scalpel its properties can be completely determined from the point spread function.

3. IF THE RESECTION IS PERFORMED ALONG A STRAIGHT LINE…

If the resection is performed along a straight line, parallelizable with the positional alignment axis of the surgical instrument (e.g. along the $0y$ axis), leading to the simplification of the expression $\Upsilon_{in}(x, y) = \delta(x)$, then in case of the isotropic circular symmetry of the point spread function we can determine the analyte distribution in the output signal along the resection axis. For the specified function with the circular symmetry:

$$\Upsilon_{out}(x,0) = \iint_{-\infty}^{\infty} \Upsilon_{\tau}(x_1, y_1)\delta(x - x_1)dx_1dy_1$$

or, more briefly:

$$\Upsilon_{out}(x,0) = \int_{-\infty}^{\infty} \Upsilon_{\tau}(x,y)dy_1 .$$

If we replace $y_1 :\Leftrightarrow y$ that is rather possible in general case, we introduce a line spread function:

$$\Upsilon_{line}(x) = \Upsilon_{out}(x,0) = \int_{-\infty}^{\infty} \Upsilon_{\tau}(x,y)dy$$

If the system possesses a point spread function with separable variables, i.e.

$$\Upsilon_{\tau}(x,y) = \Upsilon_{\tau x}(x)\Upsilon_{\tau y}(y),$$

then:

$$\Upsilon_{line}(x) = \int_{-\infty}^{\infty} \Upsilon_{\tau x}(x)\Upsilon_{\tau y}(y)dy = \Upsilon_{\tau x}(x)\int_{-\infty}^{\infty} \Upsilon_{\tau y}(y)dy$$

while another is obvious for isotropic systems:

$$\Upsilon_{line}(x) = \int_{-\infty}^{\infty} \Upsilon_{\tau}(r)dy = \int_{-\infty}^{\infty} \Upsilon_{\tau}(\sqrt{x^2 + y^2})dy$$

where r is the focusing radii of the analyzed spot.

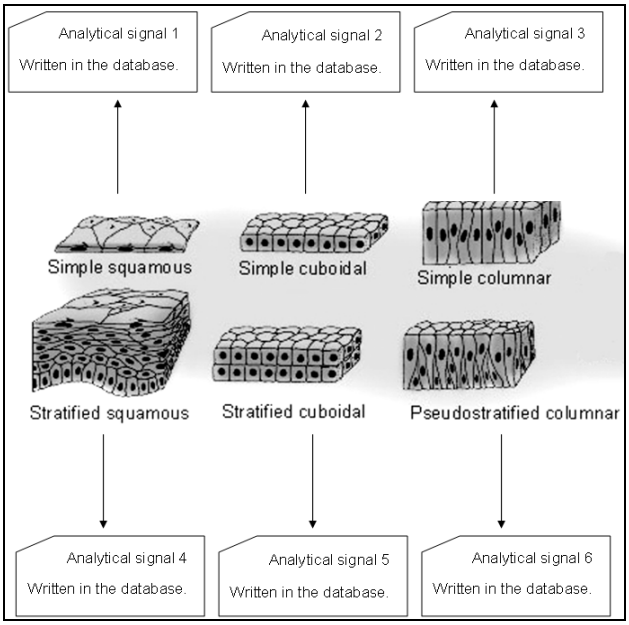

Fig. 3. Another example of the tissue signal classification for comparative intraoperation analysis followed by the control of the surgical instrument positioning accuracy.

4. CONCLUSION

If we consider each discrete cell (point) of such a measurement as a part of the detection matrix of a particular descriptor or correlation predictor, then the positioning accuracy and the correspondence between the resection discretization steps and the registration steps can be regarded as a correctness criterion of the position-sensitive analyte detection. In this connection the cells must not overlap and the analytical signals from the tissue must not interfere. However, the point spread functions extending beyond the boundaries of a single cell and leading to the correlation between the adjacent measuring positions or the memory cells/ units, reduce the information capacity of the whole analytical system and the determination accuracy of the significant biochemical components, that must be taken into account during surgical qualimetry. The model has been detailed in a recent Russian publication [1] and short English conference version [2].

A comprehensive review of microsurgical scanning qualimetry is presented by Smith et al. [3, 4]. The justification for this solution scheme is the method for hybridization and complexation of different descriptors [5, 6] on a scanning line dataflow. This approach is best illustrated by an example of the *in situ* microbeam-assisted positional-sensitive measurements of the tissue parameters during the microsurgery (micrurgy) manipulations on the living brain slices [7].

AUTHORS' CONTRIBUTION

OG: Mathematical conception, principal construction of the chip-lancet/chip-scalpel and writing of the manuscript; AJ: Micro-medical applicability realization and technical approbation of the concept. Both authors read and approved the final manuscript.

TRANSPARENCY DECLARATION

The authors declare no conflicts of interest.

REFERENCES

1. Gradov O, Jablokov A. Towards the abstract model of qualimetric microsurgical instrumentation: formal theory and metrological ideology [in Russian]. Biotechnosphera. 2014; 33(3): 39-41.
2. Gradov O, Jablokov A. Towards the qualimetric microsurgical instrumentation abstract theory (Q-MIAT). Proc. X Russian-Germany Conference on Biomedical Engineering, Sec. Mechatronics Biomed Engin., 2014.
3. Smith S, Lin VD, Berliz J, Panov WW, Gradov OW, Jablokov AG. Intraoperational physicochemical and physiochemical qualimetry as a general principle of multifactor monitoring of surgical manipulations (international bibliographic review). Part 1: General principles of monitoring and control [in Russian]. Int Rev Clin Pract Health [Mezhdunarodnye obzory: klinicheskaya praktika i zdorovie]. 2014; 7(1): 17-30.
4. Smith S, Lin VD, Berliz J, Panov WW, Gradov OW, Jablokov AG. Intraoperational physicochemical and physiochemical qualimetry as a general principle of multifactor monitoring of surgical manipulations (international bibliographic review). Part 2: Intraoperational spectroscopy, spectrozonal and multi-spectral monitoring [in Russian]. Int Rev Clin Pract Health [Mezhdunarodnye obzory: klinishecskaya praktika i zdorovie]. 2014; 8(2): 5-20.

5. Orehov FC, Gradov OW. On-line compatibility of COBAC, QSPR/QSAR and SBGN technologies: the unity of theory and practice for biomedical equipment design and biochemical diagnostic analysis. Proc. X Russian-Germany Conference on Biomedical Engineering, 2014.
6. Orehov FC, Gradov OW. Complexation between COBAC, QSPR/QSAR and SBGN [in Russian]. Biotechnosphera. 2014; 33(3): 29-31.
7. Gradov OW, Zaytsev EW, Jablokov AG. Applications of loop galvanometers from the light-beam oscillographs with electronic servocontrol in tschachotin´s microbeam setups for cell & tissue irradiation with the beam position regulation [in Russian]. Biomed Eng Electr [Biomedicinskaja inzhenerija i elektronika]. 2014; 6(2): 20-53.

ISSN 2449-8947 MicroMedicine Review Article

Cancer - constricting mankind from top 5 killer diseases

Amit Gupta[1]*, Sushama R. Chaphalkar[2]

[1]Department of Immunology, Vidya Pratishthan's School of Biotechnology, Vidyanagari, Baramati, District Pune, Maharashtra, India;
[2]Director, Vidya Pratishthan's School of Biotechnology, Vidyanagari, Baramati, District Pune, Maharashtra, India.
* Corresponding author: Dr. Amit Gupta, Assistant Professor (Immunology); e-mail: amitrrl@yahoo.com; amitgupta@vsbt.res.in

Received: 10 June 2015; **Revised submission:** 14 August 2015; **Accepted:** 18 August 2015

ABSTRACT

Cancer is the uncontrolled growth of abnormal cells in one or both of the tissues/organs. While the capability of normal cells reproduce and develop into healthy tissue but these abnormal cells reproduce faster and never grow into normal organ tissue. Due to uncontrolled cell division, lumps of cancer cells (tumors) then form, grow and spread to other parts of the body. Over the past three decades, the concept of cancer and its types has greatly expanded. Clinicians have take advantages of these initial discoveries related to signs and symptoms of disease and have consistently used scientific breakthrough to design new treatments against particular type of cancer. Recently lung, colorectal, breast, pancreatic and prostate are top five killer diseases in human all over the world.

Keywords: Cancer; Lymphatic; Colorectal; Prostate; Pancreatic.

1. INTRODUCTION

Cancer is a collection group of related human diseases which is characterized by the uncontrolled growth and spread of abnormal or unhealthy cells. Due to uncontrolled cell division of unhealthy/ diseased cells cannot be stopped; it can result in death [1, 2]. Generally, cancer can start or grow almost anywhere in the human body, which is made up of billions or trillions of cells but in case of normal human healthy cells grow and divide continuously to form new (fresh) cells as per the body requirements. When these human healthy cells turn old or presently in a damaged (adverse) condition, these cells will not survive, immediately fresh healthy cells take their place. In addition, cancer is also caused by external factors (i.e. tobacco, infectious organisms) and internal factors (i.e. inherited genetic mutations, hormones and immune conditions). These immunological factors (external or internal) may act together or in sequence to cause cancer [1- 3]. The most common as well as standard treatment for cancer therapy include: surgery; radiation; chemotherapy; hormone/ immune therapy and targeted therapy (drugs that specifically interfere with cancer cell growth). Normally, these cancerous cells predominantly look like normal cells when observed under the microscope and cannot be able to differentiate between normal cells and cancer cells [2-4]. One of the most crucial differences is that normal/healthy cells mature into very distinct cell types with

specific functions, cancer cells do not [3, 4]. In addition, these cancer cells generally ignore the signal from the cell to stop dividing but start spreading from one place (where it first started) to another place in our body is called metastatic cancer and its process called metastasis [5, 6]. Now a day, more than 100 types are identified and usually named for the organs or tissues where the cancers form e.g. epithelial, lung and brain cancer (originated or grown from the cells of epithelial or squamous, lung and brain).

In case of cancer, the first changes normally occurred in the genes inside the organ cells which are responsible or provide some signal to the infected cells to grow faster [5, 6]. These infected (precancerous) cells when observed under the microscope may look like abnormal cells but at this junction it may not form a mass or tumor and also not be able to seen on X-ray. With the increasing passage of time, these precancerous cells may acquire other gene changes and transformed into true cancer [5, 6]. In that case, cancer cells make some chemicals to form new blood vessels and these vessels provide the nourishment to the cancer cells which can continue to grow and form a tumor and also are seen or observed under imaging system i.e. X-ray. In some circumstances, cancer cells released from the tumor (newly formed) and spread to other parts of the body. The identification as well as discovery of these cancerous cells with stem cell like properties in solid tumors is emerging as important criteria for cancer research and may explain the resistance of these tumors to current therapeutic applications [6, 7]. These cancerous cells affect the normal functions of the cell, including proliferation and programmed cell death (apoptosis). The occurrence of cancer disease is almost in every part of the world which is characterized or ranked by the number of cases including its deaths in both the sexes including men and women as shown in Table 1.

2. LUNG CANCER (INCLUDING BRONCHIAL CANCER)

Lungs are found in our chest and divided into right lung (three lobes) and left lung (two lobes). The left lung is smaller because the heart takes up more room on that side of the body. During breathing, air circulation enters through our mouth or nose and enters into pharynx and finally reaches to the lungs with the help of windpipe i.e. trachea and it divides into tubes called the *bronchi* (singular, *bronchus*), which enter the lungs and divide into smaller bronchi. Again, these bronchi divide to form smaller branches called *bronchioles*. At the junction of the bronchioles, small tiny air sacs are present called as *alveoli* [8, 9].

Lung cancer originated from the cells lining of the bronchi and parts of the lung such as the bronchioles or alveoli. Lung cancer is the leading cancer killer disease [10] in men and women in every ethnic group and becomes the second most disease type after heart on the basis of deaths (according to Centers for disease control and detection). About 90 % cases of lung cancers are due to smoking, only about 5.5% are currently diagnosed as well as cured. Although the cure/treatment rate for cancer disease is rising very slowly, the rate of improvement has been very slower than for other common cancers [10]. Smoking and use of tobacco products are the major causes of lung cancer [11] and generally attack between the ages of 55 and 65, according to the NCI. It is of two major subtypes:

1. Non-small cell lung cancer (most common, 3 types) e.g. adenocarcinoma (slow growing, outer area of the lung); squamous cell carcinoma (center of the lung) and large cell carcinoma (anywhere in the lung, rapid rate).
2. Small cell lung cancer (spreads more quickly, starts near the center of the chest in the bronchi and spread much faster than Non-small cell lung cancer).

There are 4 stages of lung cancer [10, 11] i.e. stage 0 (non-invasive, cured with surgery alone); stage 1, II, III (size of primary tumor and cancer spread to its original position); stage IV (difficult to treat, metastasized to different organs). So, lung cancer is often a life-threatening disease [10, 11] because it tends to spread in this way even before it can be detected on an imaging test such as a chest x-ray. One of the products i.e. Tobacco (smoke contained 55 carcinogens evaluated by International Agency for Research on Cancer, IARC) is responsible for causing at least 30 % of all cancer deaths, causing 87% and 70 % of lung cancer deaths in men and women [11]. Out of 55 carcinogens, polycyclic aromatic hydrocarbons [12] (especially benzo[a]-

pyrene, BaP-more carcinogenic, induce lung tumors in mice but not in rats), tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and high-molecular-weight compounds have been detected but are incompletely characterized with respect to their carcinogenicity are likely to play major roles in lung cancer induction [13]. In contrast, there are number of co-carcinogens are present in cigarette smoke i.e. catechol, methylcatechols, pyrogallol, decane, undecane, pyrene, benzo[e]pyrene and fluoranthene [14]. In addition cigarette smoke contains high levels of acrolein, which is toxic to the pulmonary cilia including nitrogen oxides, acetaldehyde and formaldehyde, which could contribute indirectly to pulmonary carcinogenicity [15].

Table 1. Estimated incidence of all cancers (excluding non-melanoma skin cancer) worldwide in 2012.

	Men			Women			Both sexes		
Estimated numbers (thousands)	**Cases**	**Deaths**	**5-year previous**	**Cases**	**Deaths**	**5-year previous**	**Cases**	**Deaths**	**5-year previous**
World	7410	4653	15296	6658	3548	17159	14068	8202	32455
More developed regions	3227	1592	8550	2827	1287	8274	6054	2878	16823
Less developed regions	4184	3062	6747	3831	2261	8885	8014	5323	15632
WHO Africa region (AFRO)	265	205	468	381	250	895	645	456	1363
WHO Americas region (PAHO)	1454	677	3843	1429	618	4115	2882	1295	7958
WHO East Mediterranean region (EMRO)	263	191	461	293	176	733	555	367	1194
WHO Europe region (EURO)	1970	1081	4791	1744	852	4910	3715	1933	9701
WHO South-East Asia region (SEARO)	816	616	1237	908	555	2041	1724	1171	3278
WHO Western Pacific region (WPRO)	2642	1882	4493	1902	1096	4464	4543	2978	8956
IARC membership (24 countries)	3689	1900	9193	3349	1570	9402	7038	3470	18595
United States of America	825	324	2402	779	293	2373	1604	617	4775
China	1823	1429	2496	1243	776	2549	3065	2206	5045
India	477	357	665	537	326	1126	1015	683	1790
European Union (EU-28)	1430	716	3693	1206	561	3464	2635	1276	7157

In addition, environmental tobacco smoke has been proven to cause lung cancer in nonsmoking adults. The consumption rate of tobacco [15, 16] is an essential risk factor for many chronic diseases (cardiovascular (heart) diseases, respiratory diseases etc). In India, around 275 million tobacco users in India, report submitted by Tobacco Control Policy Evaluation Project India predicts. As per the report, it is estimated that 1.5 million (approx.) tobacco-related deaths annually by 2020. Recently, in March

2015, world conference theme "Tobacco and non-Communicable Diseases" in Abu Dhabi, UAE focused on lung cancer will be a key issue.

Fig. 1. Health risks of tobacco include heart and lung disease.

3. COLON AND RECTAL CANCER

The colon and the rectum (colorectal) are parts of the large intestine (lower part of the body's digestive system). During digestion, food entered from the mouth and moves towards the stomach and reaches into the small intestine and then finally into the colon. The major role of colon absorbs water and nutrients from the food and stores waste matter (stool). Stool moves from the colon into the rectum before it leaves the body.

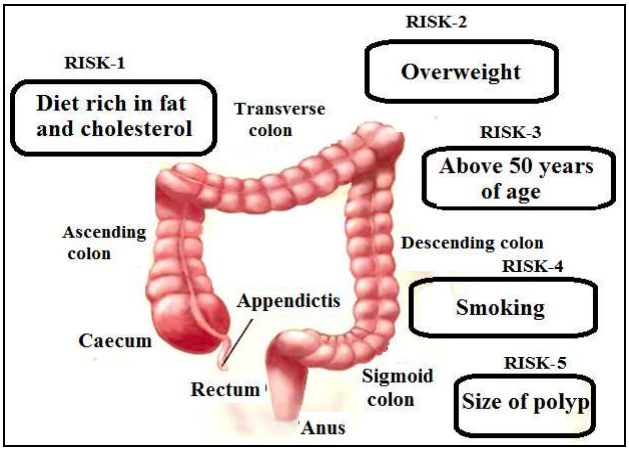

Fig. 2. Colorectal cancer (risk factors).

Colorectal cancer (malignant tumor, origin from the inner wall of large intestine) is the second most common [17] type of cancer (on the basis of estimated deaths in year 2015 as shown in Table 1) in men and women in the United States. In colon or rectum, one small tiny structure formed inside the inner wall called polyp. With the passage of time, some polyps are highly cancerous in nature [17, 18]. To avoid colorectal cancer, the exact way is to finding and removing the polyps through surgery/ chemotherapy/radiotherapy etc. Generally, colorectal cancer can be diagnosed by barium enema or colonoscopy (biopsy confirmation of cancer tissue). The treatment for colorectal cancer [19] depends on the size, area, location and the extent of cancer spread including the health of the patient.

Colon cancer is normally affected in both men and women of all racial and ethnic groups but the incident rate is still higher in men as compared to females. Tumors of colon are more frequent in women than in men where as rectal cancer are more in men than in women [18, 19]. This cancer is generally diagnosed or observed in men and women (> 50 years or older). If there is regular screening test for colon and rectal cancer, as many as more than 80% of deaths from colorectal cancer could be prevented. In addition, several studies have reported that those people who participate in regular physical activity including its diet (rich in cereal fiber, green vegetables and calcium rich foods) prevent (50 %) the risk of colorectal cancer [20]. Being overweight or obese has been consistently associated with a higher risk of colorectal cancer.

To inhibit colorectal carcinogenesis used only non steroidal anti-inflammatory drugs (e.g. Sulindac, aspirin, Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors) possibly by reducing endogenous prostaglandin production through COX inhibition and possibly it may reduce the risk of colorectal cancer after extended treatment [20, 21].

There are number of inflammatory diseases which are associated with colon cancer. One of the inflammatory bowel diseases i.e. Crohn's disease (autoimmune disease, gastrointestinal tract causing inflammation) is also known as Crohn-Leśniowski Disease [22, 23] and showed its various consequences at any stage of life (15 to 30 years). This disease affects more in Europe and North America (3.2 per 1000 people) but less common in Asia and Africa [22]. In general, Crohn's disease showed wide range of symptoms such as diarrhea, vomiting, weight loss, skin rashes etc [23]. Generally, smokers are three to four times likely to develop this disease and the first symptom i.e. abdominal pain is normally

observed in those persons who are suffering from this disease [24]. In addition, this disease also effects on other organ systems as well e.g. uveitis (inflammation of interior portion of eye) occurred only when exposed to light and also showed its effect in the white portion of the eye (sclera) causing inflammation called as episcleritis [23, 24]. Both episcleritis and uveitis can lead to loss of vision if untreated but the cause of this disease is still unknown. Lot of research work is done, most of the researchers showed that there is some genetic link of this disease. In addition, researchers claimed that only two genes is responsible for causing this disease previously but researchers recently claimed that thirty genes are involved. The most important gene which is mutated i.e. CARD15 gene (NOD2 gene) and is responsible for causing this Crohn's disease [25].

One of the inflammatory bowel diseases i.e. Crohn's disease which closely resembles with ulcerative colitis [26] showed its similar symptoms. Both the diseases are generally affected on the colon portion and the main difference between two diseases as shown in Table 2.

Table 2. Comparative difference between Crohn's disease and Ulcerative colitis.

Factors	Crohn's disease	Ulcerative colitis
Age	15 to 30 years	15 to 25 years
Smoking	Higher risk	Lower risk
Cytokine response	Associated with Th17	Associated with Th2
Colon involvement	Usually	Always
Anus involvement	Common	Rarely
Bile duct involvement	No increase	Higher rate
Disease distribution	Patchy areas of inflammation	Continuous area of inflammation
Autoimmune disease	Recognized	Not recognized
Surgical cure	Often returns following removal of affected part	Usually cured by removal of colon

4. BREAST CANCER

Breast cancer begins when normal (healthy) cells in the breast grow uncontrollably, forming a mass of tissue called as tumor. It is most frequently diagnosed cancer which is reported over one million cases in women [27]. Every year more than 500,000 women die from this disease. Generally, breast cancer spreads only in women and transferred to other parts of the body with the help of blood/ lymph vessels. Normally, it is commonly spread to the regional lymph nodes and these nodes are commonly present in the neck, under the arm and chest bone and also spread to the brain (minute quantity), bones, lungs and liver [28]. Most of breast cancers start from the ducts or lobes. About 75% of all breast cancers begin in the cells lining the milk and lobules ducts are called ductal and lobular carcinomas. In addition, if the disease spread outside the duct or lobule to the surrounding tissue called as invasive or infiltrating ductal or lobular carcinoma [28-30]. Generally, cancer is present only in duct or lobule called as in situ (in place); if cancer detected only in duct portion called as ductal carcinoma in situ (DCIS), the ultimate treatment (traditional and hormonal therapy) to remove DCIS which prevents the growth as well as development of invasive breast cancer to other parts of the body where as if cancer detected only in lobule called as lobular carcinoma in situ (LCIS) but oncologists not considered as cancer and is regularly monitored and treatment (hormonal therapy) with imaging tests [27-29]. Other, less common types of breast cancer includes medullary, mucinous, tubular and papillary breast cancer. The majority of cases of breast cancer occur in women over the age of 50 and some cases those women who have a late pregnancy (over 35 years) are more

likely to develop breast cancer [27, 28].

There are number of genes that are present in breast which has the capability to control cell division. When these genes do not work properly, it creates genetic error or mutations. Mutations may be inherited (abnormal genes that transferred from mother or father to child; specific genes such as BRCA1 and BRCA2 are tumor suppressor genes; 5-10% reported in US) or spontaneous (occur any time during life; 90-95% cases reported in US). In addition, there are three specific cell surface receptors as per the classification of breast tumors i.e. oestrogen receptor (ER), progesterone receptor (PR) and the Human Epidermal Growth Factor Receptor (HER)2/neu receptor [30, 31].

Out of three, the most common type of breast cancer i.e. Hormone Receptor-Positive (accounting 75% of all breast cancers; grows in the presence of oestrogen and progesterone [31], and its therapies related to cancer is to inhibit the growth effects of hormones). Another type of breast cancer i.e. HER (human epidermal growth factor) 2-positive breast cancer produces lot of protein called as HER2/neu [30, 31]. Those tumours that do not over express HER2/neu are described as HER2-negative. In contrary, triple negative breast cancer (TNBC, accounts 15% of all breast cancers, more aggressive and difficult to treat) is a rarer form of breast cancer [32, 33] which is a sub-type of HER2-negative disease. TNBC refers to only those tumour cells which lack estrogen and progesterone receptors and do not over express the HER2 protein [31, 34]. Other possible targets for new breast cancer drugs have been identified in recent years. Drugs based on these targets (as mentioned above) are now being studied, but most of them are still in the early stages of clinical trials.

5. PANCREATIC CANCER

The pancreas is a glandular organ (i.e. about 6 inches long, located deep in our belly between stomach and backbone) in the digestive system (surrounded by other organs i.e. liver and intestine and secreting pancreatic juice containing digestive enzymes) and endocrine system of vertebrates that makes/produce insulin, glucagon, somatostatin and other hormones. These pancreatic hormones enter into the bloodstream and travel throughout the body e.g. insulin helps control the amount of sugar in the blood [35].

Now a day, pancreatic cancer is one of the most emerging lethal human cancers and continues to be a major unsolved health problem at the start of the 21st century. The major signs and symptoms of pancreatic cancer are jaundice, pain in the abdomen and weight loss [36]. There are four stages of pancreatic cancer:

Stage I - Detection of tumor in pancreas;
Stage II - cancer (tumor) may spread to the lymph nodes;
Stage III - tumor invaded nearby blood vessels;
Stage IV - cancer has spread to distant organ (liver or lungs).

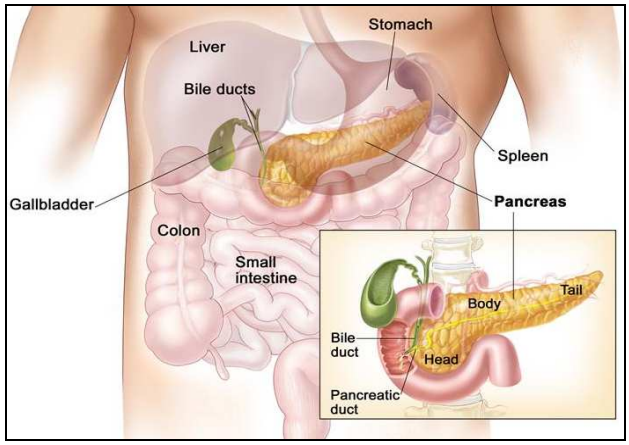

Fig. 3. Pancreas.

In the last few years, number of researchers focused on pancreatic cancer [36] and there is involvement in the detection of DNA damage derived from carcinogen exposure and endogenous metabolic processes e.g. smoking-related aromatic DNA adducts [36]. These observations suggest that the human pancreas is susceptible to carcinogen exposure and DNA damage, which might contribute to genetic mutation, and in turn cancer development [37]. The risk factors for pancreatic cancer include:

- Smoking and overweight
- Hereditary conditions (breast and ovarian cancer syndrome; Lynch syndrome, Peutz-Jeghers syndrome)
- Personal history of diabetes or chronic pancreatitis.

Tumors that form in islet cells are called islet cell tumors, pancreatic endocrine tumors, or

pancreatic neuroendocrine tumors (pancreatic NETs). It may be benign (not considered as cancer) or malignant (cancer, also called as pancreatic endocrine cancer or islet cell carcinoma). These Pancreatic NETs may be functional (tumors make extra amount of hormones i.e. insulin, glucagon etc showed some sign and symptoms) or nonfunctional (tumors do not make extra amounts of hormones).

6. PROSTATE CANCER

Prostate cancer (starts in the gland cells called as adenocarcinoma.) is the most common cancer in men all over the world. The prostate gland (makes fluid that forms part of semen) lies just below the urinary bladder in front of the rectum [38]. It surrounds the urethra (the tube that carries urine and semen through the penis and out of the body). Almost all prostate cancers are adenocarcinomas and showed no early symptoms. The growth of prostate cancer usually very slow; those people who are older than 60 years, the death rate of this disease burden is very less or rare. There may be number of drugs available in the market which is already approved by Food and drug administration (FDA) for pancreatic cancer such as enzalutamide, abiraterone acetate, bicalutamide, docetaxel, jevtana, leuprolide acetate, goserelin acetate etc.

In prostate gland, the epithelial cells produce a protein called prostate specific antigen (PSA) and it maintain the semen in its liquid state and some of them escape into the blood stream. If PSA level is high, it indicates prostate cancer or some kind of diseases related to prostate [38-40]. In some cases, the prostate gland may continue to grow especially the part around urethra (difficulty to pass urine) which is normally observed in older men. In addition, if the size of the prostate gland is too large, the condition is called Benign Prostatic Hyperplasia (BPH). BPH is not a type of cancer, but it must be treated [39, 40].

Finally, cancer has surpassed heart disease (cardiovascular disease) as the biggest killer observed in Australia, according to a new report from the World Health Organization (WHO). Scientists predicted that the global cancer rates will enormously increase by three-quarters over the next two decades and they expect 20 million new cases by 2025.

CONCLUSION

Cancer research has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome (mutations that produce oncogenes with dominant gain of function and tumor suppressor genes with recessive loss of function). It will be possible to understand with precision why treatment with specific anti-tumor or anti-cancer drugs succeed or fail. In cancer research, first of all understand the mechanism of this disease and tried to synthesize anti-cancer drugs singly or in combination with chemotherapeutic drugs to reached to the target site and declined all its stages of disease burden of top 5 cancer killers.

AUTHORS' CONTRIBUTION

AG: Writing of the manuscript including data collection and revised the manuscript critically for important intellectual content. AG and SRC read and approved the final manuscript.

TRANSPARENCY DECLARATION

Authors declare that there is no conflict of interest.

REFERENCES

1. Chabner BA, Bural AL, Multani P. Translational research: walking the bridge between idea and cure. Cancer Res. 1998; 58: 4211-4216.
2. Sikora K. Developing a global strategy for cancer. Eur J Cancer. 1999; 35: 24-31.
3. Doll R. The Pierre Denoix memorial lecture: nature and nurture in the control of cancer. Eur J Cancer. 1999; 35: 16-23.
4. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancer. Nature. 1999; 396: 643-649.
5. Klein CA. Cancer: The metastasis cascade. Science. 2008; 321 5897): 1785-1787.
6. Chiang AC, Massague J. Molecular basis of metastasis. New Engl J Med. 2008; 359(26): 2814-2823.
7. Nguyen DX, Massague J. Genetic determinants of cancer metastasis. Nature Rev Gen. 2007; 8: 341-352.
8. Meenakshi S, Manjunath KY, Balasubramanyam V. Morphological variations of the lung fissures and

lobes. Indian J Chest Dis Allied Sci. 2004; 46(3): 179-182.

9. Gonlugur U, Efeoglu T, Kaptanoglu M, Akkurt I. Major anatomical variations of the tracheobronchial tree: bronchoscopic observation. Anat Sci Int. 2005; 80(2): 111-115.
10. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, et al. Cannabis use and risk of lung cancer: A case-control study. Eur Respir J. 2008; 31(2): 280-286.
11. Fox JL, Rosenzweig KE, Ostroff JS. The effect of smoking status on survival following radiation therapy for non-small cell lung cancer. Lung Cancer. 2004; 44(3): 287-293.
12. Seto H, Ohkubo T, Kanoh T, Koike M, Nakamura K, Kawahara Y. Determination of polycyclic aromatic hydrocarbons in the lung. Arch Environ Contam Toxicol. 1993; 24: 498-503.
13. Staretz ME, Murphy SE, Patten CJ, Nunes MG, Koehl W, Amin S, et al. Comparative metabolism of the tobacco-related carcinogens benzo[*a*]pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and *N*8-nitrosonornicotine in human hepatic microsomes. Drug Metab Dispos. 1997; 25: 154-162.
14. Leanderson P, Tagesson C. Cigarette smoke-induced DNA-damage: role of hydroquinone and catechol in the formation of the oxidative DNA adduct, 8-hydroxydeoxyguanosine. Chem Biol Interact. 1990; 75: 71-81.
15. Delclos KB, Kadlubar FF. Carcinogenic aromatic amines and amides. In: Guengerich FP, editor. Comprehensive toxicology: chemical carcinogens and anticarcinogens. Oxford (U.K.): Elsevier Science; 1997; 12: 141-170.
16. Henry CJ, Kouri RE. Chronic inhalation studies in mice. II. Effects of long-term exposure to 2R1 cigarette smoke on (C57BL/Cum × C3H/AnfCum) F1 mice. J Natl Cancer Inst. 1986; 77: 203-212.
17. American Joint Committee on Cancer. Colon and rectum. In: AJCC Cancer Staging Manual 7th ed. New York: Springer 2010; 143-164.
18. American Cancer Society. Cancer Facts and Figures 2015 Atlanta, American Cancer Society; 2015.
19. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA. 2000; 284: 1954-1961.
20. Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, Norat T. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ. 2011; 343: d6617.
21. Hendriks YM, deJong AE, Morreau H, Tops CM, Vasen HF, Wijnen JT, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): A guide for clinicians. CA Cancer J Clin. 2006; 56: 213-225.
22. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012; 380(9853): 1590-1605.
23. Lalande JD, Behr MA. Mycobacteria in Crohn's disease: How innate immune deficiency may result in chronic inflammation. Expert Rev Clin Immunol. 2010; 6 (4): 633-641.
24. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. Gastroenterol. 2011; 140(6): 1704-1712.
25. Prescott NJ, Fisher SA, Franke A, Hampe J, Onnie CM, Soars D, et al. A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn's disease and is independent of CARD15 and IBD5. Gastroenterol. 2007; 132(5): 1665-1671.
26. Tysk C, Lindberg E, Järnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut. 1988; 29(7): 990-996.
27. Avis N, Crawford S, Manuel J. Quality of life among younger women with breast cancer. J Clin Oncol. 2005; 23: 3322-3330.
28. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011; 47(1): 74-83.
29. Stein LF, Zisman G, Rapelyea JA, Schwartz AM, Abell B, Brem RF. Lobular carcinoma in situ of the breast presenting as a mass. Am J Roentgenol. 2005; 184(6): 1799-801.
30. Berg WA, Mrose HE, Ioffe OB. A typical lobular hyperplasia or lobular carcinoma in situ at core-needle breast biopsy. Radiology, 2001.
31. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomized phase 2 study. Lancet Oncol. 2015; 16(1): 25-35.
32. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, et al. Randomized phase II

trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO Study. J Clin Oncol. 2012; 30(22): 2718-2724.

33. Anders CK, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer. 2009; 9: S73-S81.
34. Sinnatamby CS. Last's anatomy: regional and applied. 10th edn. Edinburgh, UK: Churchill Livingstone; 1999.
35. Aliustaoglu M, Bilici A, Seker M, Dane F, Gocun M, Konya V, et al. The association of pre-treatment peripheral blood markers with survival in patients with pancreatic cancer. Hepatogastroenterol. 2010; 57(99-100): 640-645.
36. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene. 2002; 21 (48): 7435-7451.
37. Rosenberg JE, Kantoff PW. Prostate cancer. In Nabel EG ed., ACP Medicine section 2011; 12(9) Hamilton ON: BC Decker.
38. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. New Engl J Med. 2004; 350(22): 2239-2246.
39. Barry MJ. Clinical practice. Prostate-specific-antigen testing for early diagnosis of prostate cancer. New Engl J Med. 2001; 344(18): 1373-1377.
40. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. New Engl J Med. 2012; 366(11): 981-990.