The Role of KRAS in Endometrial Cancer: A Mini-review

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Running title: The Role of KRAS in Endometrial Cancer (Review)

Abstract. Endometrial cancer (EC) is the most common cancer of the female genital tract, resulting annually in 76,000 related deaths worldwide. EC originates either from oestrogen-related proliferative endometrium (type I, endometrioid), or from atrophic endometrium (type II, non-endometrioid). Each type of EC is characterized by different molecular profile alterations. The Kirsten rat sarcoma viral oncogene homolog (*KRAS)* gene encodes a signalling protein which moderates response to various extracellular signals *via* down-regulation of the mitogen-activated protein kinase (MAPK) or phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene (PI3K/AKT) pathways. This article reviews the role of *KRAS* in predicting transition from hyperplastic endometrium to early-stage well-differentiated EC, as well as further invasive proliferation of the tumour to advanced-stage disease. KRAS seems to be directly associated with type I EC, and most studies support its early involvement in carcinogenesis. Current evidence correlates *KRAS* mutations with increased cell proliferation and apoptosis, as well as up-regulation of endometrial cell oestrogen receptors. Tumours positive for *KRAS* mutation can harbour hypermethylation-related changes in genome expression, and this can be the cause of concurrent loss of DNA repair proteins. Despite some evidence that *KRAS* mutation status affects cancer progression, a consensus is yet to be reached. Based on the available evidence, we suggest that screening for *KRAS* mutations in patients with hyperplastic endometrium or early-stage type I EC, may provide important information for prognosis stratification, and further provision of personalised treatment options.

Key Words: Endometrial cancer, KRAS, endometrial hyperplasia, molecular biomarkers, review.

Endometrial Cancer (EC) is the most common cancer of the female genital tract in developed countries (1). Each year 319,500 women are diagnosed with EC resulting in 76,000 deaths worldwide (2). EC develops from the inner lining of the uterine corpus (3), and it is currently divided into two types as firstly described by Llobet *et al.* (4). Type I tumours tend to be low or intermediate tumour grade; they overlap considerably (80%) with oestrogen-related endometrioid carcinomas. Contrary to type I, type II EC results from a sequence of genetic alterations occurring in atrophic endometrium; this can occasionally reflect a progression from polyps or pre-cancerous lesions to EC. Type II EC is mostly considered as non-endometrioid serous carcinomas (4); it tends to be high grade, deeply invasive into the myometrium, and of more advanced stage at presentation (4, 5). The estimated 5-year overall survival for patients with any type of EC is 81.5% (any stage) (6).

Current Staging

EC staging consensus keeps with the 2009 International Federation of Gynaecology and Obstetrics (FIGO) revised classification. Revised FIGO staging defines four stages (I-IV) following radical surgical resection (7). Stage I refers to a uterus-confined tumour, stage II to involvement of the cervix, stage III to adnexal or lymph node involvement, and stage IV to the presence of any metastatic deposits outside the pelvis (7).

Treatment Stratification

To-date, the stratification of treatment options relies on the disease stage; this includes certain histopathological features which are integrated into the FIGO staging. The cornerstone of EC treatment is to offer (radical) excision of the tumour; this includes

total hysterectomy with/without bilateral salpingo-oophorectomy, and if indicated, systematic pelvic/para-aortic lymphadenectomy. Besides its role in treatment, radical surgery is also the basis for staging and stratifying patients for further adjuvant treatment options (8-10). Gupta *et al.* suggest an EC risk group classification; this is primarily based on disease staging after primary resection and stratifies the need for further adjuvant treatment depending on the potential for disease recurrence (11). Adjuvant treatment options include chemo-radiotherapy, pelvic external beam radiation therapy or vaginal cuff brachytherapy. Based on this model, surgery is the only treatment in early, low-risk EC, whereas intermediate high-risk EC would require additional adjuvant treatment (11).

Molecular Staging

Although FIGO remains the gold standard in EC staging, there is an increasing need to identify novel molecular biomarkers in order to achieve individualised treatment options. Several efforts have been described in the literature, however, consensus is yet to be reached. All efforts aim to provide a more accurate framework which can predict both prognosis as well as response to treatment and the need for additional adjuvant therapy schemes.

A classic example is The Cancer Genome Atlas (TCGA) classification. TCGA provides a molecular taxonomy for EC based on an integrated multi-platform incorporating genomic, transcriptomic and proteomic profiling (1, 12). TCGA classifies EC into four groups, each of which is based on different histopathology or molecular sub-type, as well as prognostic potential. Group 1 includes tumours with a hypermutant profile and mainly DNA polymerase epsilon, catalytic subunit (POLE) exonuclease inactivation mutations, which have a favourable overall prognosis. Group

2 refers to EC which is associated with microsatellite instability (MSI), and more specifically with hypermethylation of the promoter region of the mutL homolog 1 (*MLH1)* gene; the latter has been found to be the primary MSI-associated mechanism of carcinogenesis in sporadic colorectal cancer (CRC) (13). Group 3 includes tumours with low somatic copy number alterations (SCNA); the latter refers to various segmental aneuploidies, focal events, and whole-chromosome aneuploidies (14). SCNA are strongly associated with chromosomal instability; these mechanisms explain why cancer cells can potentially deviate from a diploid karyotype and can also be the fundamental cause for a degree of general heterogeneity within an individual tumour. Groups 2 and 3 have similar prognosis. Group 4 represents a high SCNA group, which mostly incorporates *TP53* mutation, and includes serous-like EC, indicating a poor overall prognosis.

Further to stratifying prognosis, the incorporation of molecular features into the classification of EC aims to optimise personalised treatment options and to predict potential responses to (neo)adjuvant treatment (12). Recent studies have shown that in the case of Kirsten rat sarcoma viral oncogene homolog (*KRAS)*-mutant EC, a combination therapy of mitogen-activated extracellular kinase (MEK) inhibitors plus anti-oestrogen agents may alter oestrogen signalling and thus improve the response rate (15).

KRAS: A Marker in Cancer Molecular Biology

KRAS is a proto-oncogene (Gene ID: 3845) located at chromosome 12 (12p12.1) and is primarily involved in the cellular response to extracellular signals. It is strongly associated with down-regulation of mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene (PI3K/AKT)

pathways (16-18). *KRAS* encodes a 21_kDa signalling protein which connects activated membrane receptors to MAPK and PI3K/AKT pathways (5). Mutant *KRAS* promotes down-regulation of MAPK or PI3K/AKT, which further results in excessive cell proliferation and subsequently in carcinogenesis (5). *KRAS* mutations refer to a frequent alteration of guanine to adenine (G>A), a mutation most frequently found in codon 12. Codons 12 and 13 in exon 2 constitute 90% of all *KRAS* mutations (19). In total, there have been 85 different mutations reported, many of which are pathway-specific (20).

KRAS is tethered to several cell membrane receptors and acts as a signalling transducer molecule. A classic example of such receptors are the surface tyrosine kinase receptors, including the epidermal growth factor receptor (EGFR) across the cell membrane of colonic and rectal epithelial cells. There is a large family of anti-EGFR chemotherapy agents, for example cetuximab and panitumumab, which target these receptors. *KRAS* mutations can cause resistance to EGFR inhibitors (20). Hence, especially in the case of CRC, *KRAS*-mutant status is directly associated with chemotherapy resistance. Therefore, *KRAS* is currently being used in clinical practice as a predictive biomarker for response to anti-EGFR chemotherapy agents (21-25).

KRAS Mutations as Biomarkers of Early-stage Type I EC

Type I and II EC are thought to be associated with different distinct mutations (4, 5). *KRAS* mutations have been mostly associated with type I oestrogen-related EC and their frequency is estimated at around 10-30% (4, 5).

In their review of mechanisms of EC development, Banno *et al.* supported the assumption that *KRAS* mutations occur at the early stages of the EC pathway (5). Further to this, *KRAS* mutations are present in 6-16% of endometrial hyperplasia

specimens (26). Similar notions have been discussed in the case of CRC, where in the classic adenoma–carcinoma pathway, *KRAS* mutations seem to appear early in the neoplastic route. Several studies concluded that *KRAS* may play a significant role in early stage CRC (27-29). In 1988, Vogelstein *et al.* stated that early mutations of adenomatous polyposis coli gene result in deregulation of the wingless-related integration site (WNT) pathway (30); *KRAS* mutations follow deregulation of the WNT pathway and certainly take place prior to *TP53* gene inactivation. Similarly, in the case of EC, *KRAS* mutations appear to be a stage ahead of *TP53* involvement, and *TP53* signifies the transition from low-grade to high-grade type I EC (5).

Further to this, Tsuda *et al.* stress the role of *KRAS* in predicting invasive proliferation of well-differentiated (grade I) tumours (31). Therefore, the role of KRAS in both an early checkpoint of transition from hyperplasia to EC, as well as a marker of the invasive potential in the case of grade I tumours, is clear.

Another interesting feature is the association of *KRAS* mutations with MSI-positive EC. Microsatellites are short repetitive DNA sequences which are involved in the DNA repair system. The vast majority of MSI involvement is either *via* direct base substitutions (point mutations), or *via* hypermethylation of promoters of involved genes (epigenetic changes). In the case of Lynch syndrome, the whole series of mismatch repair (MMR) genes, including *MLH1*, mutS homolog 2 (*MSH2*), mutS homolog 6 (*MSH6*) and post-meiotic segregation increased 2 (*PMS2*), is affected (13). Nevertheless, in sporadic CRC and type I EC, MMR defects are primarily a consequence of hypermethylation of gene promoters, and this primarily affects the *MLH1* (4, 13). A classic example was shown by Muraki *et al.,* who reported hypermethylation of *MLH1* promoter in 40% of type I ECs (32). *KRAS* promoter can equally be affected by hypermethylation and this can explain its concurrent presence

with defective expression of MMR genes (in MSI-positive EC). Both hypermethylation changes, as reflected by reduced presence of DNA repair proteins (MMR), and *KRAS* mutations, are generally thought to occur early in the EC pathway.

Translation of KRAS Mutation Status into Clinical Information for Type I EC

A narrative review of the literature was performed to summarize the current views on the prognostic and predictive value of *KRAS* mutations in EC. PubMed database was searched using any (AND, OR) combination of keywords "*KRAS*" and "Endometrial Cancer". Any original study which involved *KRAS* mutation in EC was identified and critically commented on.

Most studies focus on explaining the role of *KRAS* in type I oestrogen-related EC. van der Putten *et al.* supported the view that *KRAS* mutations are found adjacent to hyperplastic endometrial tissue (33). Based on this, *KRAS* status was used as a prognostic marker to describe a possible transition from hyperplastic tissue to malignancy; 27% of their type I EC specimens were positive for *KRAS* mutation, most of which were next to hyperplastic endometrium. In 5% of cases, hyperplastic (non-malignant) endometrial specimens were also positive for *KRAS* mutation. Further to this study, Zauber *et al.* supported the involvement of *KRAS* early in the carcinogenesis pathway, suggesting that biopsies confirming endometrial hyperplasia should be analysed for *KRAS* status, along with MSI status (34). Similarly, Berg *et al.* concluded that *KRAS* involvement happens early, and that molecular alterations related to *KRAS* mutations and inflammation are more common in obese patients (35). Similarly, Duggan *et al.* concluded that there is early-stage involvement of *KRAS* gene in type I EC, prior to clonal expansion (36).

Many studies correlated *KRAS* status with certain histopathological features; Xiong *et al.* supported the role of *KRAS* mutations in the formation of superficial epithelial changes in endometrioid EC, which has been further associated with focal mucinous differentiation (37). A similar association between *KRAS* and mucinous differentiation was reported by He *et al.* (38). Another interesting study by Steward *et al.* identified *KRAS* mutations in 12 out of 42 endometriosis-associated endometrioid adenocarcinomas (39).

As discussed previously, current literature concludes that *KRAS* mutations are primarily found in type I oestrogen-related EC (5). An interesting question would be to explore the relationship between the *KRAS* gene and oestrogen receptors (ER), as there is extremely limited evidence for this. Tu *et al.* supported the assumption that the transcriptional activity of the ER is up-regulated by *KRAS* mutation (40). In other words, ER expression may be seen as a regulator of the RAS signalling pathway which directly affects directly the tumorigenesis of EC.

Several studies support the role of *KRAS* as a potential prognostic marker, both in terms of transition from pre-malignant to malignant cell status, as well as progression from early to more advanced invasive cancer. Ninomiya *et al.* identified K- and NRAS-mediated signalling pathways as potential inducers of cell apoptosis (41). Birkeland *et al.* noted an increase in *KRAS* amplification and *KRAS* mRNA expression during transition from primary to metastatic disease (42). Alexander-Sefre *et al.* suggests a molecular assessment of the depth of myometrial invasion of EC based on *KRAS* (43). Mizuuchi *et al.* correlated the presence of *KRAS* mutation (codon 12 or 13) with poor prognosis (44). Ito *et al.* attributed *KRAS* mutations as being responsible for more aggressive clinical behaviour of EC in postmenopausal women (type II EC) (45). On the other hand, Varras *et al.* (46) and Trowbridge *et al*. (47) did

not find correlation of *KRAS* status with any clinicopathological features. From the aforementioned evidence, it is apparent that a consensus on the exact way that *KRAS* overall affects EC prognosis is yet to be achieved.

Another interesting question is the association of *KRAS* status following tamoxifen exposure after breast cancer. Wallen *et al.* supported the existence of a link between tamoxifen use and *KRAS* codon 12 mutation (48). Nagy *et al.* noted a higher trend in *KRAS* mutation following exposure to tamoxifen (49).

Finally, although *KRAS* has an established predictive value in CRC, there are extremely limited data on this aspect in the case of EC. Byron *et al.* state that *KRAS* and fibroblast growth factor receptor 2 (*FGFR2)* mutations may alter the effectiveness of anti-FGR or anti-MEK biological therapies (50).

A promising study by Alomari *et al.* showed that *KRAS* mutation had a positive predictive value of 88% in diagnosing complex atypical hyperplasia (51). Based on the previous discussion, this could be an extremely important finding which may alter the current management of endometrial hyperplasia. Current practice in the United Kingdom, as defined by the Green-top guideline (No. 67), suggests first line management of endometrial hyperplasia with atypia in premenopausal women who wish to maintain fertility, by offering the Levonorgestrel Intrauterine System (LNG-IUS) and second-line by administering oral progestogen supplements or combination of both for at least 6 months (52). Identifying novel biomarkers which can predict the course of lesions and their progression to EC would be useful to optimise care provision and reduce anxiety from both the patient's and clinician's point of view.

Limitations

We recognise a series of limitations in this narrative mini-review. Although PubMed was searched systematically using certain key words, only the studies that were thought to be relevant and of high quality were considered in raising the discussion points. Secondly, most of the included cohorts were small with several limitations. Furthermore, existing evidence was conflicting. Lastly, a single biomarker was searched, which may provide a biased view as it may be optimistic to explain a complex carcinogenesis progression using a single gene.

Conclusions and Future Endeavours

Table I summarises the current knowledge on the role of *KRAS* in EC. Although evidence is limited and occasionally conflicting, there is a clear trend in the literature showing that *KRAS* plays a role early in EC progression, especially when the disease originates from hyperplastic endometrium. Given the lack of focused biomarkers, it would be interesting to conduct a prospective cohort study to delineate the role of *KRAS* in predicting response of hyperplasia to standard treatment or cancer progression after hyperplasia with or without atypia. In conclusion, findings of this review may allow for revision of the current management of pre-malignant endometrial lesions, especially hyperplasia with or without atypia. Screening of such cases for *KRAS* mutation would allow individualisation of treatment approach *via* flagging potentially high-risk pre-malignant cases for relapse of hyperplasia or future cancer progression.

Conflict of Interest

None of the Authors has any conflict of interest to declare in regard to this article.

Authors' Contributions

MS conceived the methodology and reviewed structure, drafted the manuscript and is the guarantor for the accuracy of the data. EIE contributed to literature screening and editing parts of the article. ZA contributed to editing parts of the article. KS, VS, EE contributed to literature screening. SP, SV, TH, JO, FW are equal contributors, senior authors of the article and clinicians with interest in Surgical Oncology (SP) and Advanced Gynecological Surgery and Oncology (SV, TH, JO, FW), and edited the article. All Authors have agreed to the final version of the article.

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Table I. Summary of the role of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation in endometrial cancer (EC).

I	*General information*				
	KRAS is a **proto-oncogene** primarily involved in cellular response to several signals; Most authors describe *KRAS* as a **signalling transducer** protein molecule.		Mutations cause **down-regulation** of MAPK/PI3K/AKT pathway	*Location*: 12p12.1 *Encodes*: 21 kDa protein *Mutation*: G>A, most common at codon 12, 13 (90%); 85 different mutations in total	Involved in ***several carcinogenesis pathways*** (lung, CRC, endometrial *etc.)*; most authors attribute *KRAS* mutations to being fairly ***early*** in the process
II	*What we know about KRAS*				
	Associated with **type I EC (endometrioid)** and subsequently hyperplastic endometrium; supposed to be an early stage mutation.	Can be present with **hypermethylation** of mismatch repair gene promoters (*MLH1* gene); therefore, associated with microsatellite unstable EC	Mutations present in 6-16% *of* **endometrial hyperplasia** specimens; and 10-30% of type I EC. Positive predictive value of *88%* in diagnosing complex atypical hyperplasia	Potentially dual role: -***Transition*** from hyperplastic endometrium to early stage malignancy - ***Progression*** from early to more advanced invasive cancer.	Relationship with **ER**: Transcriptional activity of the ER might be up-regulated by *KRAS* mutations.
III	*What we do not know about KRAS*				
	Prognostic and predictive (response to chemotherapy) value still equivocal for EC.	Limited use in clinical practice.	Limited value in type II non-endometrioid EC	Association of *KRAS* and non-malignant conditions *i.e.* endometriosis	Association of *KRAS* mutations with exposure to tamoxifen following breast cancer chemotherapy.
IV	*Future Directions – Applicability in Clinical Practice*				
	Can we screen endometrial hyperplastic specimens for *KRAS* to flag high-risk cases for potential transition to malignancy?		Could *KRAS* predict response to (neo)adjuvant chemotherapy? Could we stratify need for adjuvant treatment options following early-stage type I EC based on *KRAS* mutation (high risk for aggressive EC pattern).		Should *KRAS* be included as a screening tool for polyps or other (pre-/non-)malignant conditions *i.e.* endometriosis in pre-menopausal women?

ER: Oestrogen receptor; MAPK/PI3K/AKT; MLH1: mitogen-activated protein kinase/phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene; *MLH1*: mutL homolog 1.

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